REVIEW

Synthetic Route to Ergot Alkaloids

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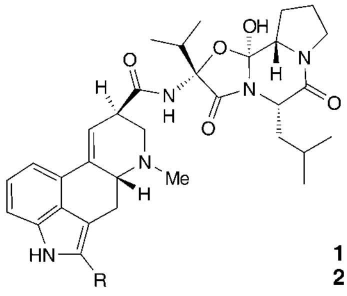
Dedicated to Professor *Rolf Huisgen* on the occasion of his 85th birthday

Rye is sometimes infected by a fungus called *Claviceps purpurea*. The term ergot designates the dark, brown, tuberous bodies which can be collected before or during harvesting and represent one of the most remarkable drugs of our therapeutic arsenal. Actually, the most significant alkaloids are metabolic products of these fungi. We elaborated three alternative total synthetic pathways to construct the ergoline skeleton, one of which – suitable for scaling up – finally resulted in (+)-lysergic acid (**32a**) and α-ergocryptine (**1**) (*Schemes 5* and *6*).

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



1 R = H; α-ergocryptine
2 R = Br; bromocryptine

The first synthesis of racemic lysergic acid was effected by *Woodward* and *Kornfeld* [3] in 1956. One of their main problems was to prepare ring C from the otherwise easily accessible 1*H*-indole-3-propanoic acid (**3**) since the ring closure of the corresponding acid chloride occurred at the more reactive pyrrole ring instead of the benzene ring. Thus the *Woodward* group reduced the pyrrole ring, its NH moiety was protected by benzoylation, and thereafter, the ring closure took place regioselevtively as desired. The drawback of this approach is that, sooner or later, the dihydropyrrole moiety must be reoxidized to a pyrrole ring. Moreover, it is difficult to perform an efficient synthesis leading to enantiomers since the method involves introduction of an unnecessary chiral center by the reduction. The earlier described resolution of the racemic compound needs further and rather inconvenient steps [4].

So far, the total synthesis of (±)-lysergic acid has been achieved by nine groups, but the number of publications dealing with the synthetic efforts is much higher [5]. Among these approaches, one can find about a dozen methods trying to construct the ergoline ring, some of which were successful; others remained at the level of attempt. Seven of the nine successful syntheses used the reduced indoline (=2,3-dihydro-1*H*-indole) derivative as the starting compound. *Oppolzer* and co-workers [6] performed the first total synthesis avoiding the reduction step, but their procedure again cannot be scaled up. A second approach to the racemic acid was published recently [7].

We decided to construct the ergoline skeleton starting from 1*H*-indole, thus avoiding the reoxidation problem, and at the same time making an efficient synthesis of the natural enantiomer possible. An ideal starting material was *Uhle*'s ketone **4a** having the intact 1*H*-indole ring, although the original synthesis of **4a** is rather tedious. *Uhle* started his synthesis of the ergoline skeleton with acetylation and subsequent bromination, and he claimed that the first obtained bromo derivative **4b** could be subjected successfully to a substitution reaction with various amines [8]. Early in the seventies, *Bowman* and co-workers reinvestigated a few results of *Uhle*'s synthesis and established that one of the key steps, alkylation of several types of amines with **4b**, always failed [9]. The approach starting from **4a** by *Stoll* and co-workers used the *Stobbe* condensation as a key step, but the reaction sequence could not be carried out [10], thus the synthesis of lysergic acid starting from *Uhle*'s ketone **4a** remained a challenge.

Results and Discussion. – 1. *Synthesis of (+)-Lysergic Acid.* In 1994, *Uhle*'s ketone **4a** became easily accessible from 1*H*-indole-3-propanoic acid (**3**) by *Goto*'s method¹) [11] (*Scheme 1*). In connection with our attempt to find a reasonable total synthesis of the ergoline skeleton, we wished to reinvestigate the cyclization of ring D. We had reported [12] the first successful reaction sequence to this end by applying an unprecedented intramolecular *Stobbe* condensation taking advantage of a lithium complex formed as an intermediate as follows. When the enamine mixture **5** (36% yield from **4a**), obtained from *Uhle*'s ketone **4a** in three steps, was treated with $NaCNBH_3$ (THF/MeOH/HCl or AcOH), the successful reduction of the C=C bond was accompanied by undesired oxidation of ring C leading to **6**, which might have occurred

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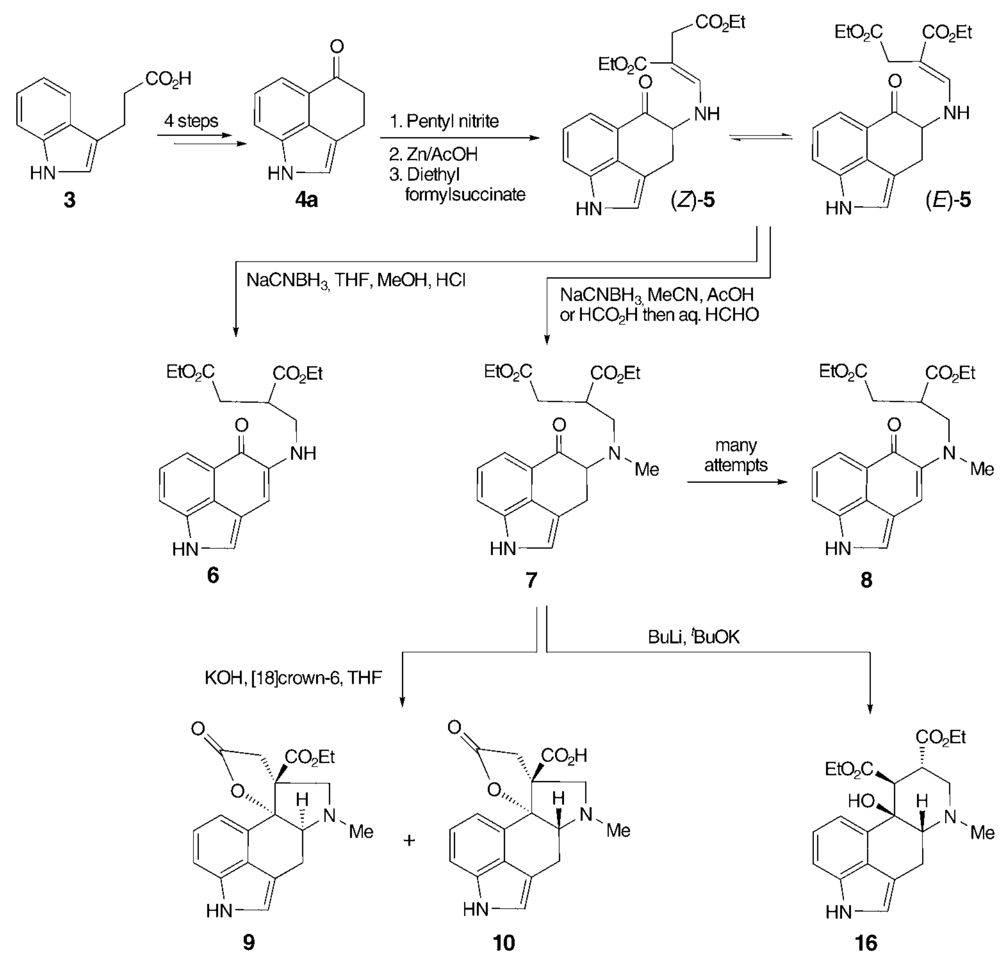
¹) Although *Goto*'s method has given a really short route to tricyclic **4a** and **4c**, the application of the expensive and dangerous BuLi at −78° can interfere with their scale-up preparation. In our modification, powdered KOH was applied for the deprotonation of **3** at 0°. After acylation at room temperature, the obtained crude product was transformed directly to **4c** in 43–46% overall yield.

during the workup by air oxidation. This oxidation process could be avoided if the $NaCNBH_3$ reduction was performed in MeCN and AcOH or HCOOH, and the mixture – without isolation – was treated with aqueous formaldehyde solution (30 min). After a simple workup (extraction, column chromatography), compound **7** was obtained as diastereoisomer mixture in 70% yield. Our derivative **7** proved to be the *N*-deacetyl analog of *Uhle*'s key intermediate (1-Ac-**7**).

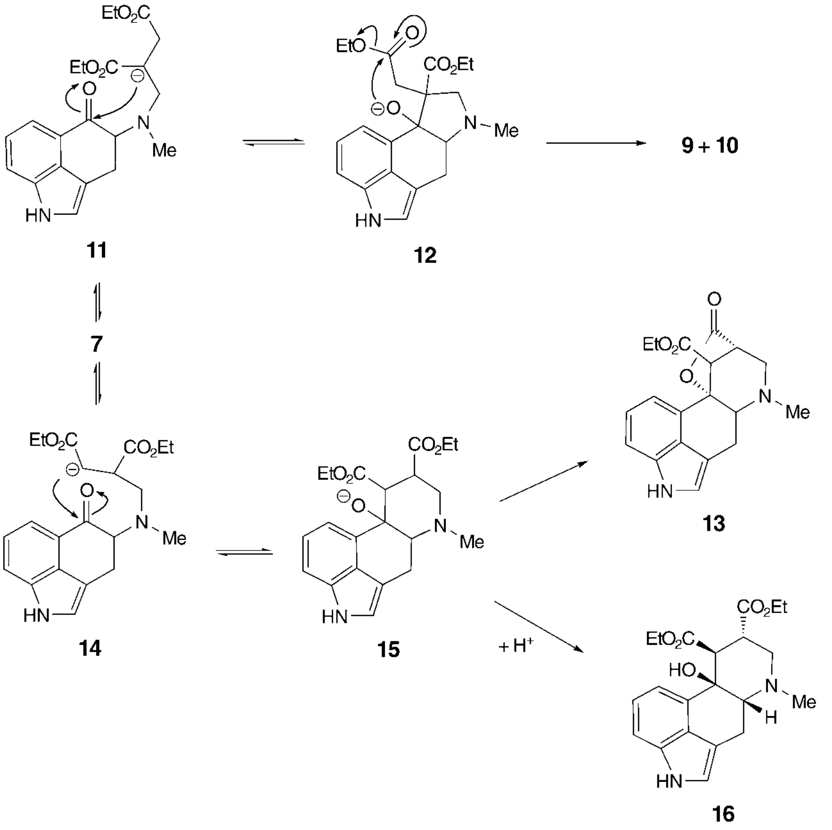
Scheme 1



To obtain the ergoline skeleton by intramolecular *Stobbe* condensation, about a dozen of bases (*e.g.*, ^{t}BuOK/^{t}BuOH, NaH/benzene + EtOH, K_2CO_3/DMF, KF/Al_2O_3, TlOEt/THF, *etc.*) were tried without any success. All runs afforded compound **8** as a red oil (yield 20–40%; *Scheme 1*). However, treatment of **7** with KOH (14 equiv.) in the presence of [18]crown-6 (8 equiv.) in THF (30 min, 0°) afforded the two isomeric pentacyclic lactones **9** (18%) and **10** (16%) after workup and subsequent column chromatography. Compound **6** was also isolated in 15–20% yield. The acid derivative **10** was presumably formed by hydrolysis during the workup of the reaction mixture.

Based on the generally accepted mechanism of the *Stobbe* condensation [13], a possible reaction sequence leading to lactones **9** and **10** may be the following. In the first step, carbanion **11** is formed which reacts with the carbonyl function in the first cyclization step (*Scheme 2*). The formed alcoholate **12** attacks at the carbonyl group of the ester function, affording lactone isomers. Because of the lack of a H-atom at the C-atom bearing the carboxyl or carboxylate group, the reaction stops on the lactone stage, which is generally an intermediate of the *Stobbe* condensation leading to an unsaturated half ester.

Scheme 2

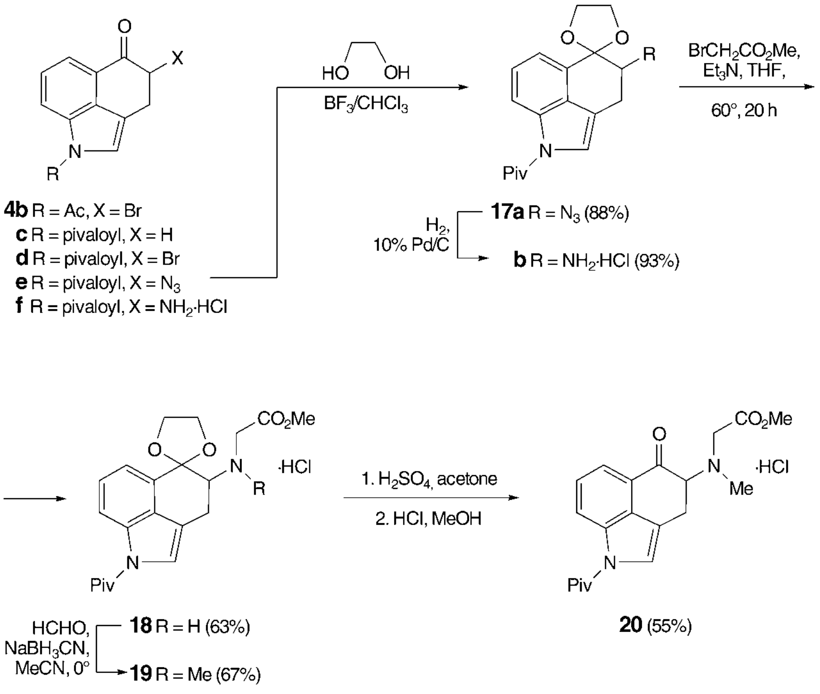


To rationalize some of the chemical behaviors described in this paper, we performed some calculations. The question is, why only the five membered lactones **9** and **10** were formed and not the also expected lactone **13**? Is there a big energy barrier between the two possible reaction routes? Assuming a product-like transition state, we calculated the relative stability of **9** and **13** by the AM1 [14], MNDO [15], and PM3 [16] methods. Calculations revealed that **13** is less stable by 1–2 kcal/mol than **9** at each semiempirical level. This relatively small energy difference does not explain why we could not find the expected **13** or its half-ester derivatives at all, thus we intend to study the problem later on.

Being aware of the mechanism of the *Stobbe* condensation [13], as a working hypothesis, we assume that the equilibrium among the intermediates **11**, **12**, **14**, and **15** is pushed irreversibly towards **9** and **10** (*Scheme 2*). Since the O–Li bond is much stronger (81.4 kcal/mol) than the O–K or O–Na bonds (66.0 and 61.3 kcal/mol, resp.) [17], we tried to stabilize the intermediate **15** as its Li salt. Therefore, the so-called superbase (a mixture of BuLi solution and ^{t}BuOK) was used for the condensation of **7** in THF at –70°. After workup, we could, although in moderate yield (22%), indeed isolate the expected compound **16** as a result of an intramolecular aldol-type reaction (*Scheme 1*). We were, however, unable to transform **16** into lysergic acid.

We investigated another approach [18] to the required skeleton starting from the *N*-pivaloyl derivative **4c** of *Uhle*'s ketone, obtained in three steps from 1*H*-indole-3-propanoic acid (**3**) according to the above mentioned method1) of *Goto* and co-workers [11] (*Scheme 3*). Transformation of **4c** into the α-amino ketone **4f** *via* bromination (→**4d**) and bromo→azido exchange (→**4e**) was described earlier by us [19]. Direct alkylation of this amine with bromoacetic acid esters was unsuccessful because of the susceptibility of the products to very easily oxidize and rearrange into naphthalene derivatives. Having protected the keto group of the azido intermediate **4e** as a ketal (see **17a**), however, alkylation of the corresponding amino intermediate **17b**, obtained

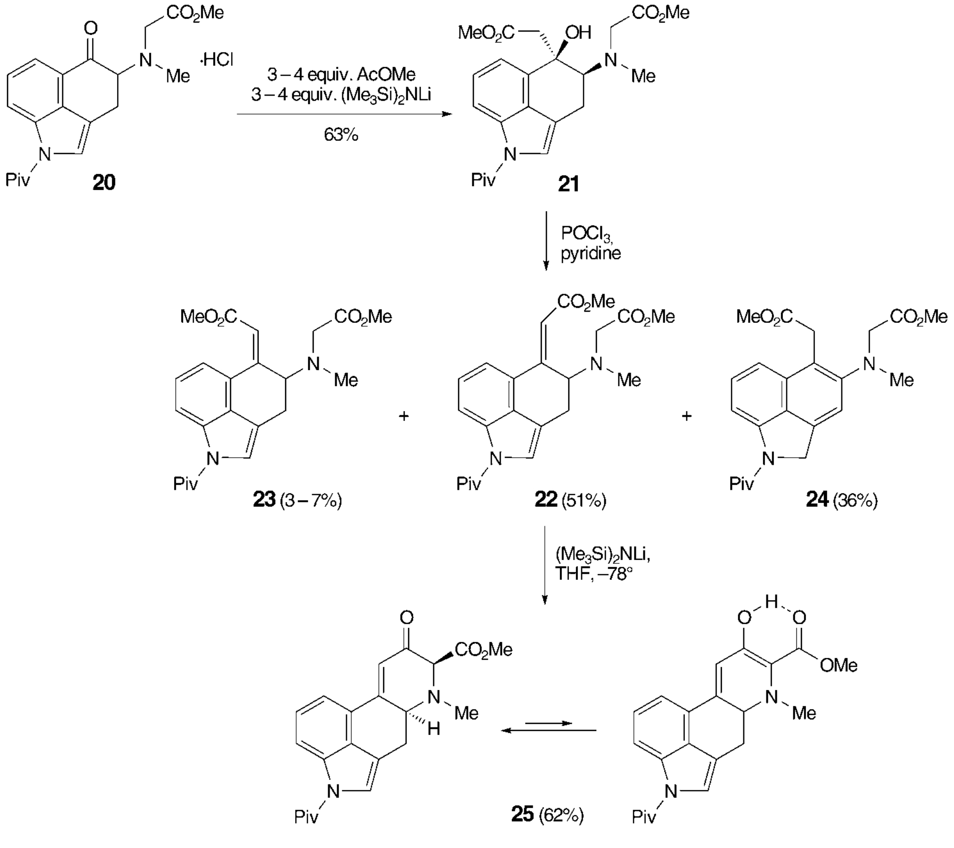
Scheme 3



after catalytic reduction of **17a**, was performed smoothly. *N*-Methylation of ester **18** with formaldehyde and $NaCNBH_3$ supplied the tertiary amino derivative **19** which, after deprotection with H_2SO_4, resulted in the *N*-acylated, *N*′-alkylated intermediate **20** as a stable hydrochloride salt.

Following the envisaged reaction sequence to build up ring D of the ergoline skeleton, *Wittig–Horner* and *Knoevenagel*-type reactions were attempted to form a C=C bond in place of the carbonyl function at position 5. Though *Wittig–Horner* reaction of the unsubstituted *Uhle* ketone with ethyl (diethylphosphinyl)acetate [20] or *Knoevenagel–Doebner*-type condensation of *Uhle*'s ketone [20] or 4-acetamido-*Uhle*'s ketone [9] with malononitrile or ethyl cyanoacetate could be performed in reasonably good yield, similar processes with our *N*-acylated, *N*′-alkylated intermediate **20** failed. However, using methyl or ethyl acetate lithiated with $(Me_3Si)_2NLi$ at −78° [21], we were at last successful in achieving our goal and preparing hydroxy diester **21** from the freshly prepared base of HCl salt **20** (*Scheme 4*). In our earlier attempts, we were unable to eliminate H_2O from a related derivative already possessing the ergoline skeleton, *i.e.*, **16**, but in case of **21**, the $POCl_3$/pyridine system worked, and a mixture of

Scheme 4



the stereoisomeric unsaturated esters **22** and **23** was obtained in reasonably good yield, beside 36% of naphthalene derivative **24** formed by endocyclic H_2O elimination or C=C bond migration. The mixture in which the (*Z*)-isomer **22** dominated could be separated by column chromatography. The structures of **22**–**24** were elucidated by ^{1}H-NMR spectroscopy including NOE measurements. Finally, *Dieckmann* cyclization of the (*Z*)-isomer **22** yielded tetracyclic ergoline derivative **25**; therein, lithium bis(trimethylsilyl)amide proved to be the best base. According to ^{1}H-NMR as well as IR spectroscopy, derivative **25** exists both in the crystalline form and in $CHCl_3$ solution mainly (85%) in the keto form, as the thermodynamically more stable tautomer. The orientation of the ester group is quasi-equatorial with a *cis* arrangement between the H-atoms at C(5) and C(7), as unambiguously established by NOE measurements. However, also this method (*Schemes 3* and *4*) could not be further elaborated to achieve the synthesis of (+)-lysergic acid.

The third route [22] finally has brought the desired results. To our pleasant surprise, we found that, contrary to [9], bromo ketone **4d** [19] can be subjected to a substitution reaction with amine **26** providing us with the so far unknown but much sought-after, even mistakenly claimed [8], product **27a** (yield 35%) if one has the patience to allow the reaction to proceed at room temperature in toluene (*Scheme 5*). The amine component **26** was already known and could easily be prepared [3]. After a simple deacylation (→**27b**; 80%) with methylamine and subsequent deprotection of the ketone function, the desired compound **28** (80%) was for the first time in our hands. The yield was even better (56%) if we allowed amine **26** to react with the *N*-unprotected bromo ketone **4g** which had been prepared *via* ketalization of **4d** to **17c**, followed by *N*-deacylation and deketalization (**17c**→**17d**→**4g**) in high yields (70% combined yield from **4d**). This sequence yielding **27b** and leading from **27b** to **28** proved to be a real shortcut. The ring closure of **28** leading to the unsaturated ketone (±)-**29**[2]) by intramolecular aldol condensation seems to be an easy task, but with a great number of well-established agents (from ^{t}BuOK through super bases to $(Me_3Si)_2NLi$), not even a trace of the desired tetracyclic compound could be detected. It is worth noting, and not easy to explain, that in the dihydro-1*H*-indole series, this ring closure had been carried out [3]; however, a similar intramolecular ring closure of compounds with a sulfone group instead of the indole N-atom also failed. We succeeded in performing the reaction with a LiBr/Et_3N system [24][25], which was first used for condensation by *Eschenmoser* and co-workers in the case of different S-containing compounds. LiBr or Et_3N alone were totally ineffective. Presumably, LiBr leads to a complementary activation of the two carbonyl groups in the presence of basic amine, since lithium ions have a higher affinity toward an O- than an N-atom. The function of the amine is purely to abstract the proton in the α-position with respect to the O-complexed ketone carbonyl. An especially good result was achieved by performing the two consecutive steps (deprotection and ring closure; **27b**→**28**→(±)-**29**) without isolation of the intermediate **28** to give a 60% combined yield of crystalline unsaturated ketone (±)-**29**. The resolution of *rac*-**29** was performed with 2,3-di-*O*-benzoyltartaric acid yielding

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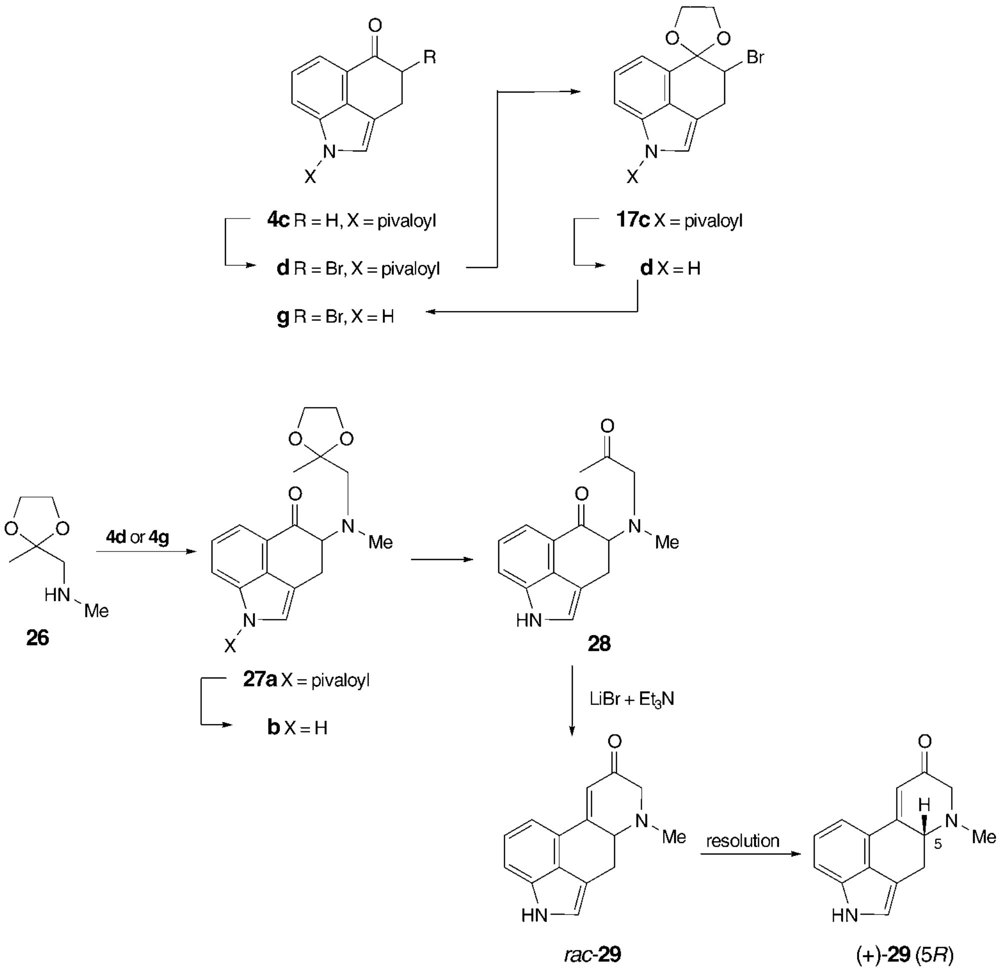
[2]) The first synthesis of (±)-**29** has been performed *via* oxidation of the corresponding alcohol having the 2,3-dihydro-1*H*-indole skeleton [23]; only one characterization data (m.p. 145–148°) of (±)-**29** has been described.

Scheme 5



(+)-**29**; the latter was also prepared by degradation of natural lysergic acid [26][3]) [27], and by comparison, the absolute (5*R*)-configuration of our synthetic compound was established.

To proceed, we allowed (+)-**29** to react with the isonitrile derivative **30** in the presence of base [28] to yield the formamide derivative **31** (77%), followed by acidic hydrolysis (*Scheme 6*). A mixture of (+)-lysergic acid (**32a**) and its epimer **32b** was obtained; after treatment with base, almost pure (+)-lysergic acid (**32a**) was isolated as a result of epimerization, although in poor yield (10%). A much better result was achieved by treating intermediate **31** with base affording a nitrile mixture **32c**/**32d** 1:1

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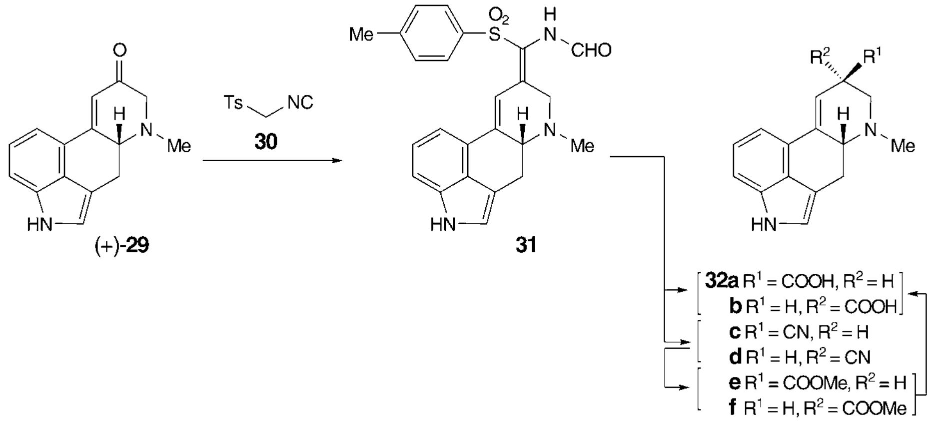
[3]) A few characterization data of (+)-**29** (m.p. 164–166°, $[\alpha]_D = +703$ ($c = 1$, MeOH), UV spectrum) have been described.

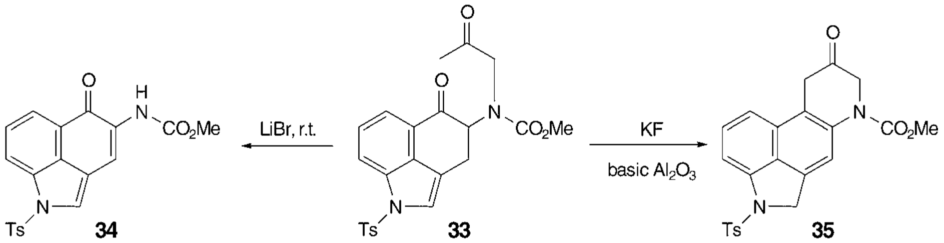
(70%) and converting the latter by *Pinner* reaction (MeOH/HCl) into the lysergic acid esters **32e**/**32f** 3 : 2 (72%). There is no need to separate the two nitriles or esters since the basic hydrolysis of **32e**/**32f** resulted in pure (+)-lysergic acid (**32a**; 54%) through concurrent hydrolysis and epimerization of **32b**.

Scheme 6



In connection with the intramolecular aldol cyclization step of the synthesis, it is worth mentioning and emphasizing the difficulties encountered by both the *Bowman* group [9] and ourselves. The former succeeded in preparing the doubly protected diketone intermediate **33** which seemed to be suitable for the above cyclization process as well. However, their attempts to obtain an α,β-unsaturated ketone, failed. During our research [29], we also prepared this diketone intermediate **33**, and – in accordance with *Bowman* and verified by *Novartis* researchers [25] – we found that metal alkoxides MeONa, EtONa, ^{t}BuOK in several types of solvents) could not induce the desired cyclization. Other strong bases ($((Me_3Si)_2NLi$, Lithium diisopropylamide (LDA), BuLi/^{t}BuOK) gave unsuccessful results, too. With LiBr, besides the starting material **33**, only an oxidized compound **34** was obtained in low yield (*Scheme 7*). A similar C–N bond cleavage in urethanes has already been observed and described in our earlier publication [12]. Since we successfully used KF/Al_2O_3 as base in a cyclization step in the course of our practical synthesis of epibatidine [30], a solution of **33** in benzene was allowed to react with this reagent, resulting in the first successful intramolecular aldol

Scheme 7

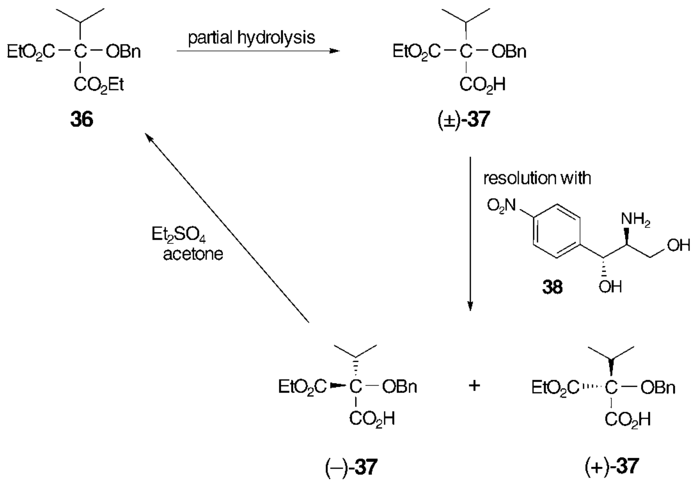


cyclization of **33** to give the tetracyclic ketone **35** in 63% yield; however, rearrangement of the ring system was evidenced by NMR measurements. This result can be explained by an indole → naphthalene isomerization *via* migration of C=C bonds though up to now, this rearrangement was described only for lysergic acid derivatives [31].

2. *Improving the Efficiency of the Peptide Part Synthesis.* Above, we described the synthesis of the (+)-lysergic acid (**32a**) component of α-ergocryptine (**1**). The synthesis of the peptide part has already been described [32] by a research group from *Sandoz Pharmaceutical Co.* Our task was to improve the efficiency, especially the efficiency of the reaction sequence concerning configuration, and to make a scale-up procedure possible.

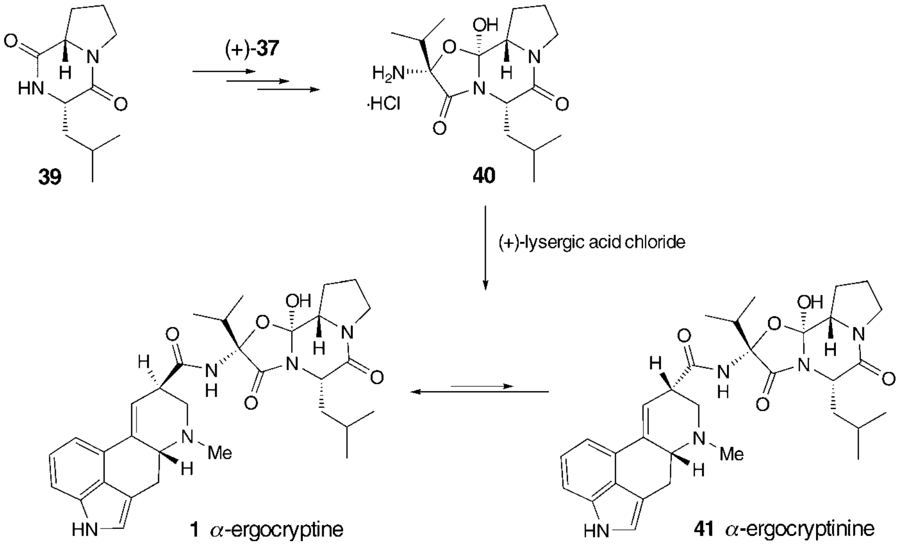
At the outset, isopropylmalonic acid ester was oxidized by benzoyl peroxide. According to the original procedure, excess of the benzoyl peroxide had to be eliminated by charcoal, but following this route, we observed explosions in *ca.* 20% of the cases. To avoid this danger, $Na_2S_2O_3$ or $NaHSO_3$ was successfully used instead of charcoal. The resulting compound was debenzoylated and the OH group protected as the benzyl ether (→ **36**). Partial hydrolysis of diester **36** gave rise to the half ester (±)-**37** (*Scheme 8*). In *Sandoz*'s original reaction sequence, this acid was resolved by the consecutive application of (−)- and (+)-pseudoephedrine, a rather inconvenient and the low-yielding process. Instead of pseudoephedrines, we used (+)-(1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (**38**) for resolution. Compound **38** is the unwanted and thus discarded enantiomer formed during the manufacturing procedure of the antibiotic chloramphenicol [33]. The desired salt of the (*R*)-isomer (+)-**37** crystallized from the solution in excellent yield. Isolation of (+)-**37** was accomplished by acidic treatment. By this method, both (−)-**37** and **38** were recovered easily. To make the process even more economic, the undesired (*S*)-enantiomer (−)-**37** was esterified with diethyl sulfate to the original, achiral diester **36** which was recycled into the reaction sequence. We may call this manipulation *dechiralization*.

Scheme 8



The so-called aminocyclol hydrochloride (**40**), the partner needed for coupling with (+)-lysergic acid (**32a**), was prepared from Z-protected L-proline *via* lactam **39** (*Scheme 9*). The L-proline derivative was treated with L-leucine methyl ester 4-methylbenzenesulfonate salt according to the mixed anhydride (carbonochloridic acid ester) method. After deprotection by hydrogenolysis followed by heating, the L-prolyl-L-leucine lactam **39** was isolated in good yield. The malonic acid derivative (+)-**37** was transformed to the acid chloride and allowed to react with lactam **39**, the product was deprotected by hydrogenolysis, and the resulting cyclolester was hydrolyzed to the so-called cyclolcarboxylic acid. After several steps, **40** was obtained [32]. Several methods were tried for the coupling of (+)-lysergic acid (**32a**) with the peptide part **40**. The most practical route was found by using lysergic acid trifluoroacetate, which was allowed to react with PCl_5. The reaction conditions (temperature, excess of reagent) are critical. The approximate amount (80%) of acyl chloride in the obtained reaction mixture was estimated by IR spectroscopy. By reacting the suspension of the aminocyclol hydrochloride (**40**) in CH_2Cl_2 with lysergic acid chloride hydrochloride [34] at $-12°$ in the presence of pyridine, α-ergocryptine (**1**) was isolated in 41% yield (as its phosphate salt) [35]. In the coupling procedure, due to a partial epimerization of the lysergic acid part at C(8), α-ergocryptinine (**41**) [32] was also formed and isolated (31%) after chromatographic workup. Since a thermodynamic equilibrium exists between the two stereoisomers in favor of **1** (**1**/**41** 3 : 1) in boiling MeOH or in other solvents [36], in principle there is a possibility to transform **44** into **1** on a preparative scale. This aspect, however, was not closely investigated.

Scheme 9



Conclusions. – In our recent publications three alternative pathways to the ergoline skeleton have been described. While two of them could not be carried on to the total synthesis of the desired ergot alkaloids, the third one allowed a practical, direct synthesis of (+)-lysergic acid (**32a**). Along this route, the 1*H*-indole moiety remained intact throughout, thus avoiding the necessity to introduce a superfluous chiral center by reduction. Furthermore, we could perform the resolution of an earlier intermediate, *i.e.*, (±)-**29**, thus avoiding the rather tedious and uneconomic resolution of the end product.

Since several natural alkaloids, *i.e.*, (+)-isosetoclavine [26], (+)-lysergene [37], and (−)-agroclavine [37], have been prepared *via* a semisynthetic route from (+)-9,10-didehydro-6-methylergoline-8-one[3]) ((+)-**29**) obtained by degradation of natural (+)-lysergic acid [26][27], our successful approach to (+)-**29** can now be regarded as the achievement of the total syntheses of the mentioned alkaloids.

By using our modified approach, the peptide part of the alkaloid was synthesized without any by-product since the undesired enantiomeric ethyl malonate derivative (−)-**37** was successfully recycled.

Upon coupling the lysergic acid and peptide parts, we have completed an efficient total synthesis of α-ergocryptine (**1**) and α-ergocryptinine (**41**).

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