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Articles

Practical Synthesis of 8α-Amino-2,6-dimethylergoline: An Industrial Perspective†

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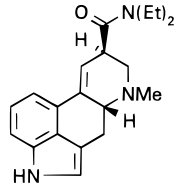
Abstract:
8α-Amino-2,6-dimethylergoline is the key intermediate for the synthesis of a number of ergot derivatives under clinical development. They are structurally related to the better known lysergic acid and its derivative, the diethylamide (LSD). The use of lysergic acid or its isomer, paspalic acid, both of which are readily available by fermentation on an industrial scale, as a starting material for the synthesis of 8α-amino-2,6-dimethylergoline appears to be the obvious choice as the basic structural elements already exist. Whereas the transformation of the acid function to the amino moiety proceeded under well-established conditions, the introduction of the single methyl group posed a major challenge to the industrial chemist. Various methodologies are available to solve this problem, and the approach that involves direct metalation and methylation is found to be most suitable for up-scaling to multiton quantities. The importance of using on-line monitoring techniques (FT-IR) in process research and development will be exemplified by this report.

Introduction

The potent and versatile physiological activities of natural ergot alkaloids prompted a thorough chemical and pharmacological investigation of the structure−activity relationship of this class of natural products for many years.[1] From numerous structural modifications of the ergolines and ergolenes[2] have emerged important drugs for human medicine; they include lysergic acid diethylamide (**1**, LSD), a potent hallucination agent;[3] the 9,10-dihydro derivatives of the ergotamine and ergotoxine group **2a/2b**, which are therapeutics for cardiovascular diseases;[4] and 2-bromo-α-ergocryptine (**3**) (bromocryptine), a potent prolactin inhibitor and postsynaptic dopamine receptor agonist effective for the treatment of Parkinson disease.[5]



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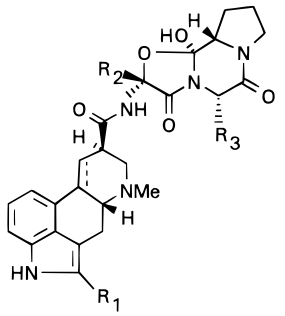


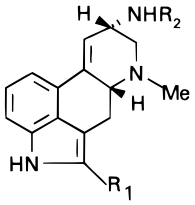
2a ergotamine series: R_1 =H, R_2 =CH_3, R_3 =CH_2Ph
2b ergotoxine series: R_1 =H, R_2=$CH(CH_3)_2$, R_3=$CH_2CH(CH_3)_2$ or CH_2Ph
3 R_1 =Br, R_2 =$CH(CH_3)_2$, R_3 =$CH_2CH(CH_3)_2$

Newer findings recently have revealed that derivatives of the 8α-aminoergolenes and the corresponding ergolines **4/5** also possess similar potent dopaminergic activity.[6] In particular, the diethylurea derivative **5a** (Lisuride) showed remarkable serotonin antagonist properties and has been used clinically for the treatment of migraine.[7]

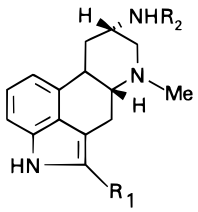
We and others have been interested in ergolines of the general type **6**, which are substituted at position 2. In particular, halogen- or methyl-substituted derivatives display potent antidopaminergic and/or α_2-receptor blocking activity and are therefore possible candidates for the treatment of psychosis belonging to the schizophrenic syndrome.[8]

† Dedicated to Professor D. Seebach, ETH-Zuerich, Switzerland, on the occasion of his 60th birthday.

(1) Stoll, A.; Hofmann, A. In *The Alkaloids;* Manske, R. H. F., Homes, H. L., Eds.; Academic Press: New York, 1965; Vol. 8, p 772.
(2) Ergolines are generally referred to as alkaloids having the basic structure (6a*R*)-*trans*-4,6,6a,7,8,9,10,10a-octahydroindolo[4,3-*f,g*]quinoline; ergolenes are dehydroergolines and differ in the position of the double bond (8,9 or 9,10); see: Ninomiya, I.; Kiguchi, T. In *The Alkaloids*; Brossi A., Ed.; Academic Press: New York, 1990; Vol. 38, p 14 and references cited therein.
(3) Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 944. Stoll, W. A. *Schweiz. Arch. Neurol. Psychiatr.* **1947**, *60*, 279. Hofmann, A. *Die Mutterkornalkaloide;* F. Enke Verlag: Stuttgart, 1964; p 183. Hofmann, A. *Die Geschichte des LSD 25* (The history of LSD 25). *Triangel* **1955**, *2*, 117.
(4) Berde, B.; Stürmer, E. In *Ergot Alkaloids and Related Compounds*; Schield, H. B., Ed.; Springer Press: Berlin/Heidelberg/New York, 1978. Schardt, F.; Miskra, R. B. *Ther. Ggw.* **1982**, *121*, 26.
(5) Schneider, H. R.; Stadler, P. A.; Stütz, P.; Troxler, F.; Seres, J. *Experientia* **1977**, *33*, 1412. Flückiger, F.; Wagner, H. R. *Experientia* **1968**, *24*, 1130. Kebabian, J. W.; Calne, D. B. *Nature* **1979**, *277*, 93.
(6) Zirkan, V.; Semonsky, M.; Rezabek, K.; Auskova, M.; Seda, M. *Collect. Czech. Chem. Commun.* **1972**, *37*, 2600. Koller, W. C.; Herbster, G. *Neurology* **1987**, *37*, 723. Pfeiffer, R. F. *Clin. Neurobiol.* **1985**, *8*, 64.
(7) Zirkan,V.; Semonsky, M. *Collect. Czech. Chem. Commun*. **1963**, *28*, 1080 and 1196 and references cited therein. Votava, Z; Lamplova, J. *Neuro-Psychopharmacol*. **1961**, *2*, 68. Schachter, M.; Blackstock, J.; Dick, J. P. R.; George, R. J. D.; Marsden, C. D.; Parkes, D. *Lancet* **1979**, 1129.
(8) Sauer, G.; Schröter, B.; Wachtel, H. (Schering AG). Deutsche Offenlegungsschrift DE 3620293A1, 1987.



4 $R_1 = R_2 = H$
5a $R_1 = H$, $R_2 = CONEt_2$



5b $R_1 = CH_3$, $R_2 = CONEt_2$
5c $R_1 = CH_2N^+(CH_3)_3I^-$, $R_2 = H$
6 R_1 = halogen, alkyl, R_2 = alkanoyl
7 $R_1 = CH_3$, $R_2 = H$

Whereas the introduction of halogen at position 2 by electrophilic substitution has been demonstrated to be commercially feasible and attractive,[5] introduction of a corresponding methyl group has not been an easy undertaking. Herein we report a practical and scaleable synthesis for 8α-amino-2,6-dimethylergoline (**7**), a key intermediate for a number of clinical development compounds.

Strategy. 8α-Amino-2,6-dimethylergoline (**7**) is needed in multiton quantities; the synthetic route of choice has to be amenable for scale-up and should be easily transformed into an ecoefficient manufacturing process. Potential approaches are as follows:

1. Partial Synthesis. An obvious approach to 8α-aminoergoline is to start with lysergic acid (**8a**) or its isomer, paspalic acid (**8b**), both of which are accessible via microbial fermentation[9] on a technical scale. As the basic structural elements already exist, it seemed straightforward to essentially convert the carboxyl moiety into an amino function (with inversion of configuration), to be followed by the direct introduction of a methyl group, or a one-carbon unit which could easily be transformed into a methyl group, at position 2 (Scheme 1).

2. Biomimetic Synthesis. Tryptophan has been shown to be a precursor in the biosynthesis of lysergic acid and related ergot derivatives.[10] Conceivably, 2-methyltryptophan or the more readily available 2-methylindole could even be used as feedstock for the fermentation to afford 2-methyllysergic acid or its derivatives, which could then be transformed to the desired 8α-amino derivative as before (Scheme 2).

Unfortunately, feeding experiments using neither D,L-2-methyltryptophan, prepared from 2-methylindole according to the literature[11] as well as the corresponding L-derivative (prepared via enzymatic hydrolysis of the corresponding methyl ester[12]), nor 2-methylindole showed any sign of incorporation.[13] This approach was quickly abandoned.

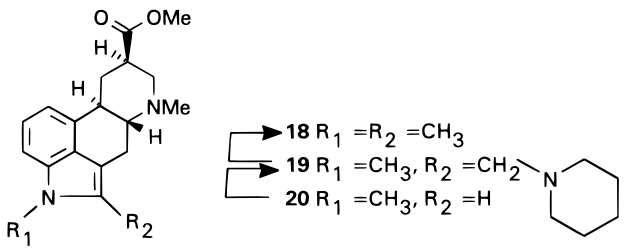
3. Total Synthesis. Although a number of total syntheses of lysergic acid have been reported,[14] the strategies employed could not easily be scaled up due to their length and intrinsic difficulties. The synthesis of the corresponding 2-methyl derivative would also require de novo reaction conditions to be investigated.[15] This approach requires extensive experimentation, and our development timelines precluded any further efforts at this stage.

Chosen Strategy. In view of the urgent need to develop a practical and commercializable industrial process for the manufacturing of 8α-amino-2,6-dimethylergoline (**7**) and its derivatives, our efforts have concentrated on the first approach.

Although extensive investigation in the reduction[16] of **8a/8b** to dihydrolysergic acid (**9**) as well as its subsequent transformation to 8α-amino-6-methylergoline (**13**) via the dihydro ester **11** and hydrazide **12** has been undertaken within our company over a number of years[17,18] (Scheme 3), *much effort is still required to further optimize these steps with respect to yield, practicability, economy of equipment, and needs/cost of investment on a commercial scale.*

The major challenge remained the introduction of the single methyl moiety into position 2 of the ergoline skeleton. A direct method for this transformation has so far not been reported in the literature. The best known procedure was a two-step sequence developed by Stütz and Stadler.[19] Accordingly, dihydrolysergic acid methyl ester (**10**), easily available from **9** via acid-catalyzed esterification, reacted in the presence of Lewis acid, e.g., boron trifluoride or titanium tetrachloride, with 2-methoxy- or 2-chloro-1,3-dithiolane, to afford 2-(1,3-dithiolan-2-yl)dihydrolysergic acid methyl ester (**16**) in good to moderate yield (Scheme 4). Reductive desulfurization with Raney nickel gave the corresponding 2-methyl derivative **17**. Unfortunately, the ecological and economical problems associated with this methodology, including safe handling (transport, storage, disposal, etc.) of ethanedithiol and Raney nickel are so immense that they preclude any interest in further development.[19]

Bernardi and Temperilli[20] reported the preparation of 1,2-dimethyldihydrolysergic acid methyl ester (**18**) by hydrogenation of the corresponding 2-piperidinomethyl derivative **19** under high pressure and temperature; the latter has been prepared from the 2-unsubstituted ergoline **20** by a Mannich-type reaction. Similarly, diethylurea derivative **5b** has been prepared by sodium borohydride reduction of the quaternary ammonium salt **5c**.[8] Unfortunately, both procedures were considered not amenable to scale-up due to the moderate reported yields, number of steps involved, and conditions/equipment required.

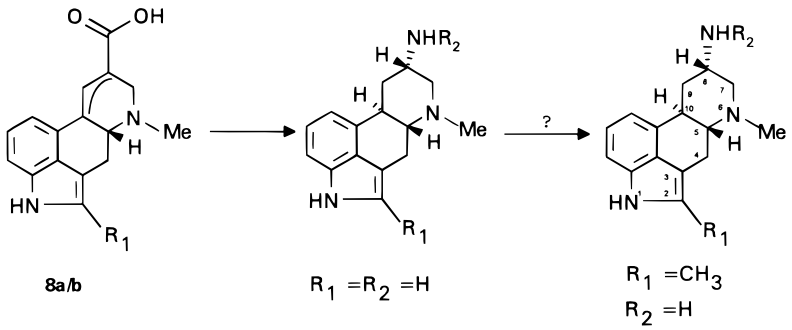


18 $R_1 = R_2 = CH_3$
19 $R_1 = CH_3$, $R_2 = CH_2$–N
20 $R_1 = CH_3$, $R_2 = H$

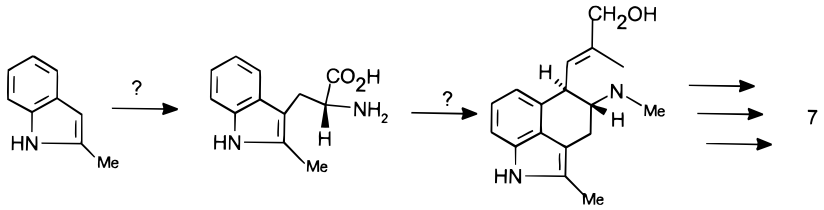
The most attractive approach remained to be the heteroatom-facilitated direct orthometalation−methylation[21] of a

(9) Kobel, H.; Schreier, E.; Rutschmann J. *Helv. Chim. Acta* **1964**, *47*, 1052. Kobel, H. *Chem. Rundsch.* **1974**, *27*, 57.
(10) Ramstad, E. *Lloydia* **1968**, *31*, 327. Voigt, R. *Pharmazie* **1968**, *23*, 285, 353, and 419. Bellatti, M.; Casnati, G.; Palla, G.; Minghetti, A. *Tetrahedron* **1977**, *33*, 1821. Weygand, F.; Floss, H. G. *Angew. Chem., Int. Ed. Engl.* **1963**, 243.
(11) Casnati, G.; Ricca, A. *Gazz. Chim. Ital.* **1963**, *93*, 355. We thank Mr. P. Engeli for the preparation of D,L-2-methyltryptophan and its corresponding L derivative.
(12) Kezdy, F. J.; Jindal, S. P.; Bender, M. L. *J. Biol. Chem.* **1972**, *247*, 5746.
(13) Unpublished results; we are grateful to our colleagues at Biochemie Kundl, Austria, for carrying out these experiments.

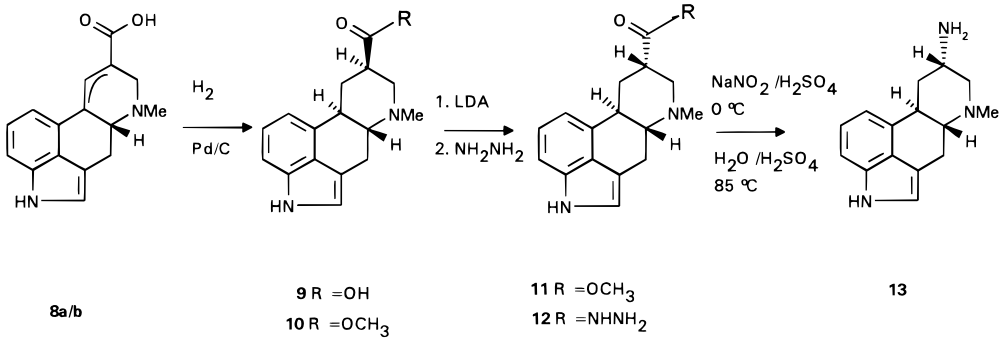
Scheme 1



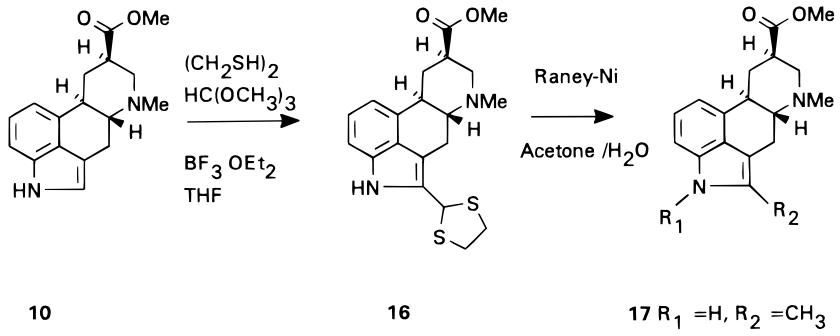
Scheme 2



Scheme 3



Scheme 4



N-protected ergoline intermediate such as **14** (Scheme 5). This can easily be made available from paspalic acid according to Scheme 3.

A further shortcut[22] could even be envisaged by a combined isomerization−metalation−methylation scheme in a one-pot procedure, starting with the *N*-BOC derivative **21** (Scheme 6).

Results and Discussion

Optimization of the Hydrogenation of Paspalic Acid. Technical grade paspalic acid (**8b**), which is obtained essentially as a mixture with lysergic acid (**8a**) in varying ratios (55−85 parts vs 45−15 parts) has conventionally been converted to dihydrolysergic acid (**9**) via catalytic hydrogenation under basic conditions at elevated hydrogen pressure, employing either Raney nickel or Pd/C as catalyst.[23] This process is well established, but in view of the relatively high

(14) For a general review, see ref 2; other important original works on total synthesis: Kornfeld, E. C.; Fornfold, E. J.; Kline, G. B.; Mann, H. J.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1954**, *76*, 5626. Rebek, J., Jr.; Thai, B. F.; Shue, Y. K. *J. Am. Chem. Soc.* **1984**, *106*, 1813.

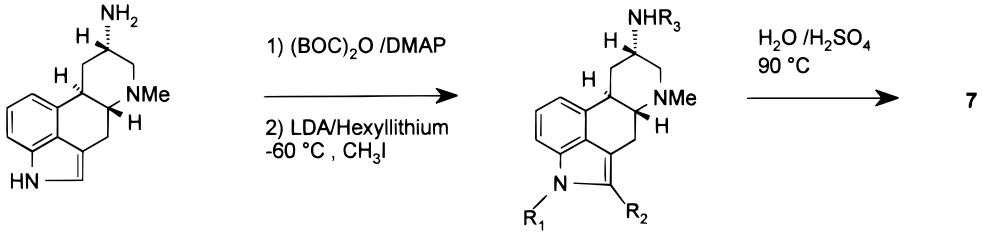
(15) A total synthesis for the 2-methyl derivative has now been achieved in our laboratories by E. Waldvogel, E. Kuesters, and P. Engeli. Preliminary results have recently been published at the French−American Chemical Society annual meeting held in Tucson, AZ (March 1997).

(16) Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1946**, *29*, 635. Cerny, A.; Semonsky, M. *Pharmazie* **1971**, *26*, 740. See also work from Zirkan *et al.* in ref 6.

(17) Benes, J.; Cerny, A.; Miller, V.; Kudonac, S. *Collect. Czech. Chem. Commun.* **1982**, *47*, 1333. Brich, Z.; Mühle, H. (Sandoz AG). EP 48695; *Chem. Abstr.* **1982**, *97*, 72651 p.

(18) Hofmann, A. *Helv. Chim. Acta* **1947**, *30*, 44.

Scheme 5

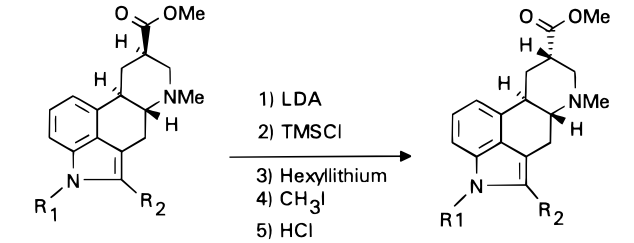


13

14 R_1, R_3 = BOC, R_2 = H

15 R_1, R_3 = BOC, R_2 = CH_3

Scheme 6



21 R_1 =BOC, R_2 =H

22 R_1 =BOC, R_2 =H

31 R_1 =BOC, R_2 =CH_3

amount that we have to produce eventually, we decided to look for alternatives where no special equipment is required. Hydrogen transfer conditions[24] are particularly attractive; in addition, this technology has been applied to other ergot derivatives.[25] Using formic acid as the hydrogen donor and Pd/C as catalyst, **8a/8b** was reduced to give a mixture of the desired product **9** and its isomer **24** in low to moderate yield[26] (Scheme 7). Probably under the acidic reaction conditions reported, **8a/8b** epimerized to isolysergic acid (**23**), which then resulted in a significant amount of the isoacid **24**.[1,16]

On the other hand, we found that when the reaction was performed under basic conditions, over 80% of the desired dihydro acid **9** could be isolated, without any significant formation of **24** or any other major by-products.[27] The best results were obtained in a mixture of water-methanol-piperidine with piperidine formate as the hydrogen donor in the presence of 1% Pd/C at 40 °C and under atmospheric pressure. The product thus obtained is basically analytically pure and could be used directly for the subsequent reaction without further purification. The process can be carried out in a normal multipurpose reactor; no formation of carbon monoxide could be detected.[24,28]

Esterification of Dihydrolysergic Acid (9). Acid **9** was converted to the corresponding methyl ester **10** by a conventional acid-catalyzed esterification reaction. Using the procedure as described, the desired product could be isolated efficiently by precipitation after concentration and neutralization of the crude reaction mixture in high yield and good quality.

Epimerization of Dihydrolysergic Acid Methyl Ester (10) to Isoester 11. Epimerization at C-8 of dihydrolysergic acid methyl ester (**10**) is so far best performed via base-induced isomerization.[17] Other known methods, e.g., hydrogenation[29] of the $\Delta^{7,8}$-unsaturated ester **25** (Scheme 8), or reduction of amide derivatives of isolysergic acid **23** with lithium and liquid ammonia,[30] are considered too problematic for any large-scale process.[31] Deprotonation of **10** with LDA, followed by kinetically controlled protonation, gave a mixture of the corresponding isoester **11** and **10** (4:1). The isolated yield of pure **11** after crystallization unfortunately amounted to a moderate 60−65%.

This ratio could not be influenced to favor the more selective formation of **11** either by variation of base or by temperature.[17] We speculate that the lithium ester enolate complex **26** that favors the selective protonation from the β-face might be destroyed before the desired process is

(19) Stütz, P.; Stadler, P. A. *Helv. Chim. Acta* **1972**, *55*, 75. The methodology described for the introduction of the one-carbon unit requires the use of methylene chloride (environmental pollutant, carcinogen) as solvent, boron trifluoride etherate as Lewis acid (fire hazard, halogenated reagent), ethanedithiol (malodorous, hazardous to the environment) and a *large* amount of Raney nickel. *We were not able to find a supplier who would reprocess used Raney nickel contaminated with sulfur!* The only disposal method available is by land fill, which is presently not an acceptable solution, particularly for the amount involved.

(20) Bernardi, L.; Temperilli, A. *Chim. Ind. (Milan)* **1972**, *54*, 997.

(21) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (N.Y.) **1979**, *26*, 1. Snieckus, V. *Chem. Rev.* **1990**, *90*, 880.

(22) Unfortunately, when varying amounts of LDA and TMSCl were used, followed by methyl iodide, no selective methylation at C-2 could be observed; methylation occurred also at C-8, giving a mixture of diastereoisomers (α or β substitution), contaminated by a nonmethylated ester but isomerized at C-8 (α carbomethoxy group). In one experiment, we isolated a 2-trimethylsilyl-substituted derivative, but further conversion of this compound to the corresponding 2-methyl derivative failed.

(23) Jacobs, W. A.; Craig, L. C. *J. Biol. Chem.* **1936**, *113*, 767. Stoll, A.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 2070. Stoll, A.; Hofmann, A.; Petrzilka, T. *Helv. Chim. Acta* **1946**, *29*, 635. Cerny, A.; Semonsky, M. *Pharmazie* **1971**, *26*, 740.

(24) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. Johnstone, R. A. W.; Wilby, A. H.; Entwistle, J. D. *Chem. Rev.* **1985**, *85*, 129.

(25) Mayer, K.; Eich, E. *Pharmazie* **1984**, *39*, 537. Magone, K. E.; Toldy, L. Hungarian Pat. 1729154, 1979.

(26) Santay, C.; Keve, T.; Danasi, L.; Felmeri, J. Hungarian Pat. 178704, 1983. We were not able to reproduce the results as reported using paspalic acid as starting material. Instead, as indicated here, a significant amount of dihydro isoacid **24** was isolated.

(27) Using the conditions described, we were able to obtain extremely pure dihydro acid **9** which is >99% pure; before recrystallization, the crude product (>90%) contains a small amount of decarboxylated product, starting material, and other unknowns. The relatively "low" yield is due to mechanical loss during recrystallization.

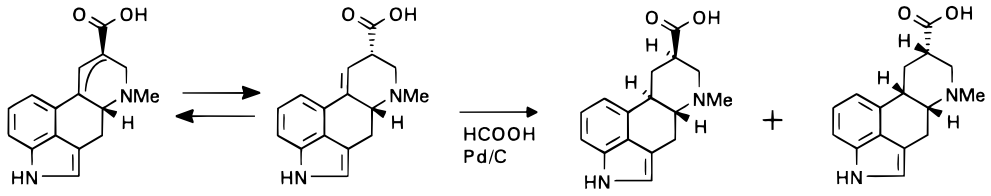
(28) Under conditions for a normal hydrogen transfer reaction carried out in the presence of formic acid, the formation of CO as a by-product has been reported in the literature (ref 24). Due to its toxicity, a special monitoring device would be required.

(29) Stütz, P.; Stadler, P. A.; Vigouret, J. M.; Jaton, A. *J. Med. Chem.* **1978**, *21*, 754.

(30) Sauer, G.; Haffer, G.; Wachtel, H. *Synthesis* **1986**, 1007.

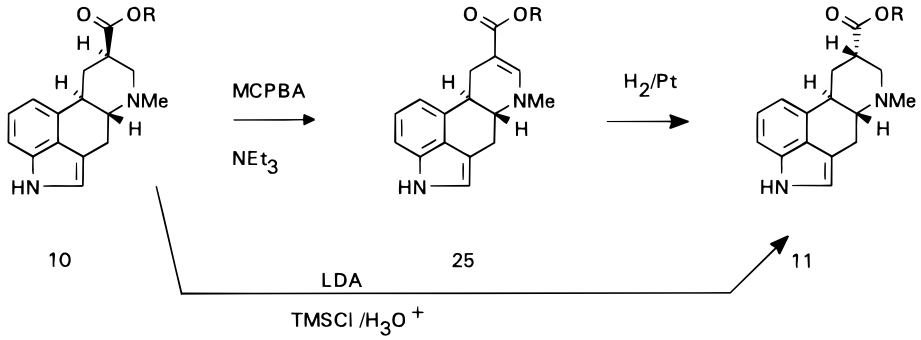
(31) The described synthesis via ester **25** is considered to be unattractive for the following reasons: (a) there are two steps; (b) oxidation with *m*-chloroperbenzoic acid is not suitable for scale-up (safety considerations); (c) catalytic hydrogenation requires the use of an autoclave. The reduction of isolysergic acid with lithium/liquid ammonia also requires special dedicated apparatus which is not available within our company. In addition, it is very difficult to remove the acid **24** which is a by-product of the reaction.

Scheme 7



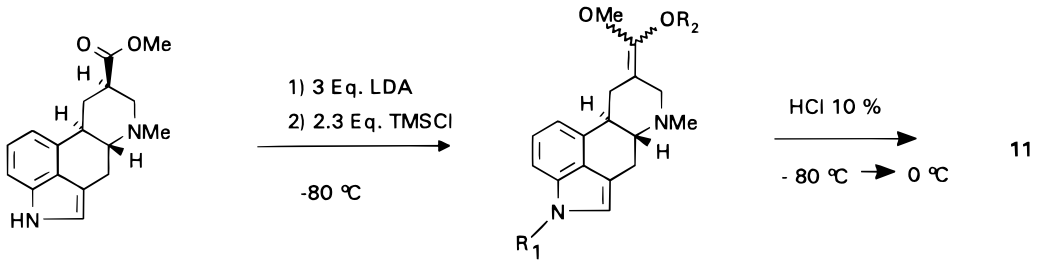
8a/b **23** **9** **24**

Scheme 8



10 25 11

Scheme 9



10 **11**

26 $R_1 = R_2 = Li$
27 $R_1 = R_2 = Si(CH_3)_3$

completed (Scheme 9). To prevent this, we assumed that by fixing this favorable "conformation" as the silyl ketene acetal **27**, prepared in situ by treatment of **26** with trimethylsilyl chloride, a higher selectivity of protonation from the β-face will occur.[32] Indeed, under these improved conditions, an epimeric ratio of 4:96 of the esters **10** and **11** is observed in the crude product after acid quench, with a resulting isolated yield of isoester **11** of 91−93%.

A very important tool for the development and optimization of this process has been the use of FT-IR in monitoring the course of the reaction.[33] As shown in Figure 1, the characteristic bands which appear between 1600 and 1800 cm^{-1} in the IR spectrum are clearly indicative of the sequence of events which take place during the reaction (Scheme 10):

(1) the concentration of the ester **10** decreases during the addition of lithium diisopropylamide solution [disappearance of C═O stretching frequency at 1735 cm^{-1} (band A, files 12−29)];

(2) there is a concurrent increase of the band at 1667 cm^{-1} (band B, files 12−29), which corresponds to the C−C−O antisymmetric stretching frequency of the ester enolate formed with LDA;

(3) band A disappears completely at the end of the addition, whereas band B attains its maximum, indicating that the deprotonation process is addition controlled;

(4) band C, which is attributed to the C═C stretching vibration of the silyl ketene acetal (1710 cm^{-1}), begins to appear with the addition of trimethylsilyl chloride to the ester enolate (Scheme 11) with a concurrent decrease of band B (files 44−90);

(5) during protonation, band C decreases with a corresponding increase of band A, again due to the formation of isoester **11** (the C═O absorption of both esters appears at 1735 cm^{-1}, file 100).

In principle the silylation of enolate **26** could have likewise occurred at C-8 of the ergoline skeleton. However, from our IR data, we could not see the appearance of any new band which could be attributed to a new carbonyl absorption. Furthermore, NMR analysis of a sample of the isolated silyl ketene acetal indicates an *E*:*Z* ratio of 3:2 at the double bond (despite the observation of only one IR absorption band at 1710 cm^{-1}; this could be due to insufficient resolution of two closely appearing absorptions). Thus, it could be concluded that the geometry of the silyl

(32) Without the formation of the silyl ketene acetal, deprotonation/reprotonation can take place due to the presence of diisopropylamine still in solution. This could already lead to a mixture of the ester isomers.
(33) Preliminary results have been presented (W. Prikoszovich) at the 2nd Annual User Forum ASI Applied Systems, Annapolis, MD, June 4−7, 1995.

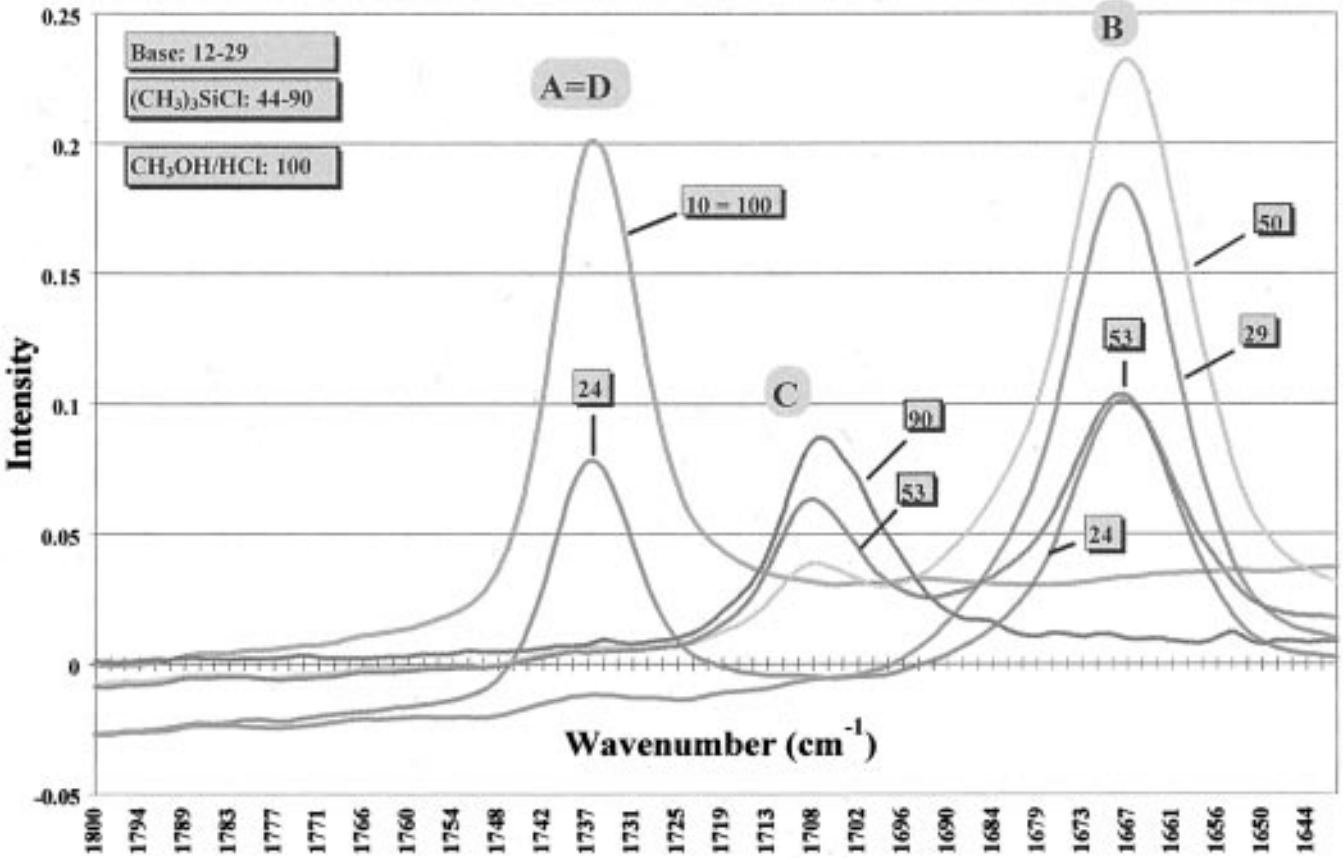


Figure 1. **Deprotonation, silylation, and reprotonation of 10.**

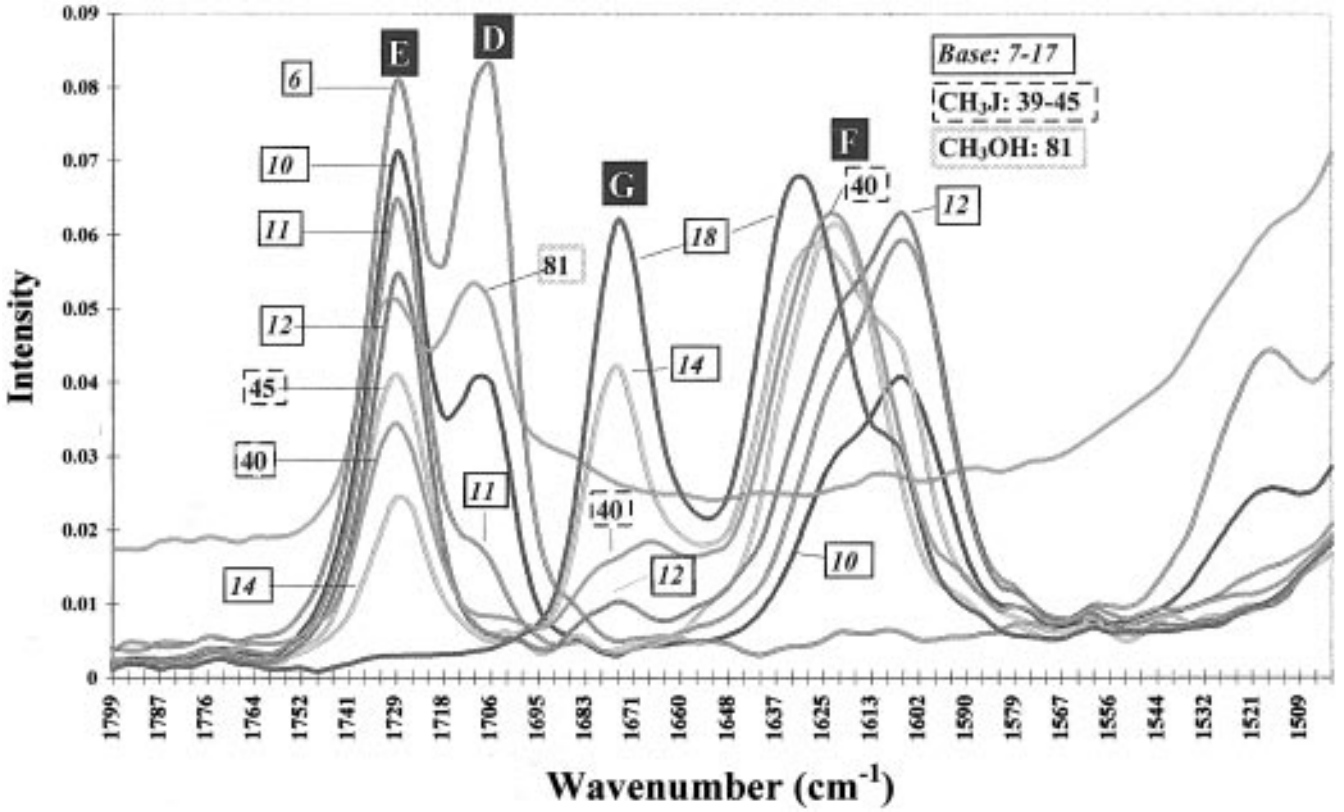
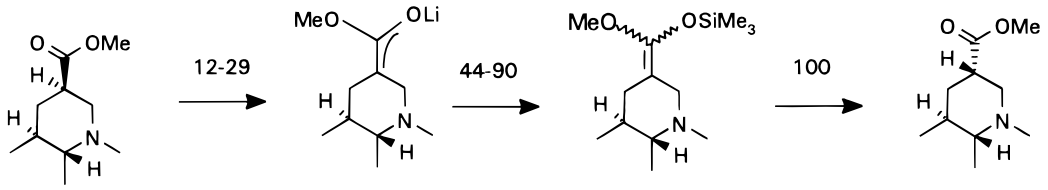


Figure 2. **Metalation−methylation of 14.**

ketene acetal has no influence on the preference of the attack of the proton.

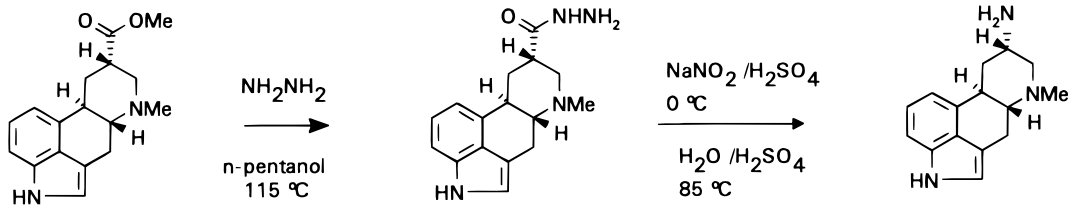
Curtius Rearrangement to 8α-Amino-6-methylergoline (13). The synthesis of 8α-amino-6-methylergoline (**13**) from isoester **11** followed in close analogy the procedure described by Hoffmann[18] (Scheme 11). The hydrazide **12**, prepared by reaction of **11** with excess hydrazine hydrate in 1-pentanol[34] at 115 °C, was not purified, but the crude material

Scheme 10



10 **26** **27** **11**

Scheme 11



11 **12** **13**

was dissolved in dilute acetic acid and treated subsequently with $NaNO_2$ and sulfuric acid, followed by warming of the reaction mixture to 85 °C to complete the rearrangement.[35] The use of excess hydrazine hydrate at elevated temperature and the thermal stability of the reaction mass were originally of great concern to us. However, after extensive reaction calorimetry studies and thermal stability tests of the intermediates, we concluded that the process can be carried out safely. An additional built-in process safety measure, namely, to have a sufficient amount of reserve solvent ready to be added to the reaction mixture in case the internal reaction temperature begins to rise above a critical temperature, has enabled us to produce **13** in multikilo batches safely without any problem.[36]

Introduction of a Methyl Group at Position C-2. For the planned orthometalation−methylation reaction of aminoergoline **13**, we have chosen the BOC group, which can easily be introduced and removed under mild conditions, as the protecting group for the amino function at C-8 and the metalation-directing group at C-2. The first BOC group can be selectively introduced to the C-8 nitrogen without the use of any additional base, whereas, in the presence of a catalytic amount of (dimethylamino)pyridine, the indole nitrogen is subsequently acylated. The overall reaction was carried out in one pot and proceeded in 92% isolated yield.

The introduction of the methyl group at C-2 proved to be more demanding; Levy[37] previously used the BOC group for the first time to functionalize unsubstituted indoles at the 2-position via lithiation with *tert*-butyllithium. For our purpose, the use of a less pyrophoric base had to be sought. Again the use of FT-IR facilitated the development of a robust process for the metalation−methylation reaction. Although the direct deprotonation at C-2 and the subsequent formation of the $C-CH_3$ moiety could not be directly observed, the course of the reaction could be followed indirectly again by the changes in the absorption range between 1600 and 1800 cm^{-1}. The carbonyl absorptions of the carbamate groups are distinguishably different and appear at 1706 cm^{-1} (C-8 amine, band D) and 1729 cm^{-1} (indole N-1, band E), respectively (see Figure 2).

Initial studies of the reaction showed that the metalation of the di-BOC-ergoline derivative **14** in position 2 was not complete, even with excess lithium diisopropylamide (3.1 equiv). This phenomenon could best be observed in FT-IR. The band at 1729 cm^{-1} was still present at approximately 1/4 of its original height. After considerable experimentation, it was found that the addition of a mixture of 0.35 equiv of LDA and 2.7 equiv of *n*-hexyllithium (or *n*-butyllithium[38]) in THF−hexane to a solution of 1 equiv of **14** in THF at −60 °C produced a good yield of the desired methylated product **15**. Under these conditions, less than 1% of BOC-deprotected products was detected,[39] whereas other ratios of *n*-hexyllithium and LDA resulted in considerable amounts of deprotected starting material (**13** and C-8 *N*-mono-BOC

(34) We have previously performed this transformation in the pilot plant with 1-propanol as the solvent at 90 °C. The reaction gave a similar yield, but it proceeded much more slowly (>24 h) and the throughput was considered to be too low for a large-scale process. In addition, the crude hydrazide had to be isolated by precipitation after the addition of water. The hydrazine still present in the filtrates was destroyed by oxidation with excess NaOCl before the filtrates were discharged.

(35) The rearrangement proceeds with very high selectivity. Less than 0.5% of the β-isomer could be detected from the crude reaction mixture, and its content in the purified isolated product is below the detection limit (0.05% in HPLC).

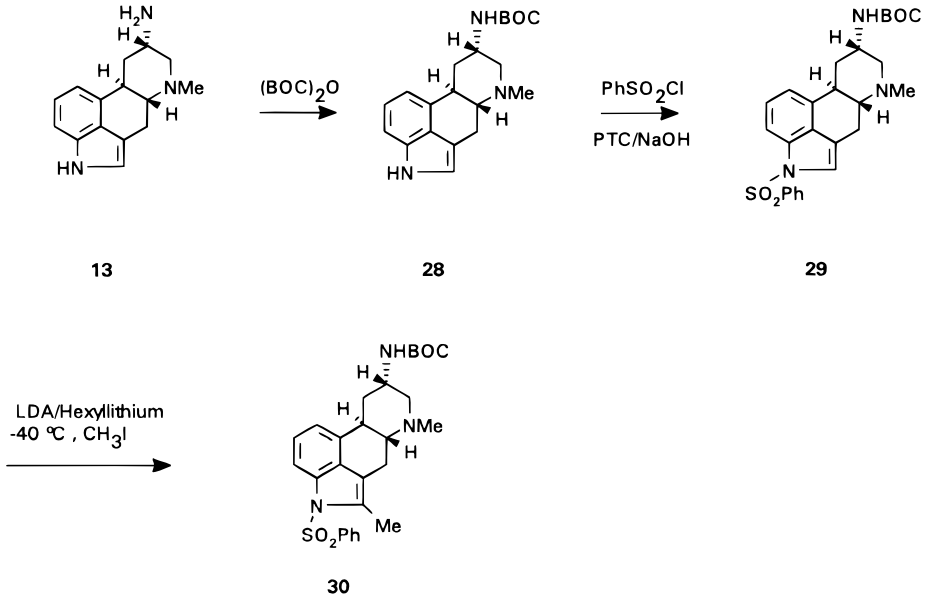
(36) Excerpts of thermal safety data from our measurements: (a) the addition of hydrazine at 70 °C is endothermic; (b) the reaction mass after complete addition of hydrazine exhibited no safety relevant exothermic process until 230 °C; (c) during the warming up of the mixture to reflux, the reaction proceeded exothermically (122 kJ/kg of reaction mass); this translates to a theorectical adiabatic temperature increase of approximately 50 °C; (d) the reaction mass after the completion of the reflux phase is thermally stable up to at least 230 °C. With the knowledge of these data and the information on the cooling capability of our reactor, we are confident in our developed process.

(37) Hasan, J.; Marinelli, E. R.; Lin, L. C. C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem*. **1981**, *46*, 157.

(38) The use of *n*-hexyllithium, which is now commercially available from Chemetall Germany, instead of *n*-butyllithium, allows easier recovery of the by-product (*n*-hexane rather than *n*-butane) and contributes additionally to the ecoefficiency of our process.

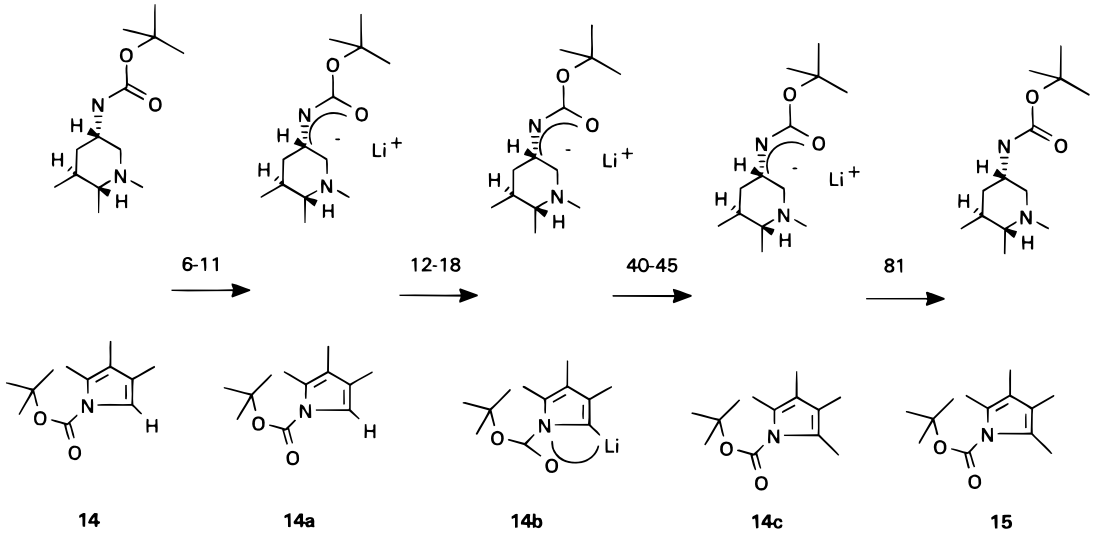
(39) No metalation will occur if the N-1 is not BOC-protected. Usually, *tert*-butyl- or *sec*-butyllithium, both of which are highly pyrophoric, is used for such a reaction.

Scheme 12



13 **28** **29** **30**

Scheme 13



14 **14a** **14b** **14c** **15**

derivative) and other decomposition products.

Due to the labile nature of the BOC group at N-1, we investigated the use of the benzenesulfonyl moiety as the protecting/ortho-metalation-directing group. It has been reported that the ortho-directing properties should be better although its subsequent removal could be less facile.[40] Accordingly, the mono-BOC derivative **28** was prepared as before in high yield. Introduction of the benzenesulfonyl group at N-1 also proceeded smoothly under phase transfer catalysis conditions[41] (Scheme 12). However, the metalation−methylation reaction was less satisfactory than with the di-BOC derivative. Even at higher temperature (−40 °C) and much longer reaction time, the amount of nonmethylated product remained over 13%. This approach was quickly abandoned as the removal of the benzenesulfonyl group proved also to be difficult.

Our effort then concentrated on the use of the di-BOC derivative **14**. We envisioned that the reaction proceeded as outlined in Scheme 13. Initial amounts of LDA will first remove the amide proton of the carbamate function at C-8. This is confirmed by the gradual decrease of the IR absorption band at 1706 cm^{-1} (band D, C═O of C-8 carbamate; files 6−11) and the concurrent increase of the band at 1606 cm^{-1} (band F; N−C−O oscillator of the carbamate enolate **14a**). With the addition of further base, the absorption started to shift to 1633 cm^{-1} (see Figure 2) and attained its maximum when the second equivalent of base had been added (files 12−18). The C═O stretching vibration of the carbamate at N-1 (band E, 1729 cm^{-1}) began to decline only when the second equivalent of base was being added. At the same time, a new absorption appearing at 1675 cm^{-1} (band G) began to form and attained its maximum also after the second equivalent of base was added. This band represents probably the N-1 carbamate complex of the carbonyl group with Li^+ (**14b**; C═O absorption weakened due to complexation). During the addition of the third equivalent of base, no change in the region of 1600−1800 cm^{-1} was observed.

(40) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.
(41) Illi, V. O. *Synthesis* **1979**, 136.

The intensity of band G began to weaken with the start of the addition of methyl iodide with the concurrent reappearance of band E (files 40−45), indicating that the lithio complex of the N-1 carbamate C═O was being destroyed (**14c**). Despite the use of excess methyl iodide[42] for the alkylation process, we never observed any N-alkylation at the C-8 carbamate. This is also confirmed by the observation of the FT-IR spectrum whereby no reappearance of the absorption at 1706 cm^{-1} could be seen before workup (band D reappeared upon quenching with methanol; file 81).

HPLC analysis of the crude reaction product revealed the presence of approximately 3% of nonmethylated product; this could unfortunately not be deduced from the on-line monitoring techniques. Acidic workup and crystallization from methanol afforded **15** in 77% yield with high purity (>98% HPLC). We do not know the exact nature of the function of LDA in the process that we have employed, but small changes in the reaction conditions led to significantly inferior results.[43] Using these conditions, over 500 kg of the di-BOC derivative **15** have been produced.

The removal of the two protecting groups in **15** is best performed with hot dilute sulfuric acid and afforded the desired 8α-amino-2,6-dimethylergoline (**7**) in 78% isolated yield based on **15**.

Conclusion

The scale-up of the process for the preparation of 8α-amino-2,6-dimethylergoline (**7**) was investigated in detail. As compared to previously reported procedures,[17−19] the present process does not require the use of halogenated solvents, which were used routinely in the past for ergot derivatives, mainly due to their poor solubility in other solvents. For those steps for which isolation of intermediates is difficult or impossible, an FT-IR monitoring technique was applied in the laboratory, and this was found to be invaluable for the understanding of the course of the reaction. Individual steps are so optimized that they either were performed in the pilot plant without noteworthy difficulties or were found to be suitable for scale-up. The quality of all intermediates, including compound **7**, thus obtained is such that they are suitable to produce final drug substances for clinical and toxicological uses with purities of >98%. The present process is ecoefficient,[44] and should be attractive for commercialization.

Experimental Section

General Procedures. Experimental work is described only for the route which was developed; experiments either were run in the pilot plant on a multikilo scale or the conditions were optimized in our process labs, checked by our internal risk analysis process (DERA),[45] and designated to be suitable for scaling up (reduction of paspalic acid to **9** and conversion of ester **11** to **12**). Compounds **14**, **15**, and **7** were not previously reported in the literature. The other described compounds used in our present route were previously reported in the literature[16−18] with no or little spectroscopic data; we have therefore included ^{1}H NMR data for general reference. All isolated intermediates as reported are compared and shown to be identical with authentic analytical samples, and they are all assayed by RP-HPLC to be 98% or higher, with the exception of compound **15**, which normally contains 1−3% of the precursor **14**. Paspalic acid was obtained by fermentation and supplied by Biochemie Kundl (Austria), which is a division of Novartis Pharma AG. All other solvents and reagents used were of technical grade and available in bulk, and no prior purification was performed. All reactions were carried out under an atmosphere of nitrogen, unless otherwise indicated. The NMR spectrum of dihydrolysergic acid was obtained on a Brucker AMX 400 Mhz spectrometer; other NMR spectra were measured on a Brucker DPX-300 dual-head spectrometer, all using tetramethylsilane as reference. FT-IR measurements were made on a ReactIR 1000 apparatus of Applied Systems, Annapolis, MD, with a diamond sensor, and a resolution of 4 cm^{-1} was set. ReactIR software version 1.2 of Applied Systems was used.

Dihydrolysergic Acid [(5*R*,8*R*,10*R*)-6-Methyl-8-ergolinecarboxylic Acid 9)]. A reaction flask was sequentially charged, during stirring, with water (200 mL), wet Pd/C (37.8 g; Degussa, type E196 R/W; water content 57%), paspalic acid (**8b**) (80 g, 0.298 mol), methanol (200 mL), and piperidine (400 mL, 4.048 mol). Then formic acid (90 mL, 2.384 mol) was added dropwise during 15 min at 40 °C. The reaction mixture was further stirred at 40 °C for 2 h. After the catalyst was filtered off and washed with 1:1 water−methanol (80 mL), the combined filtrates were added slowly, with stirring, into 200 mL of water while the pH of the mixture was kept between 5.5 and 6 by concurrent addition of approximately 200 mL of acetic acid. The resulting suspension was adjusted to pH 6.5 with an additional amount of acetic acid and stirred overnight at 0 °C. The precipitate was filtered off, dissolved at 40 °C in a mixture of water (760 mL), aqueous ammonia (25%, 320 mL), and methanol (360 mL), and treated with charcoal (8 g) at rt for 30 min. After filtration over Cellflock the filtrate was adjusted to pH 6.5 by the addition of acetic acid (200 mL). The resultant suspension was stirred at 0 °C overnight, and the precipitate was filtered off and dried in vacuo at 120 °C to yield 65 g (84%) of dihydrolysergic acid (**9**) as off-white crystals: ^{1}H NMR (DMSO-d_6) δ 1.29−1.39 (m, 1H, H-C9$_{ax}$), 1.95−2.02 (m, 1H, H-C5), 2.12−2.19 (m, 1H, H-C7$_{ax}$), 2.36 (s, 3H, NCH$_3$), 2.47−2.50 (m, 1H, H-C4$_{ax}$), 2.7−2.82 (m, 3H, H-C10/H-C9$_{eq}$/H-C8$_{ax}$), 3.12 (dd, J = 11, 3 Hz, 1H, H-C7$_{eq}$), 3.30 (dd, J = 15, 4 Hz, 1H, H-C4$_{eq}$), 6.79 (d, J = 8 Hz, 1H, H-C12), 6.94 (s, 1H, H-C2), 7.02 (t, J = 8 Hz, 1H, H-C13), 7.12 (d, J = 8 Hz, 1 H, H-C14), 10.59 (s, 1H, H-N1).

(42) The use of dimethyl sulfate or dimethyl carbonate resulted in no methylation or more inferior results. In the plant, we have deployed a caustic scrubber during the reaction and workup. No emission of methyl iodide was detected in our exhaust system. Solvent mixtures (THF−hexanes) containing excess iodide were directly incinerated.

(43) During the whole process, LDA is always being consumed and regenerated; if only hexyllithium is used, a lower yield of the desired product is obtained due to the formation of de-BOC products.

(44) Recent references on ecoefficient processes: Glauser, M.; Mueller, P. *Chimia* **1997**, 201. Mak, C.-P.; Muehle, H.; Achini, R. *Chimia* **1997**, 184. A preliminary report of the present work was presented at *ESOC 10*, Basel, Switzerland, June 22−26, 1997.

(45) Spaar, R.; Suter, G. A Simplified Hazard Analysis Scheme for Use in Process Development. Presented at the 7th International Symposium on Loss Prevention and Safety Production in the Process Industry, Taorimina, Italy, May 4−8, 1992.

Dihydrolysergic Acid Methyl Ester [(5*R*,8*R*,10*R*)-8-(Methoxycarbonyl)-6-methylergoline (10)]. To a suspension of 175 g (0.647 mol) of dihydrolysergic acid (**9**) in 2100 mL of methanol was added in 10 min, between 45 and 50 °C, 93 mL of 98% sulfuric acid (1.78 mol). The resultant brown solution was stirred at 58 °C for 2.5 h, and then it was concentrated under reduced pressure to a volume of 1100 mL. Then, to this residue was added, at rt within 45 min, a 2% aqueous NaOH solution (3345 mL). At the end of the addition the pH should be between 7.5 and 8.5. The desired product precipitated in the form of a fine powder, and the suspension was stirrred further at rt for 16 h. After filtration, the solid obtained was washed in portions with 400 mL of water and then dried in vacuo at 70 °C for 48 h to yield 181.9 g (97%) of dihydrolysergic acid methyl ester (**10**): ^{1}H NMR ($CDCl_3$) δ 1.50−1.70 (m, 1H, H-C9$_{ax}$), 2.17−2.24 (m, 1H, H-C5$_{ax}$), 2.32−2.40 (m, 1H, H-C7$_{ax}$), 2.51 (s, 3H, NCH_3), 2.65−2.73 (m, 1H, H-C4$_{ax}$), 2.85−3.05 (m, 3H, H-C9$_{eq}$, H-C10, H-C8), 3.24−3.28 (m, 1H, H-C7$_{eq}$), 3.38−3.44 (dd, J = 14.7, 4.2 Hz, 1H, H-C4$_{eq}$), 3.74 (s, 3H, $COOCH_3$), 6.89 (s, 1H, H-C2), 6.95−6.97 (m, 1H, H-C12), 7.14−7.19 (m, 2H, H-C13 and H-C14), 7.90 (br s, 1H, NH).

Dihydroisolysergic Acid Methyl Ester [(5*R*,8*S*,10*R*)-8-(Methoxycarbonyl)-6-methylergoline (11)]. To a solution of THF (100 mL) and diisopropylamine (74.7 mL, 0.527 mol) was added, during 30−40 min at −80 °C, a solution of *n*-hexyllithium (33% w/w; 206.7 mL, 0.526 mol). The solution was stirred for 20 min at −80 °C. Then a solution of dihydrolysergic acid methyl ester (**10**) (52.6 g, 0.176 mol) in tetrahydrofuran (300 mL) was added during 30 min at −80 °C; the resultant mixture was subsequently stirred for 30 min at this temperature. Then, trimethylchlorosilane (51 mL, 0.403 mol) was added dropwise with stirring at −80 °C, and the mixture was again stirred for an additional 15 min at the same temperature. The reaction mixture was then quenched by addition to a solution of HCl/water (1:1, 292 mL), whereby the reaction temperature was allowed to rise to 0 °C. After the pH of the suspension was adjusted to 8.5 with an aqueous solution of K_2CO_3 (25%, about 400 mL), the two phases were separated. The organic layer was washed once with brine, and the combined water phases were extracted once with THF (250 mL). The combined organic phases were treated with 2.5 g of activated charcoal for 15 min, filtered over Cellflock, and washed with THF (25 mL). The filtrate was evaporated in vacuo to a volume of 135 mL, and 2-propanol (200 mL) was added. This sequence of evaporation/addition was repeated once, while the desired product **11** began to crystallize out. The suspension was stirred for 5 h at 0 °C, filtered off, washed with cold 2-propanol (30 mL), and dried for 10 h at 50 °C to yield 47 g (93.5 %) of **11**: ^{1}H NMR ($CDCl_3$) δ 1.53−1.64 (m, 1H, H-C9$_{ax}$), 2.09−2.28 (m, 1H, H-C5$_{ax}$), 2.36−2.42 (m, 4H, H-C7$_{ax}$ and NCH_3), 2.63−2.72 (m, 1H, H-C4$_{ax}$), 2.75−2.85 (m, 1H, H-C8), 3.08−3.20 (m, 2H, H-C10 and H-C9$_{eq}$), 3.33 (dd, 1H, J = 14.7, 4.3 Hz, H-C4), 3.45−3.49 (m, 1H, H-C7$_{eq}$), 3.74 (s, 3H, $COOCH_3$), 6.85 (s, 1H, H-C2), 6.93−6.97 (m, 1H, H-C12), 7.13−7.17 (m, 2H, H-C13 and H-C14), 7.94 (br s, 1H, NH).

8α-Amino-6-methylergoline (13). *Hydrazide Formation.* To a suspension of dihydroisolysergic acid methyl ester (**11**) (100 g, 0.344 mol) in 1-pentanol (200 mL) was added hydrazine hydrate (44 mL, 0.90 mol) at 70 °C. The reaction mixture was stirred at reflux temperature for 7.5 h, followed by the addition of more 1-pentanol (600 mL), during which time the reaction mixture was cooled to 80 °C. This mixture was further cooled to rt within 1.5 h, and it was stirred for 15 h at the same temperature. Under reduced pressure, 600 mL of 1-pentanol was distilled off and heptane (500 mL) was added to the suspension at 75 °C within 15 min. After being stirred for 15 min at this temperature, the suspension was cooled to 0 °C and further stirred for 2 h. The crude wet hydrazide **12** (119 g) was obtained after filtration and washing with heptane (200 mL). An analytical sample was taken and dried in vacuo (50 °C): ^{1}H NMR (DMSO-d_6) δ 1.35−1.45 (m, 1H, H-C9$_{ax}$), 1.89−1.96 (m, 1H, H-C5$_{ax}$), 2.23−2.33 (m, 4H, H-C7$_{ax}$ and NCH_3), 2.38−2.52 (m, 2H, H-C4$_{ax}$ and H-C8), 2.74−2.79 (m, 1H, H-C9$_{eq}$), 2.86−2.93 (m, 1H, H-C10), 3.12−3.26 (m, 2H, H-C4 and H-C7$_{eq}$), 4.20 (br s, 2H, NH_2), 6.70 (d, J = 7.0, 1H, H-C12), 6.90−6.97 (m, 2H, H-C2 and H-C13), 7.05 (d, J = 8.0, 1H, H-C14), 9.05 (s, 1H, CONH), 10.55 (br s, 1H, N(1)H).

Acyl Azide Formation. The crude wet hydrazide (119 g) thus obtained was dissolved in a prewarmed (50 °C) mixture of acetic acid (128 mL) and water (298 mL) and placed in a reaction flask. To this was added a solution of sulfuric acid 98% (33.6 g) in water (214 mL). The thick suspension was cooled to 0 °C, and, with good stirring, a solution of sodium nitrite (29.8 g, 0.432 mol) in water (129 mL) was added within 30 min. The brown solution thus obtained (acyl azide solution) was stirred for 30 min and then was tested for the presence of an excess of nitrite with iodide/cadmium strips. Excess nitrite was reduced by the addition, in portions, of a solution of aminosulfonic acid (7.2 g, 0.074 mol) in water (72 mL) until the blue coloration of the test strip could no longer be detected.

Curtius Degradation. Then this cold acyl azide suspension was added dropwise to a solution of sulfuric acid 98% (32.8 g) in water (496 mL) at 90 °C, at a rate such that the temperature did not fall below 85 °C. During the addition, vigorous evolution of N_2 and CO_2 was observed. The resultant solution was stirred for 30 min at 90 °C, and then an aqueous solution of 30% NaOH (452 g) was added dropwise at the same temperature, while the crude product **13** began to precipitate. The suspension was maintained at 90 °C for 30 min, then cooled to rt, and stirred for an additional 1 h. The product was filtered and washed in portions with water (1000 mL). The crude wet solid was again suspended in a mixture of methanol (201 mL), acetic acid (43 mL), and water (355 mL) and heated to 45 °C. After the addition of charcoal (16 g) in methanol (20 mL), the suspension was stirred for 15 min at 45 °C. The warm suspension was filtered over Cellflock (16 g), and the solid residue was washed with methanol (55 mL). To the combined filtrates were added, within 45 min, a solution of 30% aqueous NaOH (101 g) at 40 °C, during which time the desired aminoergoline **13** precipitated out of solution. The suspension was stirred for a further 15 min, cooled to 10 °C, and stirred for 45 min at this temperature. After filtration, the solid obtained was washed with a mixture of methanol (45 mL) and water (125 mL) and dried for 48 h at

60 °C to yield 69.5 g (78%) of 8α-amino-6-methylergoline (**13**): ^{1}H NMR (DMSO-d_6, DOAc) δ 1.56−1.67 (m, 1H, H-C9$_{ax}$), 2.00−2.08 (m, 1H, H-C5$_{ax}$), 2.30 (s, 3H, NCH$_3$), 2.33−2.38 (m, 1H, H-C7$_{ax}$), 2.52−2.66 (m, 2H, H-C4$_{ax}$ and H-C9$_{eq}$), 2.91−2.95 (m, 1H, H-C7$_{eq}$), 3.07−3.13 (m, 1H, H-C10), 3.26 (dd, J = 4.2, 14.6 Hz, 1H, H-C4$_{eq}$), 3.54 (s, 1H, H-C8), 6.63 (d, J = 7.0 Hz, 1H, H-C12), 6.93−6.98 (m, 2H, H-C2 and H-C13), 7.07−7.10 (m, 1H, H-C14), 10.40 (br s, 3H, NH, NH$_2$).

1-(*tert*-Butyloxycarbonyl)-8α-[(*tert*-butyloxycarbonyl)-amino]-6-methylergoline (14). A solution of BOC-anhydride [(BOC)$_2$O, 99.4 g, 0.455 mol] in toluene (199 mL) was added dropwise over 30 min at 53 °C to a suspension of **13** (100 g, 0.414 mol) in toluene (600 mL), during which time continuous evolution of CO_2 was observed. The resulting solution was stirred for 45 min at the same temperature. Then, under the same conditions, a solution of DMAP (1.9 g, 1.56 mmol) in toluene (60 mL) was added, followed by a solution of (BOC)$_2$O (99.4 g, 0.455 mol) in toluene (198 mL). The reaction mixture was stirred for 45 min at 53 °C and cooled to rt, and 396 mL of 5% aqueous NaOH was added. After the phases were separated, the organic phase was washed in portions with 480 mL of water and then was concentrated in vacuo to 265 mL. Ethanol (350 mL) was added to the residue, and the volume of the mixture was again reduced in vacuo to 265 mL. This process was repeated once to remove the remaining toluene. Then 583 mL of ethanol was added, and the resultant solution was heated to 50 °C. The desired product **14** was precipitated by dropwise addition of water (387 mL) over 2 h. The suspension was slowly cooled to rt and then stirred for 1 h at this temperature. The crystals were filtered off, washed in portions with a mixture of ethanol (85 mL)/water (57 mL), and dried for 10 h at 60 °C to yield 167.7 g (91.7%) of **14**: mp 153−156 °C; ^{1}H NMR ($CDCl_3$) δ 1.33−1.60 (m, 1H, H-C9$_{ax}$), 1.40 (s, 9H, BOC), 1.59 (s, 9H, BOC), 2.00−2.07 (m, 1H, H-C5$_{ax}$), 2.31 (s, 3H, NCH$_3$), 2.31−2.37 (m, 1H, H-C7$_{ax}$), 2.47−2.55 (m, 1H, H-C4$_{ax}$), 2.63−2.68 (m, 1H, H-C9$_{eq}$), 2.77−2.81 (m, 1H, H-C7$_{eq}$), 2.85−3.00 (m, 1H, H-C10), 3.24 (dd, J = 15.1, 4.1 Hz, 1H, H-C4$_{eq}$), 3.95−4.05 (m, 1H, H-C8), 5.47 (br d, 1H, NH), 6.93 (d, J = 7.3 Hz, 1H, H-C12), 7.16−7.21 (m, 2H, H-C2 and H-C13), 7.64−7.75 (m, 1H, H-C14). Anal. Calcd for $C_{25}H_{35}N_3O_4$: C, 68.04; H, 7.99; N, 9.52. Found: C, 67.73; H, 7.90; N, 9.49.

1-(*tert*-Butyloxycarbonyl)-8α-[(*tert*-butyloxycarbonyl)-amino]-2,6-dimethylergoline (15). Under an argon atmosphere, *n*-hexyllithium (88.2 mL, 0.224 mol, 33% w/w in hexane) was added dropwise to a solution of diisopropylamine (2.57 g, 0.0254 mol) in a mixture of THF (30 mL) and hexane (64 mL) at −15 °C; the resultant mixture was stirred for 30 min at the same temperature. This LDA−*n*-hexyllithium solution was added to a solution of **14** (32.0 g, 0.0725 mol) in THF (384 mL) at −60 °C during 45 min, and the mixture was then stirred for 1 h at −60 °C. A solution of methyl iodide (13.5 mL, 0.216 mol) in THF (40 mL) was added dropwise during 30 min, and the mixture was again kept for 1 h at −60 °C. The reaction was quenched by successive dropwise addition of methanol (28 mL) at −60 °C and then water (8 mL) at 0 °C. After the mixture was stirred for another 15 min, the resultant suspension was filtered through Cellflock (10 g) and washed with THF (40 mL). The combined filtrates were concentrated in vacuo to a volume of 48 mL. The oily residue was treated in two portions with methanol (2 × 66 mL each) and each time concentrated to a volume of 48 mL. Methanol (160 mL) was then added to the thick suspension, and the resultant solution was heated to 50 °C. The crude product **15** was precipitated by the slow addition of water (96 mL). The suspension was stirred for 15 min at 50 °C, then cooled to rt, and stirred for 30 min. The product was filtered off, washed with a mixture of methanol (60 mL)−water (30 mL), and dried in vacuo for 10 h at 50 °C to furnish 29.5 g (89.4%) of crude **15** as a light brown powder. Crude **15** (29.1 g) was dissolved under reflux in methanol (727 mL) and then concentrated in vacuo at 50 °C to a volume of 145 mL. During this time, **15** crystallized out. The mixture was cooled to 0 °C and stirred for 30 min. The desired product **15** (24.9 g, 76%) was obtained as an off-white powder after filtration, washing with cold methanol (20 mL), and drying for 16 h at 50 °C: mp 190 °C; ^{1}H NMR ($CDCl_3$) δ 1.33−1.60 (m, 1H, H-C9$_{ax}$), 1.40 (s, 9H, BOC), 1.60 (s, 9H, BOC), 1.94−2.02 (m, 1H, H-C5$_{ax}$), 2.33 (s, 3H, NCH$_3$), 2.33−2.46 (m, 2H, H-C7$_{ax}$ and H-C4$_{ax}$), 2.45 (s, 3H, CH$_3$-C2), 2.61−2.66 (m, 1H, H-C9$_{eq}$), 2.77−2.81 (m, 1H, H-C7$_{eq}$), 2.85−2.97 (m, 1H, H-C10), 3.11 (dd, J = 14.7, 4.2 Hz, 1H, H-C4$_{eq}$), 3.95−4.05 (m, 1H, H-C8), 5.47 (br d, 1H, NH), 6.90 (d, J = 7.3 Hz, 1H, H-C12), 7.07−7.12 (m, 1H, H-C13), 7.67 (d, J = 8.2 Hz, 1H, H-C14). Anal. Calcd for $C_{26}H_{37}N_3O_4$: C, 68.58; H, 8.19; N, 9.23. Found: C, 68.41; H, 8.15; N, 9.20.

8α-Amino-2,6-dimethylergoline (7). A solution of 98% sulfuric acid (45 g, 0.459 mol) in water (200 mL) was added dropwise to a suspension of **15** (100 g, 0.219 mol) in water (1200 mL) at 92 °C. The mixture was stirred for 1 h at 92 °C. After the mixture was cooled to 30 °C, isopropyl acetate (1600 mL) was added, and the pH of the solution was adjusted to 11 by the addition of 20% aqueous KOH (400 mL). The phases were separated, and the water phase was extracted with isopropyl acetate (1000 mL). The combined organic phases were washed with water (1600 mL) and concentrated in vacuo to a volume of 300 mL. Aminoergoline **7** precipitated after the addition of heptane (200 mL). The solid was filtered and dried for 10 h at 50 °C in vacuo to yield 50.8 g (91%) of **7** as a light brown powder: ^{1}H NMR (DMSO-d_6) δ 1.65−1.75 (m, 1H, H-C9$_{ax}$), 1.94 (br s, 2H, NH$_2$), 2.09−2.16 (m, 1H, H-C5$_{ax}$), 2.32−2.80 (m, 9H), 2.96−2.99 (m, 1H, H-C7$_{eq}$), 3.18−3.35 (m, 2H, H-C8 and H-C10), 3.43 (dd, J = 14.5, 4.2 Hz, 1H, H-C4$_{eq}$), 6.89 (d, J = 7.0 Hz, 1H, H-C12), 7.10−7.15 (m, 1H, H-C13), 7.23 (d, J = 8.0 Hz, 1H, H-C14). Anal. Calcd for $C_{16}H_{21}N_3$: C, 75.27; H, 8.29; N, 16.46. Found: C, 75.04; H, 8.33; N, 16.39.

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