Organic Process Research & Development **2006**, *10,* 198–202

Development of a Practical High-Yield Industrial Synthesis of Pergolide Mesylate

Walter Cabri,* Jacopo Roletto, Sara Olmo, Piera Fonte, Paolo Ghetti, Simonetta Songia, Elio Mapelli, Marco Alpegiani, and Paolo Paissoni

Antibioticos S.p.A., Research & Development, strada Rivoltana km6/7, 20090-Rodano (MI), Italy

Abstract:

The development of a high-yield and low environmental impact synthesis able to deliver highly pure pergolide mesylate 1 is described. The process [seven chemical steps (four telescoped), three steps of isolation of intermediate, and only one drying] affords pergolide mesylate 1 in 75−81% overall yield from dihydrolysergic acid 4 with >99.8% purity.

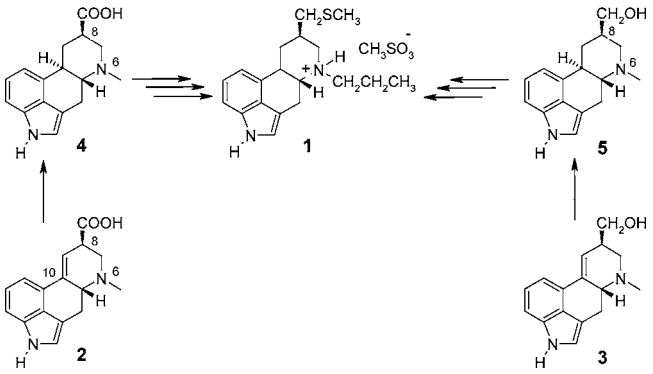
Introduction

The ergot alkaloid derivative pergolide mesylate **1**, discovered by Lilly, is an important drug for the treatment of Parkinson disease.[1] In particular, this medicine is a dopamine receptor agonist at both D_1 and D_2. More than 1,700,000 people have been treated worldwide with a very low impact of side effects. Recently, clinical studies showed that pergolide mesylate **1** may be useful for the treatment of restless leg syndrome.[2]

General Strategy

The industrial synthesis of the most important ergot alkaloids available on the market (i.e., cabergoline, nicergoline, metergoline, methylergonovine, and pergolide mesylate) starts from raw materials obtained by fermentation. Both lysergic acid **2**[3] and elymoclavine **3**[4] already have the basic four-member ring architecture and the correct configuration at C-5 and C-8 and are produced by fermentation of mutants of *Claviceps paspali* and *Claviceps purpurea*, respectively (Scheme 1). The diastereoselective hydrogenation catalysed by Raney nickel (>95%) affords the corresponding dihydroderivatives, **4** and **5**, with complete control of the C-10 configuration.[5] Independently from the starting material chosen, **4** or **5**, the synthesis of pergolide mesylate **1** must comprise the demethylation/alkylation of the N-6 nitrogen and a manipulation of the C-8 side chain to generate the thioether. Like most of the products of this chemical class,

Scheme 1. **Pergolide mesylate 1 synthesis: the starting materials**



pergolide mesylate **1** showed polymorphisms; in fact, there are two crystalline forms, forms I and II. The selective formation of the desired polymorph I is controlled by the solvent used in the salification of **10**.[6]

Previous Art: Lilly Strategies

The Korfeld/Bach Process. The processes described by Lilly researchers are the most effective in terms of yield, quality, and control of the polymorphic form of pergolide mesylate.[5−9] The first synthesis reported by Korfeld/Bach started from dihydroelymoclavine **5**. The key demethylation step was achieved via cyanation/decyanation, (Scheme 2).[7b] Pergolide base **10** was obtained by reductive amination (CH_3-CH_2CHO/HCOOH), activation of the alcohol with MsCl, and nucleophilic attack of sodium thiomethoxide. The final methansulphonate salt **1** was obtained by treatment of **10** in methanol with methansulphonic acid to control the selective formation of form I. The Korfeld/Bach synthesis had a low overall yield from dihydroelymoclavine (18−23 mol %). In addition there were several EH&S issues, such as the use of cyanogen bromide (von Braun demethylation protocol),[10] the

* To whom correspondence should be addressed. E-mail: wcabri@antibioticos.it.

(1) Pezzoli, G.; Martignoni, E.; Pacchetti, C.; Angeleri, V.; Lamberti, P.; Muratorio, A.; Bonuccelli, U.; De Mari, M.; Foschi, N.; Cossutta, E. *Neurology* **1995**, *45*, S22.

(2) (a) Trenkwalder, C.; Hundemer, H.-P.; Lledo, A.; Swieca, J.; Polo, O.; Wetter, T.C.; Ferini-Strambi, L.; de Groen, H.; Quail, D.; Brandenburg, U. *Neurology* **2004**, *62*, 1391.

(3) (a) Arcamone, F.; Chain, E. B.; Ferretti, A.; Minghetti, A.; Pennella, P.; Tomolo, A.; Vero, L. *Proc. R. Soc. London, Ser. B* **1961**, *155*, 26. (b) Arcamone, F.; Bonino, C.; Chain, E. B.; Ferretti, A.; Pennella, P.; Tomolo, A.; Vero, L. *Nature* **1960**, *187*, 238.

(4) Kren, V.; Mehta, P.; Rylko, V.; Flieger, M.; Kozova, J.; Sajdl, P.; Rehacek, Z. *Zentralbl. Mikrobiol.* **1987**, *142*, 71.

(5) (a) Misner, J. W.; Kennedy, J. H.; Biggs, W. S. *CHEMTECH* **1996**, *26*, 28.

(6) (a) Sprankle, D. J.; Jensen, E. C. In *Analytical Profiles of Drug Substances*; Brittain, H. G., Ed.; Academic: New York, 1992; Vol. 21, p 375. (b) Jegorov, A.; Horàk, Z.; Cejka, J.; Kratochvìl, B.; Cìsarovà, I. *Acta Crystallogr.* **2003**, *C59*, 575.

(7) (a) Kornfeld, E. C.; Bach, N. J. U.S. Patent 4,166,182, 1979. (b) An improved procedure for the decyanation step was later described by Misner, J.W. U.S. Patent 4,282,152, 1981.

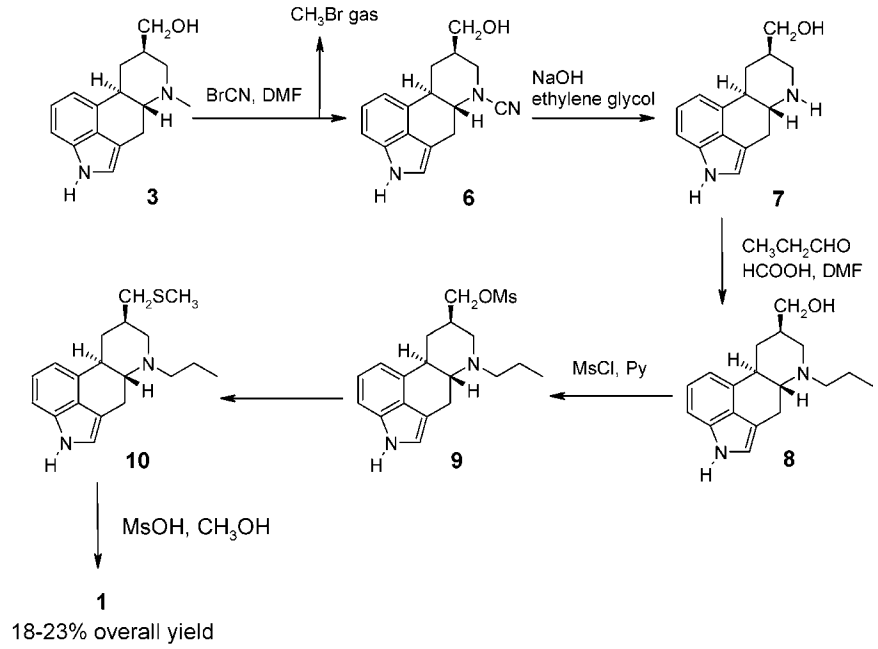
(8) (a) Misner, J. W. U.S. Patent 5,463,060, 1995. (b) Misner, J. W.; Kennedy, J. H.; Biggs, W. S. *Org. Process Res. Dev.* **1997**, *1*, 77. (c) Kennedy, J. H. *Org. Process Res. Dev.* **1997**, *1*, 68.

(9) For other processes see: a. Mangia, A.; Grisenti, P. U.S. Patent 6,395,901, 2002. (b) Wu, E. S. C.; Wu, M. U.S. Patent 6,388,079, 2002.

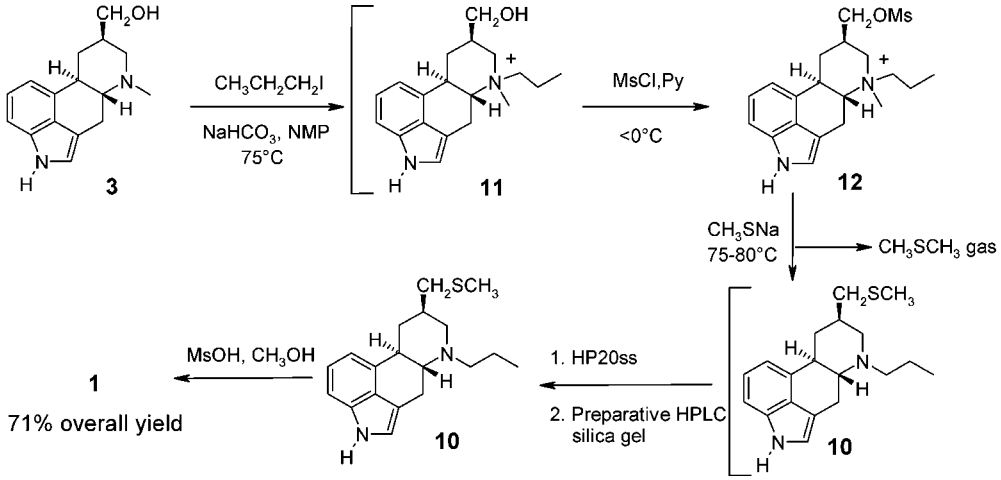
(10) (a) Von Braun, J.; Engelbertz, P. *Ber.* **1923**, *56*, 1573. (b) Cyanogen bromide: risk phrase: R14 R26 R27 R28 R34 R36 R37 R38; safety phrase: S28 S36 S37 S39 S45 S60 S61.

Published on Web 02/02/2006
10.1021/op0501747 CCC: $33.50

Scheme 2. **Korfeld/Bach process**



Scheme 3. **Misner Process**



generation as side product of the demethylation of methylbromide, and the fact that, during the manufacturing campaign, the personnel had to handle solid products at least 18 times.[5,8a,11]

The Misner Process. Misner and co-workers designed an elegant telescoped approach to pergolide base **10**, overcoming all the drawbacks of the Korfeld/Bach synthesis (Scheme 3).[5,8] The telescoped process was based on a modification of the Hutchins and Dux demethylation procedure.[12] The concomitant demethylation of N-6 and nucleophilic substitution of mesylate **12** was the core of the Misner process that represented a consistent improvement in terms of yield and safety increase (71% overall yield from dihydroelymoclavine, Scheme 2). Telescoping all the synthetic steps avoided isolation and drying of toxic and potentially allergenic intermediates, but determined a purity of pergolide free base **10** around 94−95%, when the target purity of pergolide mesylate **1** was >99.8% by HPLC. With the exception of dimer **15**, all the other impurities (**8**, **13**, **14**) are around 1−2%.

(Figure 1). Lilly researchers obtained the desired purity by a tandem chromatographic purification (HP20ss resin to eliminate **13** and preparative HPLC on silica gel to eliminate **8**, **14**, **15**).[8,13] From an EH&S point of view the Misner synthesis also had several drawbacks. The demethylation step with concomitant formation of the thioether **10** was carried out using large amounts of freshly prepared sodium thiomethoxide (CH_3SH + NaOH) to minimise the formation of **13**. Methanthiol is classified as a toxic gas and required a special permit for its manipulation.[14] The side product of the Hutchins and Dux demethylation procedure was the

(11) To reach the target quality, several recrystallisation of intermediates were necessary during the production campaign, refs 5 and 8b.

(12) Hutchins, R.O.; Dux, F. J. *J. Org. Chem.* **1973**, *38*, 1961.

(13) Dimer **15** was isolated and identified by Motta, C., Roletto, J. and Ghetti, P. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.87 (t, J = 7.3 Hz, 3H, CH_3-3′), 0.93 (t, J = 7.3 Hz, 3H, CH_3-3′a), 1.1−3.6 (m, 28H,), 2.16 (s, 3H, SCH_3), 4.12 (d, J = 7.2, 2H), 6.6−7.0 (m, 4H, CH-12, 14, 12a, 14a), 7.1−7.4 (m, 4H, CH-2, 13, 2a, 13a), 7.94 (s, 1H, NH-1). MS (EI) m/z 479 (MH^+).

(14) Methanethiol has the following characteristics: bp: 5.9 °C.; vapour pressure at 20 °C: 172 kPa; exposure limit (8 h TWA reference period): 1 mg/m^3.

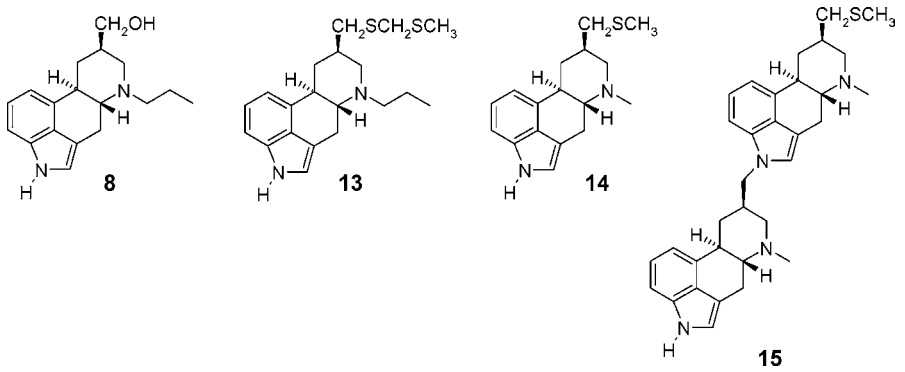
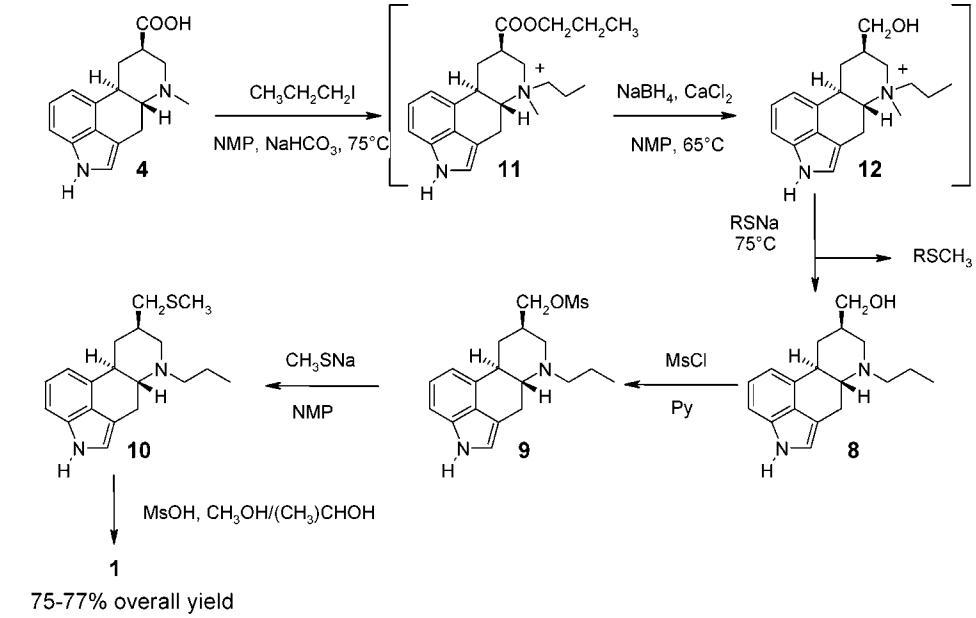


Figure 1. **Process-related impurities.**

Scheme 4. **Antibioticos Process**



dimethylsuphide. Furthermore, taking into consideration the market volume of **1** (100−200 kg), the chromatographic purification of the base **10** does not represent a major problem. However, the poor solubility of these products forced Misner and Kennedy to use toxic chloroform for the silica gel purification.[8c]

Antibioticos Strategy

The strategy designed by Antibioticos is based on the following targets: (1) The definition of an efficient and high yield original synthesis starting from commercially available dihydrolysergic acid **4**. (2) We observed that the formation of **13** (around 2%) strictly related to the use of sodium thiomethoxide at high temperature in the Hutchins and Dux N-demethylation process. Therefore, demethylation and generation of the thioether must be two different steps, and this presents the opportunity to use a demethylation protocol based on the use of a thiol that does not generate potentially toxic gas and new process-related impurities. (3) Commercially available sodium thiomethoxide must be compatible with a low-temperature nucleophilic attack to avoid the formation of **13**. (4) Precise definition of the mesylation conditions to avoid the formation of dimer **15** (process-related impurity discovered by Antibioticos researchers). In fact, impurity **15** is coming from the dimer formed during the side-chain alcohol activation, followed by nucleophilic attack. (5) All intermediates must be isolated from water and used wet in the subsequent step to minimise the personnel handling risks. (6) Identification of crystallisation procedures to eliminate the *N*-methyl derivative **14**. This impurity is critical, being absent in the commercial material that was coming from the original von Braun demethylation (Scheme 1).

The core of the process described in Scheme 4 was the one-pot transformation of dihydrolysergic acid **4** into intermediate **8**.[15] In fact, esterification of **4** with concomitant alkylation of the N-6 nitrogen with *n*-PrI in NMP, followed by reduction of the ester group with $NaBH_4/CaCl_2$ and demethylation with mercaptoethanol/NaOH, afforded in high yield (88−90%) and purity (>99%) compound **8**. NMP was identified to be the best solvent, being compatible with all the reagents, because the intermediates had a good solubility and **8** could be precipitated by addition of water. The key step of the entire process is the N demethylation, a rapid screening of nucleophiles allowed identification of mercaptoethanol as a valid alternative to sodium thiomethoxide, (Table 1).[16] With respect to the reference sodium thi-

(15) Cabri. W.; Paissoni. P.; Roletto, J.; Fonte, P.; Olmo, S. WO2003/78432.

Table 1. **Demethylation of quaternary saL 12: the thiol comparison**

$$12 \xrightarrow[\text{NMP, 75°C}]{\text{nucleophile}} 8 + 3$$

nucleophile	t	8/3
CH_3SNa	15	97/3
C_6H_5SNa	>20	90/10
$HO-CH_2CH_2-SNa$	12	98/2

omethoxide reaction (entry 1), sodium thiophenol was less selective, being the **8/3** ratio only 90/10 (entry 2). On the contrary, the sodium salt of mercaptoethanol gave the best results in terms of selectivity and reaction time (entry 3). Additional advantages of mercaptoethanol versus thiomethanol are the consistently lower vapour pressure (0.13 versus 172 kPa at 20 °C) and the generation of a side product, namely 2-(methylthio)ethanol, with a very high boiling point (169−171 °C). The combination of these two factors decrease the environmental impact of this step. Wet **8** was dried by azeotropic distillation of water with CH_2Cl_2, and after solvent exchange (CH_2Cl_2 → pyridine) methanesulphonylchoride was added at 0 °C. After complete conversion, mesylate **9** was precipitated by water addition and isolated in 97% yield and >99% purity; dimer **15** was almost undetectable. Wet **9** was dried by azeotropic distillation of water with CH_2Cl_2 and, after solvent exchange (CH_2Cl_2 → NMP), the mixture was cooled to 0−5 °C and 2 equiv of commercially available sodium thiomethoxide was added. Pergolide base **10** was isolated by water insolubilisation and drying in 96% yield and >99.7% purity by HPLC. The final salt formation was carried out in methanol/2-propanol to control the selective formation of form I and pergolide mesylate **1** was isolated in 92% yield and >99.8% purity. The lab process (20−50 g) delivers the product with an outstanding 81% yield, the industrial process at 10 kg scale reaches 75−77% overall yield from **4**. Among the solvents used, dichloromethane, pyridine, methanol, and 2-propanol were recycled. On the contrary, the recycling of NMP proved to be difficult and not cost-effective, being in mixture with water and contaminated by sulphur derivatives. This waste was treated with bleach and burned. The use of dichloromethane was compatible, the amount being very limited and the solvent recycled; other solvents such as ethyl acetate can be used as alternatives.

Conclusion

All the process design targets have been achieved. The overall yield of the Antibioticos process, 75−77% (10 kg scale) is consistently higher with respect to the Lilly one. In fact, the yield of the Misner process considering **4** as the starting material is around 67%, because the reduction of dihydrolysergic acid **4** to dihydrolysergol **5** is easily accomplished with Synergid in 95% yield.[17] From an EH&S point of view the Antibioticos process appears to be superior to the Lilly one: The E-factors (considering the solvent recovery) of the Antibioticos and Misner processes are 85 and around 200, respectively;[18] the Antibioticos process has more isolation steps, but the intermediate was always recovered wet from water, thus decreasing the possible safety and environmental drawbacks; the process avoids the use of toxic gas, chloroform, and silica gel chromatography.

Experimental Section

D-6-Propyl-8*β*-hydroxymethylergoline, 8. Into a stainless steel 800-L vessel containing NMP (40 L) under nitrogen, were sequentially added 9.3 kg of 9,10-dihydrolysergic acid **4** (34.4 mol), 8.67 kg of sodium bicarbonate (103.0 mol), and 30.4 kg of *n*-propyl iodide (178.9 mol). The mixture was heated to 80 °C. After complete conversion of **4** into **11**, monitored by HPLC, the solution was cooled to 45 °C. Five kilograms (45.1 mol) of $CaCl_2$ and 6.5 kg (172 mol) of $NaBH_4$ were added and monitored by reverse phase HPLC (the same method for all the analyses: Hypersil-C18 4.6 mm × 250 mm column, 50/50 pH 7 phosphate buffer/acetonitrile, 1.5 mL/min, 280 nm). After complete conversion of **11** into **12**, 20.6 kg of NaOH (514 mol) and 40.4 kg of $HO-CH_2CH_2-SH$ (516 mol) were sequentially added, and then the mixture was heated at 75 °C. After 12 h the conversion of **12** into **8** was completed, and 600 L of water was added. The mixture was cooled to 5 °C and filtered in a centrifuge and washed extensively with water until the test for chloride was negative, affording 17.5 kg of wet **8**.

A small portion of **8** was dried under vacuum at 60 °C for 20 h for analytical evaluation. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.85 (t, J = 7.4 Hz, 3H, CH_3-3′), 0.92 (t, J = 12.3 Hz, 1H, CH-9ax), 1.3−1.6 (m, 2H, CH_2-2′), 1.7−2.8 (m, 6H), 3.0−3.5 (m, 6H), 4.50 (t, J = 5.2 Hz, 1H, OH), 6.75 (d, J = 7.1 Hz, 1H, CH-12), 6.95 (s, 1H, CH-2), 6.98 (dd, J = 7.1, 7.7 Hz, 1H, CH-13), 7.07 (d, J = 7.7 Hz, 1H, CH-14), 10.57 (s, 1H, NH-1). IR (KBr, cm^{-1}) 3648, 3352, 3095, 2958, 1606, 749. Mp = 171.9 °C. Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85; O, 5.63. Found: C, 76.25; H, 8.63; N, 9.75. Purity by HPLC >99%.

D-6-Propyl-8*β*-mesyloxymethylergoline 9. To a stainless steel 800-L vessel containing CH_2Cl_2 (200L) under nitrogen, was added from the previouse step wet D-6-propyl-8β-hydroxymethylergoline, **8**. The mixture was heated to reflux to azeotropically remove water. When the moisture in the suspension was lower than 0.1%, pyridine (150 L) was added and the dichloromethane distilled under vacuum (GC in process control). The solution was cooled to −5 °C, and 5.9 kg (51.5 mol) of methansulphonyl chloride was added in 1 h. After complete conversion, monitored by HPLC, water (250 L) was added, and the mixture was filtered in a centrifuge and washed with water (100 L), affording 26.8 kg of wet D-6-propyl-8β-mesyloxymethylergoline **9**.

(16) The use of the Na_2S in the reaction of **8** was reported by Anastasia, L.; Cighetti, G.; Allevi, P. *J. Chem. Soc., Perkin Trans. I* **2001**, 2398. A 94/4 selectivity was achieved under different reaction conditions, sulpholane, K_3PO_4 (cat.) at 120 °C for 5 h.

(17) The Synergid process: Roletto, J.; Olmo, S. unreported results. Sandoz researchers claimed but did not describe the reduction of lysergic acid with $LiAlH_4$.

(18) Sheldon, R.A. *Pure Appl. Chem.* **2000**, *72*, 1233.

A small portion of **9** was dried under vacuum at 60 °C for 20 h for analytical evaluation. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.3 Hz, 3H, CH_3-3′), 1.1−1.3 (m, 1H, CH-9ax), 1.4−1.7 (m, 2H, CH_2-2′), 2.1−3.5 (m, 12H), 3.06 (s, 3H, SO_3CH_3), 4.1−4.3 (m, 2H, CH_2-8′), 6.8−7.0 (m, 2H, CH-12,14), 7.1−7.3 (m, 2H, CH-2,13), 7.95 (s, 1H, NH-1). IR (KBr, cm^{-1}): 3058, 2964, 1607, 1365, 1176, 748. Mp = 190.8 °C with decomposition. Anal. Calcd for $C_{19}H_{26}N_2O_3S$: C, 62.96; H, 7.23; N, 7.73; O, 13.24; S, 8.85. Found: C, 62.85; H, 7.15; N, 7.65. HPLC purity >99%.

Pergolide Base 10. In a stainless steel 800-L vessel containing CH_2Cl_2 (200 L) under nitrogen, wet D-6-propyl-8β-mesyloxymethylergoline **9**, coming from the previous step, was suspended at room temperature. The mixture was heated to reflux to remove water azeotropically. When the moisture in the suspension was lower than 0.1%, NMP (70 L) was added and dichloromethane distilled under vacuum (GC in process control). The solution was cooled to 0 °C, and 4.0 kg (57.07 mol) of solid CH_3SNa was added. The reaction was monitored by HPLC, and when the conversion of **9** into pergolide base **10** was completed, water (350 L) was added. The mixture was filtered in a centrifuge and washed with water (100 L), affording 16.3 kg of wet pergolide base **10**. A small portion of **10** was dried under vacuum at 60 °C for 20 h for analytical evaluation. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.3 Hz, 3H, CH_3-3′), 1.1−1.2 (m, 1H, CH-9ax), 1.4−1.7 (m, 2H, CH_2-2′), 2.15 (s, 3H, SCH_3), 2.0−3.5 (m, 12H), 6.8−7.0 (m, 2H, CH-12, 14), 7.1−7.2 (m, 2H, CH-2, 13), 7.90 (s, 1H, NH-1). IR (KBr, cm^{-1}) 3414, 3058, 2869, 1604, 1436, 1052, 747, 632. Mp = 217.5 °C. Anal. Calcd for $C_{19}H_{26}N_2S$: C, 72.56; H, 8.33; N, 8.91; S, 10.20. Found: C, 72.50; H, 8.35; N, 8.92; S, 10.23. Mp = 217.5 °C. HPLC purity 99.7%.

Pergolide Mesylate 1. To a glass-lined 500-L vessel containing methanol (150 L), was added at room temperature wet pergolide base **10**, coming from the previous step. The suspension was heated to 60 °C, and 2.74 kg (28.5 mol) of methanesulphonic acid was added. The resulting solution was concentrated to one-third of the original volume and cooled to 0−5 °C. The mixture was filtered, washed with 2-propanol (50 L), and dried (60 °C, 24 h) in a Hastelloy filter dryer, affording 10.6 kg of pergolide mesylate **1**. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 0.96 (t, J = 7.3 Hz, 3H, CH_3-3′), 1.2−1.4 (m, 1H, CH-9ax), 1.6−1.8 (m, 2H, CH_2-2′), 2.12 (s, 3H, SCH_3), 2.31 (s, 3H, SO_3CH_3), 2.6−3.6 (m, 12H), 6.85 (d, J = 7.1 Hz, 1H,CH-12), 7.05 (dd, J = 7.1, 8.2 Hz, 1H, CH-13), 7.09 (s, 1H, CH-2), 7.20 (d, J = 8.2 Hz, 1H, CH-14), 9.70 (s, 1H, NH^+-6), 10.88 (s, 1H, NH-1). IR (KBr, cm^{-1}) 3180, 2980, 2554, 1606, 1158, 1037, 774. Anal. Calcd for $C_{19}H_{26}N_2S$*CH_3SO_3H: C, 58.51; H, 7.36; N, 6.82. Found: C, 58.4 2; H, 7.18; N, 6.89. $[\alpha]^{20}_D$ −22.3° (c = 1, DMF). Mp = 267.4 °C (reported 258−260 dec).[6a] HPLC purity 99.8%. The final product pergolide mesylate **1** was identical to the USP reference standard.

The overall molar yield from 9,10-dihydrolysergic acid **4** to pure pergolide mesylate **1** was 75.4%.

Acknowledgment

We thank for the useful help: Simona Scuratti, Camillo Motta, and Marco Baggi from the Analitycal Development and for the Pilot Plant activities.

Received for review September 16, 2005.

OP0501747