THE SYNTHESIS OF [^{2}H], [^{3}H], and [^{14}C]-LABELED 8β-[(METHYLTHIO)METHYL]-6-PROPYLERGOLINE MESYLATE (PERGOLIDE MESYLATE), A POTENT, LONG-ACTING DOPAMINE AGONIST[1]

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SUMMARY

The [^{3}H]- and two [^{14}C]-isotopomers of 8β-[(methylthio)methyl]-6-propylergoline mesylate (pergolide mesylate) have been synthesized. The [^{3}H]-derivative was synthesized by the palladium catalyzed tritiation of the corresponding 6-allyl derivative. Reaction of 8β-[(methylthio)methyl]-ergoline with 1-[^{14}C]-1-propyl bromide yielded pergolide labeled in the 6-propyl group. Alternatively,reaction of 8β-mesyloxy-6-propylergoline with [^{14}C]-sodium cyanide, followed by base hydrolysis, yielded 8β-carboxy-6-propylergoline-[^{14}C], which was subsequently converted to pergolide mesylate radiolabeled in the 17-position via a four step sequence.

Key words: pergolide mesylate, dopamine agonist, carbon 14, tritium, deuterium

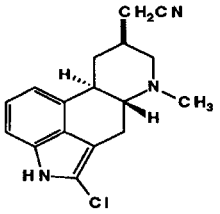
INTRODUCTION

In the search for ergoline derivatives which might possess the potent prolactin-inhibiting activity of many of the naturally occuring ergot alkaloids,[2-4] yet be free of some of the unwanted pharmacological activity and toxicity,[5] Clemens and co-workers reported on the structure-activity relationship of a series of semi-synthetic ergolines.[6] These studies culminated in the preparation of lergotrile mesylate (**1**), which was chosen for further study clinically, for use in the treatment of prolactin-dependent disorders.[6,7] Because of the similarity of the action of lergotrile on prolactin secretion, to that of *L*-dopa and apomorphine, several studies were initiated to study the effects of lergotrile and similar compounds on dopaminergic neuronal systems.[8,9,10] Subsequent pharmacological and biochemical studies have shown that these semi-synthetic ergoline alkaloids indeed possessed properties as central dopamine agonists, and studies relating to the utility of these compounds in the treatment of parkinsonism were undertaken.[11] Because of transient hepatotoxicity encountered with lergotrile at the doses necessary to treat parkinsonism, further clinical studies were suspended.[12]

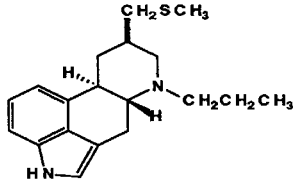
0362–4803/90/030273–23$11.50

Received July 21, 1989
Revised September 7, 1989

Pergolide mesylate (**2**) is a semi-synthetic ergoline similar to **1**, both in structure and pharmacological action, although substantially more potent and of longer duration of action than **1**.[13] Pre-clinical evaluation of **2** was undertaken in support of an eventual clinical trial, to study the utility of pergolide mesylate in the treatment of Parkinson's disease and prolactin-release related disorders.[14] Radiolabeled pergolide was required for drug metabolism and distribution studies in animals and humans. Initially, pergolide was radiolabeled in the N^6-propyl group. Parli reported that although in rats, no N-dealkylation occurred (no $^{14}CO_2$ was detected in expired air), over 35% of the radioactivity was eliminated as $^{14}CO_2$ within eight hours of dosing mice.[15] In contrast, Rubin *et al.* later reported that humans only eliminated 5% of the dose as $^{14}CO_2$ in 24 hours.[16] Pergolide which was labeled in a more stable position was needed for additional metabolism studies in animals. Tritiated material was required to conduct *in vitro* studies at the molecular level as well as for use in the development of a radioimmunoassay. In this report, we will detail the synthesis of the ^{14}C-, ^{2}H-,and ^{3}H-isotopomers of pergolide mesylate.



1 (as the Mesylate Salt)



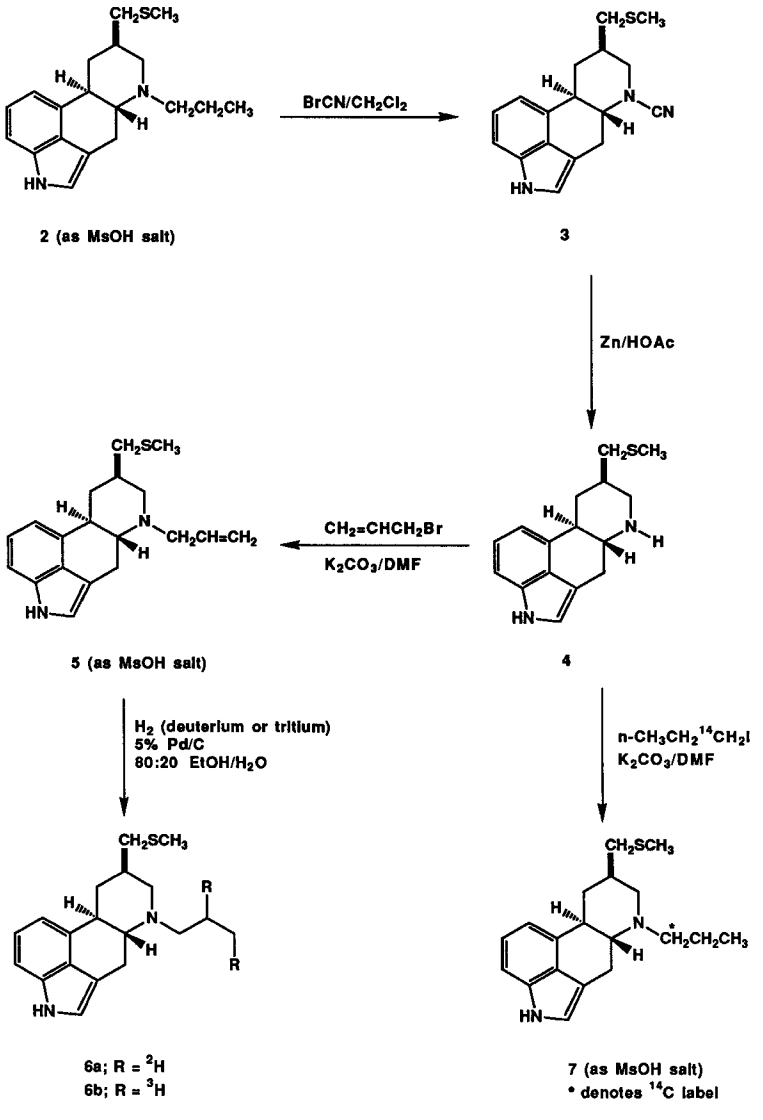
2 (as the Mesylate Salt)

RESULTS AND DISCUSSION

Although Vicario and his co-workers prepared [9,10-^{3}H]-ergolines by the reduction of the corresponding 9,10-didehydroergolines with tritium gas, and [17-^{3}H]-ergolines by the sodium borohydride-[^{3}H] reduction of 8-carbomethoxyergolines,[17] it was more convenient for our purposes to introduce tritium into 8β-[(methylthio)-methyl]-6-allylergoline (**5a**), by catalytic hydrogenation with tritium gas. This allowed us to introduce the label in the last step using material readily prepared from **2** in three steps (Scheme I). Reaction of **2**, with an excess of cyanogen bromide under von Braun conditions effected dealkylation at N^6, yielding the corresponding N-cyano compound **3** (88% yield). Reductive removal of the cyano group with zinc in refluxing acetic acid yielded **4** in 67% yield. Reaction of **4** with allyl bromide in dimethylformamide/potassium carbonate yielded the N^6-allyl derivative, which was converted to its methanesulfonate salt **5**, by treatment with methanesulfonic acid in methanol (35%).

Preliminary experiments on the atmospheric pressure hydrogenation of **5** were conducted using deuterium gas. Thus, an aqueous ethanolic solution of **5** was stirred overnight under an atmosphere of deuterium gas, in the presence of 5% Pd/C. After work-up and chromatography over silica gel, pergolide-^{2}H (which was converted to its methanesulfonate salt **6**) was obtained. Both NMR and MS (EI) indicated incomplete deuteration (presumably from deuterium-proton exchange between deuterium gas and the non-deuterated solvent at the surface of the catalyst[18]).

SCHEME I



Catalytic tritiation was conducted in the manner previously described for the deuteriation. The crude product, after removing the labile tritium in methanol was purified by preparative TLC on silica gel. The plates were developed in the dark with chloroform/methanol/ethyl acetate (160:5:35); the tritiated product **6b** was eluted from the silica gel with ethanol. The specific activity of **6b** was 25.2 Ci/mmol (61.5 mCi/mg) and had a radiochemical purity of 98% by TLC on silica gel and C18 reversed phase plates.[19]

8β-[(Methylthio)methyl]-6-propyl-[1-^{14}C]ergoline mesylate (**7**) was prepared by the reaction of secondary amine **4** with 1-[^{14}C]-1-bromopropane in dimethylformamide/potassium carbonate at

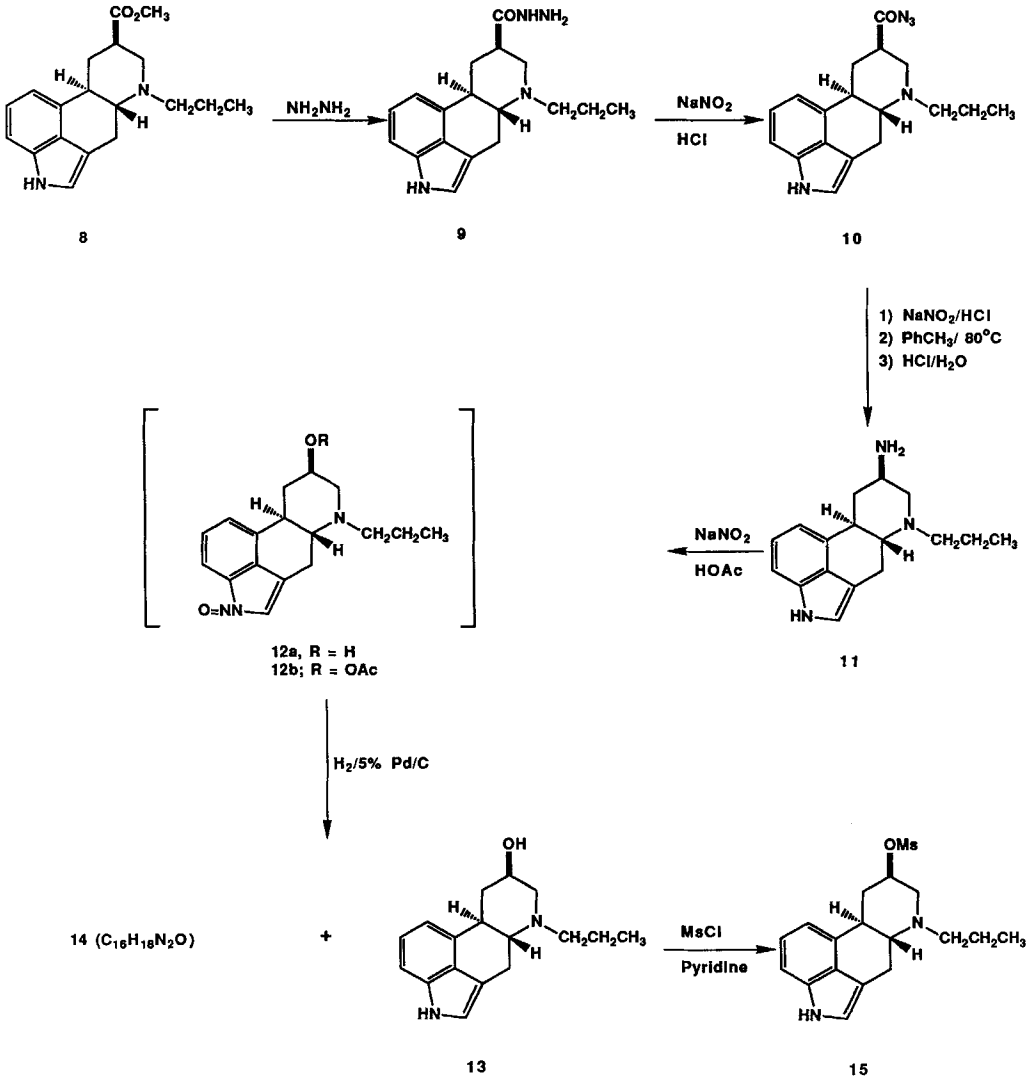
60-65° for 16 hours (Scheme I). After aqueous work-up, the crude product was chromatographed over Florisil, then converted to its methanesulfonate salt and crystallized from methanol to yield **7**. The radiochemical purity was shown to be 97.1% by silica gel TLC and 96.4% by HPLC.

Additional [^{14}C]-labeled pergolide mesylate was needed for further metabolism studies. In view of the previously reported N-dealkylation of pergolide mesylate in mice, we sought a method to radiolabel **2** in a more metabolically stable position. It was our intention to utilize 8β-mesyl-oxy-6-propylergoline (**15**) as the pivotal intermediate in the synthesis of 8β-[(methylthio)methyl]-6-propylergoline-17-[^{14}C], in a manner similiar to that recently reported by Marzoni and co-workers.[20] The synthesis of **15** was accomplished in five steps from 8β-carbomethoxy-6-propylergoline (**8**)[21] (Scheme II). Thus, reaction of **8** with anhydrous hydrazine at 65° yielded the corresponding hydrazide **9**. Diazotization of **9** with sodium nitrite in dilute hydrochloric acid yielded the acyl azide **10**, in addition to 8β-carboxy-6-propylergoline, presumeably formed via the hydrolysis of **10** (the presence of **10** and the acid as well as unreacted **9** was confirmed by FAB-MS).

Rearrangement of **10** in toluene at 80° yielded 8β-amino-6-propylergoline (**11**), after hydration of the intermediate isocyanate and subsequent decarboxylation of the resulting carbamic acid. Reaction of **11** with sodium nitrite in acetic acid and solvolysis of the resulting diazonium salt yielded a mixture of 8β-hydroxy-6-propyl-1-nitrosoergoline (**12a**) and the corresponding 8β-acetate (**12b**) as well as a third product, which was only detected by mass spectrometry. Treatment of the mixture (**12a, 12b, and 12c**) with H_2/5% Pd/C effected hydrogenolysis of the nitroso moiety, to yield after hydrolysis in aqueous base, a mixture of 8β-hydroxy-6-propylergoline (**13**) and (**14**) whose structure is currently unknown. Stoll *et al.*[22] reported the isolation of only 6-methylergoline when 8α–amino-6-methylergoline was diazotized and subsequently hydrogenated over palladium black. The molecular ion of **14** (M^+ 254) corresponds to the molecular weight of 6-propylergoline; however, the high resolution EI mass spectrum as well as microanalytical data correspond to the molecular formula $C_{16}H_{18}N_2O$/ 254.14176.

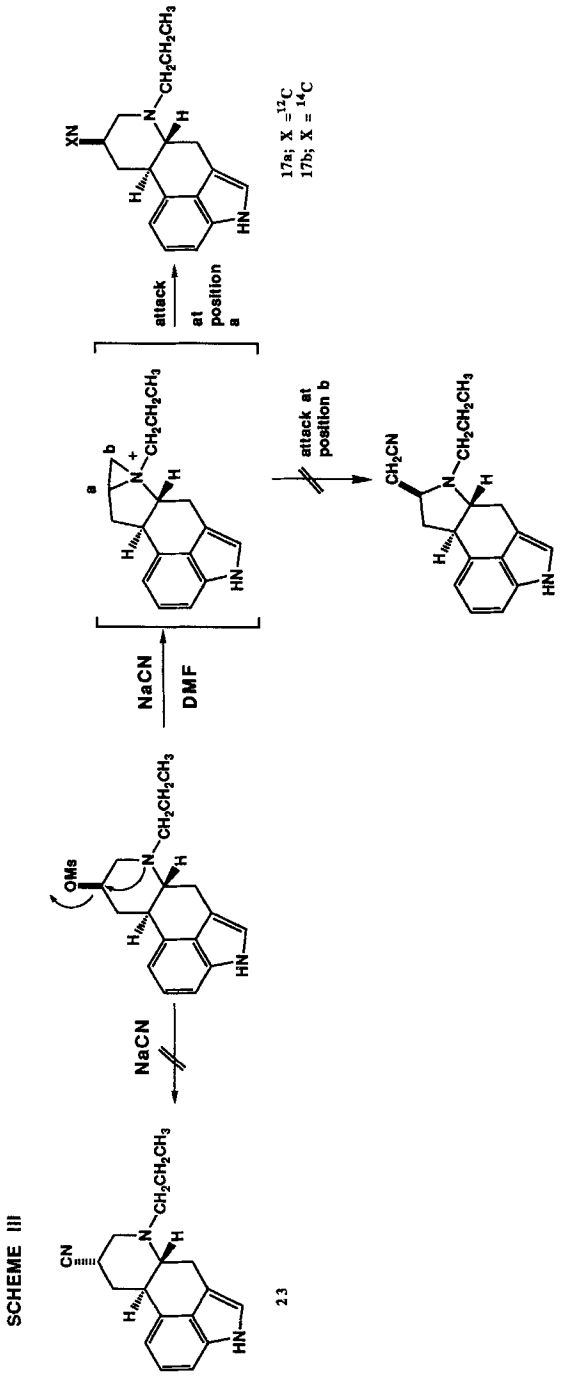
Reaction of **13** with methanesulfonyl chloride in pyridine yielded the required intermediate **15** in 56.4% yield. Reaction of **15** with sodium cyanide (or sodium [^{14}C]-cyanide) then yielded nitrile **17a** (or the corresponding ^{14}C-isotopomer **17b**)(see Scheme III). The reaction occurred with nearly complete retention of configuration at C-8, yielding >97 % of the 8β-isomer, presumably the result of transannular neighboring group participation by the 6-amino group *via* the aziridinium intermediate **16** followed by attack of the aziridinium ion by cyanide. Hammer *et al.* provided substantial evidence for such an intermediate in the displacement of N-methyl-3-chloropiperidine with a variety of nucleophiles.[23] Reaction of N-methyl-3-chloropiperidine with $AgClO_4$/acetone formed the corresponding bicyclic aziridinium perchlorate. Reaction with nucleophiles is then possible at either the bridgehead carbon (a) or at the position *alpha* to the amino group (b). Although all of the reactions described by Hammer *et al.* proceeded with net retention of configuration, regioselectivity was only achieved in the case of cyanide, benzylamine and dibenzylamine (contrary to our results, the resulting products were exclusively the ring contracted pyrrolidines resulting from reaction at position b). The reasons for our observed change in regioselectivity is under investigation and will be discussed in a subsequent communication.

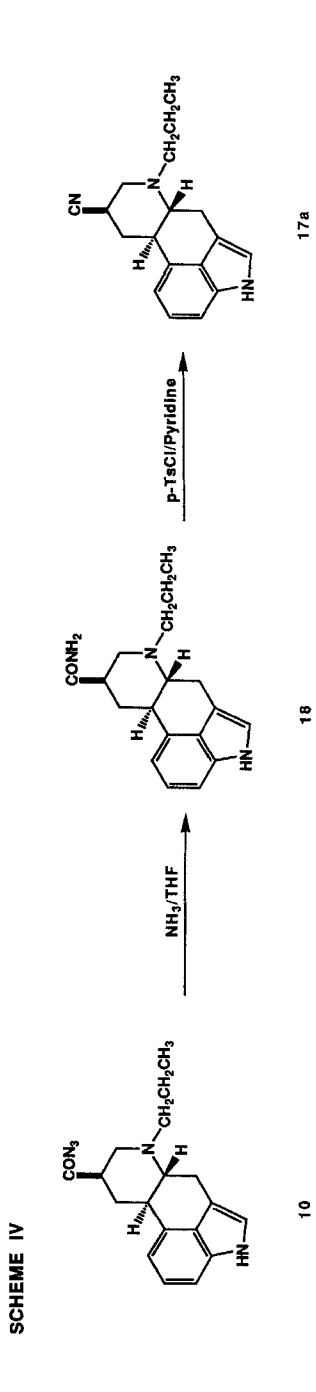
SCHEME II



Further confirmation of the structure of **17a** was made after the unambiguous synthesis of both the α- and β-nitriles (Scheme IV). β-Acyl azide **10** was treated with ammonia to afford the 8β-carboxamide **18**, which was dehydrated by the method described by Bosisio *et al*[24] with *p*-toluenesulfonyl chloride/pyridine to yield the 8β-nitrile which was indistinguishable from **17a** by NMR, HPLC, and TLC (silica gel, ethyl ether, $r_f = 0.63$).

The 8α-nitrile **23** was prepared in an analagous manner from the 8α-hydrazide **21** (via the acylazide) which was synthesized from α-ester **20** (Scheme V). Reaction of β-ester **8** with 4-chloroperbenzoic acid at -40° (following the procedure described by Stutz and Stadler[25]), followed by reaction of the intermediate N-oxide sequentially with acetic anhydride and


SCHEME III
CN
CH2CH2CH3
OMs
NaCN
NaCN
DMF
attack at position a
attack at position b
CH2CN
23
17a; X = 12C
17b; X = 14C

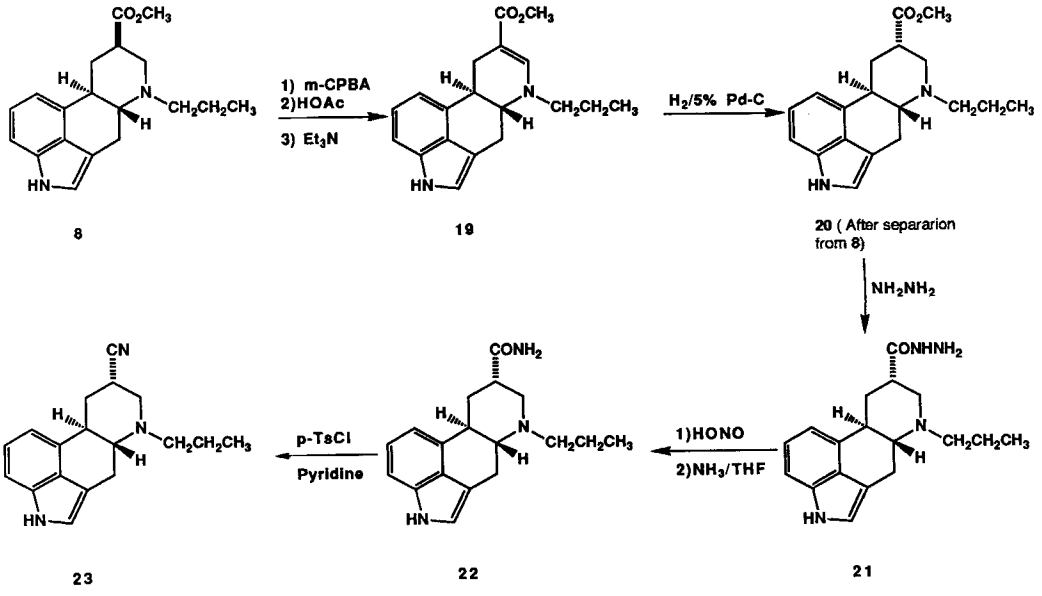

SCHEME IV
CON3
NH3/THF
CONH2
p-TsCl/Pyridine
CN
10
18
17a

triethylamine, yielded after chromatography, 8-carbomethoxy-7,8-didehydro-6-propylergoline (**19**). Catalytic hydrogenation over 5% Pd/C, yielded a mixture of **8** and its 8α–epimer (**20**). These two epimeric esters were conveniently separated by flash chromatography, eluting with diethyl ether. Reaction of **20** with anhydrous hydrazine yielded 8α-hydrazide **21**. Reaction with *in situ* generated nitrous acid, followed by conversion to 8α-amide by reaction with ammonia, and subsequent dehydration, yielded 8α-nitrile (TLC silica gel, ethyl ether, $r_f = 0.76$)

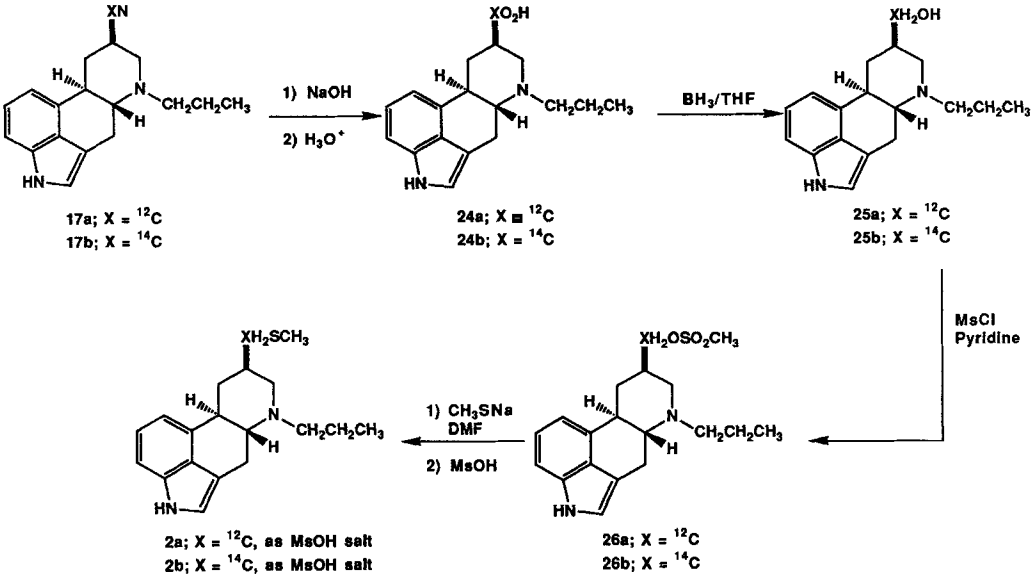
The stereochemistry at C-8 was determined by complete assignment of the 250 MHz NMR spectrum of **17a** in pyridine/d_5 with the aid of two dimensional proton-correlated COSY and ^1H-^{13}C-correlated NMR experiments.[26] The quartet at δ1.67 ppm (9β, *axial* proton) was coupled to both the 8α (*axial*) and the 10α (*axial*) protons as well as the 9α-*equatorial* proton (J = 13 Hz). Similiar coupling was observed in the NMR of **8** (in which the 8-carbomethoxy substituent is also *beta*.) In the corresponding 8α-carbomethoxy epimer, the 9-*axial* proton appears as a doublet of triplets ($J_{8eq\text{-}9ax}$ is 5 Hz, $J_{9ax\text{-}10ax}$ and $J_{9ax\text{-}9eq}$ = 13 Hz).[27] Ninomiya *et al.* reported similiar results for the epimeric 6,8-dimethylergolines festuclavine and pyroclavine.[28]

Base hydrolysis of nitriles **17a,b** in ethanol yielded the carboxylic acids **24a,b**, which were reduced with borane in tetrahydrofuran to yield 8β-hydroxymethyl-6-propylergoline (**25a**) or the analogous ^{14}C-isotopomer **25b** Scheme VI). Following activation of **25a** (or **25b**) by conversion to their mesylate esters **26a,b** (by reaction with methanesulfonyl chloride in pyridine), reaction with the sodium salt of methanethiol followed by salt formation with methanesulfonic acid afforded pergolide (**2**) or 8β-[(methylthio)methyl]- 6-propylergoline-17-[^{14}C] mesylate (**2b**). Thus, **2b** was prepared from **15** in six steps in 17.4% overall radiochemical yield, with a specific activity of 15.7 μCi/mg (or 6.44 mCi/mmol). The radiochemical purity as determined by TLC/autoradiography ranged from 97.7-99.3%.

SCHEME V

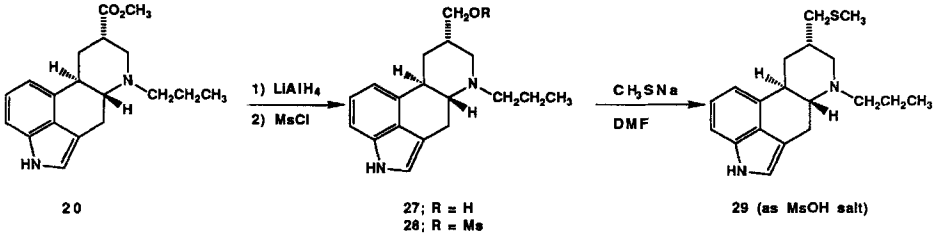


SCHEME VI



In order to ensure that the [^{14}C]-**2b** was free of its 8α-epimer, we have synthesized an authentic sample for comparison [29](see Scheme VII). Lithium aluminum hydride reduction of **20**, followed by mesylation (methanesulfonyl chloride/pyridine) and subsequent reaction with the sodium salt of methanethiol in dimethylformamide and salt formation, yielded the 8α-epimer of pergolide mesylate (**29**).

SCHEME VII



EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a General Electric QE-300 NMR spectrometer at 300 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. The spectra of **2**, **16a**, and **23** were determined on a Bruker WM-250 NMR spectrometer at 250 MHz (^{1}H) and 62.896 MHz (^{13}C). Chemical shift assignments were made on the basis of two dimensional proton-correlated COSY and ^{1}H-^{13}C correlated NMR experiments.[26] The chemical shift assignments of the remainder of the compounds were made where possible, on the basis of 2D-COSY experiments. Mass spectra were recorded on a Varian Associates MAT 731

mass spectometer (field desorption) or a Nermag R30-10 triple-stage quadrupole mass spectrometer (direct chemical ionization and fast atom bombardment). High resolution FAB mass spectra were recorded on a VG Analytical VG-ZAB 3F mass spectrometer[30] Microanalytical data were provided by the Physical Chemistry Research Department of the Lilly Research Laboratories.

Radiochemical purity (RCP) was assessed by autoradiography employing E. Merck silica gel F-254 TLC plates and Kodak X-ray film BB-5. In addition, RCP was determined using HPLC and counting one minute fractions.

Flash chromatography was performed using the method described by Still *et al*,[31] using E.M. Scientific silica gel 60 (230-400 mesh). Thin-layer chromatography was conducted using E.M. Scientific silica gel F-250 plates.

Unless otherwise noted, the organic extracts were dried over anhydrous sodium sulfate prior to concentration.

8β-[(Methylthio)methyl]-6-cyanoergoline (3):

A methylene chloride (200 mL) solution of 8β-[(methylthio)methyl]-6-propylergoline (1.20 g, 3.82 mmol, prepared from its mesylate salt by treatment of an aqueous solution with sodium hydroxide, extraction with toluene, and concentration with subsequent crystallization), cyanogen bromide (1.20 g, 11.3 mmol) was stirred under argon for six hours. The resulting solution was washed with 2% aqueous tartaric acid, water, and saturated aqueous sodium chloride. After drying, the solution was concentrated to a white foam, which crystallized upon trituration with anhydrous ether. The white solid was collected by filtration, washed with ether , and dried *in vacuo* and recrystallized from ethyl acetate to yield **3** (1.0 g, 88%): mp 176-8°; NMR (pyridine/d_5) δ 1.06 (1H, q, J = 12 Hz, 9-H_{ax}), 2.00 (3H, s, CH_3S), 2.10 (1H, m, 7H_{ax}), 2.31 (1H, dd, J = 5.8, 13.2 Hz, $CH_{ax}SCH_3$), 2.31 (1H, dd, J = 5.8, 13.2 Hz, $CH_{eq}SCH_3$), 2.69 (2H, m, 8-H_{ax}, 4-H_{ax}), 2.91 (2H, m, 5-H_{ax}, 9-H_{eq}), 3.13 (1H, m, 10-H_{ax}), 3.42 (1H, dd, J = 3.3, 14 Hz, 4-H_{eq}), 3.74 (1H, m, 7-H_{eq}), 6.92 (1H, d, J = 7 Hz, 12-H), 7.12 (1H, s, 2-H), 7.24 (1H, m, 13-H), 7.36 (1H, d, J = 8 Hz, 14-H), and 11.54 ppm (1H, bs, indole NH); IR ($CHCl_3$) 2208 cm^{-1}(CN); MS(FD) M^+ 297; UV(EtOH) $\lambda_M(\varepsilon_M)$ 291 (5750), 281 (6860), and 223 nm (32600); $[\alpha]_D$ (CH_3OH) +55.63°.

Anal. calc'd for $C_{17}H_{19}N_3S$: C, 68.65; H, 6.44; and N, 14.13. Found: C, 68.92; H, 6.52; and N, 14.36.

8β-[(Methylthio)methyl]-ergoline (4):

Zinc dust (5 g, 76.4 mg-atom) was added to a 15% aqueous acetic acid (90 mL) solution, and the resulting solution was stirred at reflux for 3 hrs. The solvent was removed *in vacuo*; the residue was triturated with ethyl acetate and extracted with 3% tartaric acid. The aqueous extract was washed with ethyl acetate, made basic with sodium hydroxide, then back extracted twice with ethyl acetate (50 mL). The combined ethyl acetate extracts were washed with water, dried, and concentrated *in vacuo* to yield **4** as a white crystalline solid which was recrystallized from ethyl acetate: 0.614 g (67%); mp 196-7°C; NMR(DMSO/d_6) δ 1.06 (1H, q, J = 12 Hz, 9-H_{ax}), 1.86 (1H, bs, 6-NH), 2.09 (3H, s, CH_3S), 2.26 (1H ,t, J= 12 Hz), 2.4-2.54 (5H, m, CH_2SCH_3), 2.60 (1H, m), 2.72 (1H, m), 2.94 (1H, m), 3.18 (1H, m), 6.74 (1H, d, J = 7 Hz, 12-H), 6.92 (1H, s, 2-H), 7.01 (1H, m, 13-H), 7.12 (1H, d, J = 8 Hz, 14-H), and 10.57 ppm (

1H, bs, indole NH); UV(EtOH) $\lambda_M(\varepsilon_M)$ 224 (31000), 280 nm (7710); MS(EI) M^+ 272 (base), 154.

Anal. calc'd for $C_{16}H_{20}N_2S$: C; 70.55; H, 7.40; and N, 10.28. Found: C, 70.41; H, 7.36; and N, 10.05.

8β-[(Methylthio)methyl]-6-[3-(1-propenyl)]-ergoline Mesylate (5b):

A mixture of **4** (0.614 g, 2.26 mmol) and potassium carbonate (0.624 g, 4.52 mmol) in 20 mL of dimethylformamide (under argon) was treated with allyl bromide (0.235 mL, 2.71 mmol), and the resulting solution was stirred at room temperature overnight. TLC (9:1 chloroform/methanol) indicated that no starting material remained. The reaction mixture was poured into water and extracted twice with ethyl acetate (100 mL). The combined extracts were washed with water (3 x 50 ml), followed by saturated brine. After drying, the solvent was evaporated to leave a white solid, which was crystallized from methanol to yield 0.431 g (61%) of **5a**: mp 177-8°C; UV(EtOH) $\lambda_M(\varepsilon_M)$ 224 (33000), 280 (8200), 291 (6530); MS(EI) M^+ 312 (base), 154; $[\alpha]_D$ (CH_3OH) = - 62.749°.

Anal. calc'd for $C_{19}H_{24}N_2S$: C, 73.03; H, 7.74; and N, 8.97. Found: C, 73.29; H, 7.88; and N, 9.00.

A methanolic (30 mL) solution of **5a** was treated with methanesulfonic acid (0.098 mL, 1.52 mmol) and heated for 15 min, then the resulting solution was allowed to cool to room temperature whereupon the mesylate salt **5b** (0.319 g) crystallized: mp 273-5°C (dec.); MS(DCI) $(M+1)^+$ = 313; $[\alpha]_D$ (CH_3OH) = - 38.67°. A small sample was recrystallized from aqueous methanol for microanalysis. NMR (pyridine/d_5) δ 1.11 (1H, q, J = 12 Hz, 9-H_{ax}), 2.05 (3H, s, SCH_3), 2.06 (1H, m, $CH_{ax}SCH_3$), 2.50 (3H, m, $CH_{eq}SCH_3$, 8-H_{ax}, 4-H_{ax}), 2.85 (2H, m, 5-H_{ax}, 9-H_{eq}), 3.00 (3H, s, CH_3SO_3H), 3.04 (1H, m, 10-H_{ax}), 3.25 (2H, m, NCH_{ax}, 4-H_{eq}), 3.45 (2H, m, NCH_{eq}, 7-H_{eq}), 5.18 (2H, m, $=CH_2$), 6.00 (1H, m, =CH), 7.02 (1H, d, J = 7 Hz, 12-H), 7.17 (1H, s, 2-H), 7.24 (1H, m, 13-H), 7.27 (1H, d, J = 8 Hz, 14-H), and 11.53 ppm (1H, bs, indole NH).

Anal. calc'd for $C_{20}H_{28}N_2O_3S_2 \cdot 1.5\ H_2O$: C, 64.57; H, 6.69; and N, 8.97. Found: C, 64.63; H, 7.12; and N, 9.42.

8β-[(Methylthio)methyl]-6-[2',3'-$^2H_2$]-propylergoline Mesylate, 6a:

A mixture of **5b** (0.838 g, 2.051 mmol) and 5% Pd/C (0.2 g) in 50 mL of 80:20 ethanol/water was stirred overnight under one atmosphere of deuterium gas. The catalyst was removed by filtration, and the filtrate concentrated *in vacuo* at 45°C. The resulting white residue was redissolved in methanol (50 mL) and mixed with 5 g of Florisil. The desired product was eluted with a chloroform/methanol gradient (100% chloroform to 20% methanol). The combined fractions were concentrated and the residue was suspended in methanol (25 mL) and treated with methanesulfonic

acid (0.112 mL, 1.692 mmol) in methanol (1 mL). The mixture was warmed to dissolve the solids, treated with charcoal, and filtered through talc. The filtrate was concentrated to 5 mL and allowed to crystallize. Ether (25 mL) was added and the mixture was chilled overnight ; the solid was collected by filtration, washed with ether and dried to yield **6a** (0.650 g, 82%): mp 261-2°C. Mass spectral analysis (EI) indicated 42% (314, d_0), 32% (315, d_1), 22% (316, d_2), and 3% (317, d_3); NMR (DMSO/d_6) δ 0.99 (2H, m, CDH_2), 1.37 (1H, q, J = 12 Hz, 9-H_{ax}), 1.72 (<2H, m, CDH), 2.15 (3H, s, SCH_3), 2.31 (3H, s, CH_3SO_3H), 2.52 (3H, m), 2.80 (1H, m, 9-H_{eq}), 2.88 (1H, m, 4-H_{ax}), 3.00 (1H, m, 7-H_{ax}), 3.35 (3H, m, NCH, 5-H_{ax}, 10-H_{ax}), 3.56 (1H, 4-H_{eq}), 3.66 (1H, m, 7-H_{eq}), 6.87 (1H, d, J = 7 Hz, H-12), 7.09 (1H, m, 13-H), 7.10 (1H, s, 2-H), 7.22 (1H, d, J = 8 Hz, 14-H) , 9.80 (1H, bs, 6-NH^+), and 10.85 ppm (1H, bs, indole NH).

TLC (9:1 chloroform/methanol) indicated that the product was free of **5b** and co-migrated with an authentic sample of pergolide mesylate.

8β-[(Methylthio)methyl]-6-[2',3'-$^3H_2$]-propylergoline Mesylate, 6b:

8β-[(Methylthio)methyl]-6-[2',3'-$^3H_2$]-propylergoline Mesylate (**6b**) was prepared by Amersham Laboratories by catalytic hydrogenation in the presence of tritium gas, using the experimental conditions previously described for the production of the deuterium isotopomer (*vida supra*). After purification by preparative TLC, the radiochemical purity was ≥ 98% as assessed in the following systems: 1) chloroform/methanol 9:1 (98%), 2) chloroform/methanol/ethyl acetate 8:1:1 (98%), 3) benzene/ethanol 10:1 (98%), and 4) methanol (Whatman KC_{18} reversed phase, 98%). The specific activity was 61.5 mCi/mg (25.2 Ci/mmol).

8β-[(Methylthio)methyl]-6-[1'-^{14}C]-propylergoline Mesylate, 7:

A mixture of **4** (0.272 g, 1 mmol), potassium carbonate (0.207 g, 1.5 mmol), and *n*-propyl-1-[^{14}C] bromide (California Bionuclear Corp., sp. act. 30 mCi/mmol, 0.123 g, 1 mmol) in dimethylformamide (10 mL) was swept with nitrogen and heated at 60-65°C for 16 hrs. The mixture was poured into water (100 mL) whereupon a solid precipitated. The solid was collected by filtration, washed with water, and dried *in vacuo* at 60°C for four hours. The crude solid was purified by chromatography over Florisil (25 g). After a pre-wash of 90:10 chloroform/toluene (200 mL) and 95:5 chloroform/toluene (200 mL), the product was eluted with chloroform (200 mL). Some additional product contaminated with a slower moving component was eluted with 300 mL of 99:1 chloroform/methanol. The material from this contaminated fraction was re-chromatographed over 12.5 g of Florisil, eluting with 150 mL fractions of chloroform. Fractions 2-5 contained the desired product free of the slower moving contaminant.

The purified free base (0.069 g, 0.219 mmol) from both fractions were combined and dissolved in warm methanol (2.2 mL); the solution was treated with 2.2 mL of a 10mg/mL methanolic methanesulfonic acid solution (0.23 mmol). The solution was concentrated until crystallization occurred, then 10 mL of ether was added. The solid was collected by filtration to yield **7** (0.0644 g, 15.7%); sp. act. 74.3 μCi/mg (28.23 mCi/mmol). The radiochemical purity as determined by TLC-autoradiography (9:1 chloroform/methanol) was ≥97%.

6-Propylergolinyl-8β-carboxylhydrazide, 9:

Anhydrous hydrazine (20 mL) was added to **8**[21] (5.30 g, 17 mmol) and the resulting suspension was heated at 90-100°C. The ester (**8**) slowly dissolved and after 2.5 hrs, the mixture was allowed to cool to room temperature. The crystalline residue was thoroughly triturated with water and the solid was collected by filtration. The white solid was washed with water (125 mL) and dried at 40°C under vacuum to yield **9** (4.94 g, 93.2%): mp 248-250.5°C(dec.); NMR(pyridine/d_5) δ 0.72 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.40 (1H, m, $CH_3\underline{CH_2}$), 2.05 (1H, q, J = 12 Hz, 9-H_{ax}), 2.55 (2H, m, NCH_{ax}, 7-H_{ax}), 2.75 (3H, m, NCH_{eq}, 4-H_{ax}, 8-H_{ax}), 2.98 (3H, m, 5-H_{ax}, 10-H_{ax}, 9-H_{eq}), 3.37 (2H, m, 4-H_{eq}, 7-H_{eq}), 5.01 (2H, bs, NH_2), 6.95 (1H, d, J = 7 Hz, C-12), 7.13 ((1H, s, H-2), 7.14 (1H, m, H-13), 7.15 (1H, bs, NH), 7.30 (1H, d, J = 8 Hz, H-14), and 10.25 ppm (1H, bs, indole NH); UV(EtOH) $\lambda_M(\varepsilon_M)$ 223 (33300), 281 (6830), and 291 (5630); $[\alpha]_D$(pyridine) = -103.47°; MS(EI) M^+ 312.

Anal. calc'd for $C_{18}H_{24}N_4O$: C, 69.20; H, 7.74; and N, 17.93. Found: C, 68.99; H, 7.84; and N, 17.73.

8β-Amino-6-propylergoline, 11:

The hydrazide **9** (4.9 g, 15.7 mmol) was dissolved in 200 mL of 0.2 N HCl and chilled to 0 to -5°C. Sodium nitrite (1.08 g, 15.7 mmol) in water (10 mL) was added dropwise and the resulting solution was stirred at 0°C for 0.5 hr, then made basic by the addition of solid sodium carbonate and extracted with ethyl acetate (3x100 mL). The combined extracts were washed with water, dried, and concentrated *in vacuo* to yield the crude crystallization acyl azide **10** (mass spectral analysis by FAB-MS showed the presence of **10** as well as the corresponding acid **24a** and unreacted **9**).

The acyl azide **10** was re-dissolved in toluene (100 mL) and heated at 80°C for 2 hrs, then concentrated and dissolved in 100 mL of 0.2 N HCl and allowed to stand at room temperature. After 2 hrs, the solution was made basic with sodium carbonate and extracted with ethyl acetate (3x150 mL). The combined extracts were washed with water, dried, and concentrated. Recrystallization from methanol yielded 1.71 g (40.5%) of **11**: mp 183-4°C. An additional 0.262 g of **11** was recovered from the mother liquors. TLC (chloroform/methanol/ammonium hydroxide 90:10:0.2) showed **11** to be one major component plus one very minor higher r_f contaminant.
NMR (pyridine/d_5) δ 0.79 (3H, t, J = 7.3 Hz, $\underline{CH_3}CH_2$), 1.34 (1H, q, J = 12 Hz, 9-H_{ax}), 1.43 (2H, m, $CH_3\underline{CH_2}$), 2.02 (1H, m, 9-H_{eq}), 2.41 (1H, m, 5-H_{ax}), 2.52 (1H, m, NCH_{ax}), 2.72 (2H, m, NCH_{eq}, 4-H_{ax}), 2.84 (1H, m, 8-H_{ax}), 3.10 (1H, m, 7-H_{ax}), 3.14 (2H, m, 7-H_{eq}, 10-H_{ax}), 3.40 (1H, m, 4-H_{eq}), 7.02 (1H, d, J = 7 Hz, 12-H), 7.18 (1H, s, 2-H), 7.25 (1H, m, H-13), 7.36 (1H, d, J = 8 Hz, H-14), and 11.51 ppm (1H, bs, indole NH); UV(EtOH) $\lambda_M(\varepsilon_M)$ 224 (30000), 281 (6150), 291 nm (5030) ; MS(EI) M^+ 269.

Anal. calc'd. for $C_{17}H_{23}N_3$: C, 75.80; H, 8.61; and N, 15.60. Found: C, 75.55; H, 8.63; and N, 15.40.

8β-Hydroxy-6-propylergoline, 13:

A 0.2N solution of sodium nitrite (110 mL, 22 mmol) was added dropwise to an acetic acid (40 mL) solution of **11** (1.98 g, 7.35 mmol) previously cooled to 5-10°C. The mixture was stirred for 1.5 hrs, then neutralized with 5N sodium hydroxide and extracted with methylene chloride (3 x 100 mL). The combined extracts were washed with water, dried, and concentrated to a bright yellow foam. TLC (chloroform/methanol/ammonium hydroxide 90:10:0.2) showed two compounds (r_f = 0.63 and 0.97), presumeably 1-nitroso-8β-acetoxy-6-propylergoline (**12a**) and 1-nitroso-8β-hydroxy-6-propylergoline (**12b**).

The yellow amorphous solid was dissolved in glacial acetic acid (120 mL), mixed with 0.5 g of 5% Pd/C, and hydrogenated at 60 psi for 24 hrs. The catalyst was removed by filtration; the filtrate was concentrated *in vacuo*. The residue was re-dissolved in chloroform (150 mL) and washed successively with 2N sodium hydroxide and water, then dried and concentrated *in vacuo*. TLC showed two components (r_f = 0.62 and 0.90), the higher r_f component being the major component. The spots were scraped and eluted with methanol. MS(DCI) showed $(M+1)^+$ 313 (a smaller peak was present at 254) for the faster moving material and 271 for the slower material, corresponding to **13** and its acetate ester. The mixture was dissolved in methanol and 14 mL of 2N sodium hydroxide and allowed to stand at room temperature overnight. The mixture was then diluted with water and extracted with chloroform (150 mL). After washing with water and drying, concentration caused crystallization of **13** (0.50 g, 25%): mp 203-4°C; NMR (pyridine/d_5) δ 0.75 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.42 (2H, m, $CH_3\underline{CH_2}$), 1.69 (1H, q, J = 12 Hz, 9-H_{ax}), 2.40-2.57 (3H, m, NCH_{ax}, 5-H_{ax}, 7-H_{ax}), 2.76 (1H, m, NCH_{eq}), 2.78 (1H, m, 4-H_{ax}), 3.05-3.21 (2H, m, 9-H_{eq}, 10-H_{ax}), 3.47 (2H, m, 4-H_{eq}, 7-H_{eq}), 4.28 (1H, m, 8-H_{ax}), 6.34 (1H, d, J = 5 Hz, OH), 7.04 (1H, d, J = 7 Hz, 12-H), 7.16 (, 1H, s, 2-H), 7.21 (1H, m, 13-H), 7.31 (1H, d, J = 8 Hz, 14-H), and 11.49 ppm (1H, bs, indole NH); UV(EtOH) $\lambda_M(\varepsilon_M)$ 224 (26300), 281 (5340), 291 nm (4360); MS(DCI) $(M+1)^+$ 271.

Anal. calc'd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; and N, 10.36. Found: C, 74.64; H, 8.17; and N, 10.13.

The mother liquors from above were concentrated and the residue was crystallized from methanol to yield **14** (0.077 g): mp 247-8°C(dec.); NMR (pyridine/d_5) δ 0.76 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.43 (2H, m, $CH_3\underline{CH_2}$), 2.49 (1H, dd, J = 12.6, 15.2 Hz), 2.68 (1H, dt, J = .92, 12.3), 2.88 (1H, dd, J = 7.2, 8.2), 3.09 (1H, m, NCH_{ax}), 3.22 (1H, dd, J = 4, 9.7 Hz), 3.33 (1H, m, collaspes to td in D_2O), 3.51 (1H, m), 6.77 (1H, d, J = 7, 12 Hz, 12H), 7.19 (1H, m, 13-H), 7.11 (1H, s, 2-H), 7.35 (1H, d, J = 8 Hz), and 11.80 ppm (1H, bs, indole NH); IR ($CHCl_3$) 1678 cm^{-1}. HR-MS(EI) calc'd for $C_{16}H_{18}N_2O$: 254.14191. Found: 254.14176.

Anal calc'd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; and N,11.01. Found: C, 75.48; H, 7.11; and N, 10.76.

8β-Mesyloxy-6-propylergoline, 15:

A pyridine solution (2 mL) of **13** (0.146 g, 0.54 mmol) was stirred under argon and cooled to 0-10°C. Methanesulfonyl chloride (0.126 mL, 1.62 mmol) was added dropwise and the resulting mixture was stirred for 2 hrs, while allowing to warm to room temperature. The pale yellow solution was then added to 5 mL of water with stirring, then diluted with an additional 5 mL of water and chilled to 5°C. The resulting yellow precipitate was collected by filtration, washed with water and dried overnight *in vacuo*. TLC (chloroform/methanol 9:1) showed the product to be a single spot, migrating faster than the starting material (r_f = 0.79; r_f alcohol = 0.27); 0.106 g (56.4%): mp >250°C (dec.); NMR ($CDCl_3$) δ 0.71 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.32 (2H, m, $CH_3\underline{CH_2}$), 1.65 (1H, q, J = 12 Hz, 9-H_{ax}), 2.40 (2H, m, NCH_{ax}, 7-H_{ax}), 2.65 (2H, m, 5-H_{ax}, NCH_{eq}), 2.97-3.16 (3H, m, 4-H_{ax}, 9-H_{eq}, 10-H_{ax}), 3.30-3.44 (2H, m, 4-H_{eq}, 7-H_{eq}), 3.36 (3H, s, CH_3SO_2), 5.16 (1H, m, 8-H_{ax}), 6.91 (1H, d, J = 7 Hz, 12-H), 7.16 (1H, s, 2-H), 7.21 (1H , m, 13-H), 7.35 (1H, d, J = 9 Hz, 14-H), and 11.48 ppm (1H, s, indole NH); MS(DCI) M^+ 348.

Anal calc'd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; and N, 8.04. Found: C, 62.28; H, 6.74; and N, 8.31.

8β-Cyano-6-propylergoline, 17a:

Method A:

A dimethylformamide (2.5 mL) solution of sodium cyanide (0.020 g, 0.414 mmol) and **15** (0.096 g, 0.276 mmol) was stirred under argon at room temperature. After 24 hrs, TLC (9:1 chloroform/ methanol) showed that the conversion to **17a** was complete. The stirred solution was diluted dropwise with water until cloudy and stirred until crystallization occurred. The solution was diluted with 1 mL of additional water and chilled to 5°C. The crystalline solid was collected by filtration, washed with water, and dried *in vacuo* at room temperature for 16 hrs to yield **17a** (0.059 g, 76.6%): mp 182-3°C; TLC in ether (r_f = 0.625), 1:1 ether/hexane (r_f = 0.23), and 4:1 ether/ hexane (r_f = 0.51) all showed **17a** to be a single component; [^{1}H]-NMR (pyridine/d_5) δ 0.85 (3H, t, J = 8Hz, $\underline{CH_3}CH_2$), 1.42 (2H, m, $CH_3\underline{CH_2}$), 1.67 (1H, q, J = 13Hz, 9-H_{ax}), 2.51 (1H, t, J = 11.2 Hz, 7-H_{ax}), 2.51 (1H, m, 5-H), 2.59 (1H, m, NCH_{ax}), 2.72 (1H, m, 4-H_{ax}), 2.73 (1H, m, NCH_{eq}), 2.92 (1H, m, 10-H), 2.98 (1H, m, 9-H_{eq}), 3.09 (1H, m, 8-H), 3.26 (1H, ddd, J = 2.5, 4.5, 11.2, 7-H_{eq}), 3.37 (1H, dd, J = 4.5, 14 Hz, 4-H_{eq}), 6.96 (1H, d, J = 7 Hz, 12-H), 7.24 (1H, s, 2-H), 7.32 (1H, m, 13-H), 7.43 (1H, d, J = 8.5, 14-H), and 11.62 ppm (1H, bs, indole NH); [^{13}C]-NMR (pyridine/d_5) δ 11.88 ($\underline{CH_3}CH_2$), 18.58 ($CH_3\underline{CH_2}$), 27.17 (C-4), 27.68 (C-8), 32.31 (C-9), 40.17 (C-10), 54.31 (NCH_2), 55.28 (C-7), 63.75 (C-5), 109.65 (C-14), 111.25 (C-3), 112.98 (C-12), 119.21 (C-13), 121.73 (CN), 123.04 (C-13), 127.00 (C-16), 132.29 (C-11), and 134.66 ppm (C-15); MS(DCI) M^+ 279, (M-Et) 250.

HR-MS(FAB) calc'd for $C_{18}H_{21}N_3$ + H: 280.18137. Found: 280.18162.

Method B:

8β-Carboxamido-6-propylergoline (**18**)(0.297 g, 1 mmol) was suspended in pyridine (2.5 mL) and *p*-toluenesulfonyl chloride (0.380 g, 2 mmol) was added portionwise at room temperature. The mixture was then heated at 68-70°C for 1 hr; then poured over ice and extracted with chloroform (3x25 mL). The combined extracts were washed with saturated brine, dried, and concentrated to an oil which crystallized. This material was purified by flash chromatography over an 8 in x 20 mm column, eluting with ether in 10 mL fractions. Fractions 4-9 were combined, concentrated, and crystallized from ether to yield **17a** (0.152 g, 54.5%): mp 182-3°C, which was indistinguishable from that prepared by method A by NMR, TLC, and HPLC (Zorbax C-18, eluted with 75:25 CH_3OH/ 0.1M NH_4OAc at 1.5 mL/min (UV detection at 289 nm) (R_T = 4.94 min).

8β-Cyano-6-propylergoline-17-[^{14}C], 17b:

Sodium cyanide-[^{14}C] (200 mCi, 56.6 mCi/mmol, 3.53 mmol, Sigma Radiochemicals Co., Inc.) and **15** (1.23 g, 3.53 mmol) were mixed in dimethylformamide (25 mL) and stirred under argon for 3 hrs, whereupon carrier sodium cyanide (0.087 g, 1.77 mmol) was added. Stirring was continued for an additional 15 hrs (TLC, 4:1 ether/hexanes confirmed that **15** had been consumed). The mixture was concentrated to approximately 15 mL and then diluted dropwise with water (30 mL). The product crystallized and was collected by filtration, washed with water, and dried *in vacuo* at 40°C for 16 hrs to yield **17b** (0.743 g, 74.8%). Autoradiography (4:1 ether/hexanes) showed one major product (97.4%), which co-eluted with **17a.** A faster moving material, which co-eluted with **23** (the corresponding 8α-nitrile) amounted to ca. 2%. The DCI-MS showed a $(M+1)^+$ at 282.

8β-Carboxamido-6-propylergoline, 18:

A hydrochloric acid solution (0.2N x 100 mL) of the 8β-hydrazide **9** (2.0 g, 6.4 mmol) was chilled to 0-5°C and treated dropwise with aqueous sodium nitrite (0.441 g, 6.4 mmol in 5 mL of water). After stirring at 0°C for 1 hr, the mixture was neutralized with sodium carbonate (the acyl azide crystallized) and the mixture was extracted with ethyl acetate (3 x 75 mL). The combined extracts were washed with brine, dried, and concentrated *in vacuo.*

The solid acyl azide **10** was re-dissolved in 100 mL of anhydrous tetrahydrofuran and chilled to 0°C. Anhydrous ammonia was bubbled into the solution for 10 min; stirring at 0°C was continued until the acyl azide was consumed (TLC, 9:1 chloroform/methanol), then overnight at room temperature. The solution was concentrated and the residue was crystallized from chloroform to yield **18** (1.24 g, 65%): mp 209-210°C. FAB-MS and DCI-MS showed a $(M+1)^+$ at 298; NMR 0.72 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.37 (2H, m, $CH_3\underline{CH_2}$), 1.97 (1H, q, J = 12 Hz, 9-H_{ax}), 2.53 (2H, m, NCH_{ax}, 7-H_{ax}), 2.72 (3H, m, NCH_{eq}, 4-H_{ax}, 8-H_{ax}), 3.03 (3H, m, 5-H_{ax}, 9-H_{eq}, 10-H_{ax}), 3.41 (2H, m, 4-H_{eq}, 7-H_{eq}), 6.95 (1H, d, J = 7 Hz, 12-H), 7.13 (1H, s, 2-H),7.14 (1H, m, 13-H), 7.30 (1H, d, J = 8 Hz, 14-H), 7.72 (1H, bs, amide NH), 8.21 (1H, bs, amide NH), and 11.57 (1H, bs, indole NH).

HR-MS(FD) calc'd for $C_{18}H_{23}N_3O$ + H: 298.19194. Found: 298.19317.

8-Carbomethoxy-6-propyl-8,9-dehydroergoline, 19:

To a cold (-25°to-35°C) methylene chloride solution (100 mL) of **8** (8.0 g, 25.6 mmol) was added dropwise a methylene chloride solution (50 mL) of 85% *m*-chloroperbenzoic acid (6.32 g, 32 mmol). Stirring was continued for 0.5 hr, whereupon acetic anhydride (3.2 mL, 32 mmol) followed by triethylamine (22 mL, 160 mmol) was added. The resulting mixture was stirred at -35°C for 90 min, then diluted with an additional 100 mL of methylene chloride. The solution was washed successively with 5% sodium bicarbonate and brine, then dried and concentrated. The residue was purified by flash chromatography, eluting in 70 mL fractions of 9:1 chloroform/ methanol. Fractions 1-12 were combined and concentrated, then redissolved in ethyl acetate and treated with charcoal. After filtration, evaporation yielded **19** (1.5 g, 19%) as a yellow amorphous solid: mp 193-4°C(dec.)

Anal. calc d for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; and N,9.03. Found: C, 73.58; H, 6.85; and N, 8.93.

8α-Carbomethoxy-6-propylergoline, 20:

A mixture of **19** (1.5 g, 4.8 mmol), platinum oxide (0.5 g) in 50 mL of 1:2 dimethylformamide/ acetic acid was hydrogenated under 60 psi of hydrogen at 50°C overnight. TLC (ethyl ether) showed a mixture of **20** and β-ester **8** as well as an unknown product running slightly behind **8**. The mixture was purified twice by flash chromatography (eluted in 10 mL fractions with ethyl ether) to yield **20** (0.316 g, 21%) after recrystallization from methanol; mp 168-170°C (literature mp 168-170°C[27]); ^{1}H-NMR (pyridine/d_5) δ 0.86 (3H, t, J = 6 Hz, $\underline{CH_3}CH_2$), 1.49 (2H, m, $CH_3\underline{CH_2}$), 1.62, (1H, dt, J = 5, 12 Hz, 9-H_{ax}), 2.43 (1H, dd, J = 4, 11.5 Hz, 7-H_{ax}), 2.48 (1H, m, NCH_{ax}), 2.50 (1H, ddd, J = 4.5, 7, 11 Hz, 5-H_{ax}), 2.77 (1H, m, 4-H_{ax}), 2.84 (1H, m, NCH_{eq}), 2.85 (1H, m, 10-H_{ax}), 3.27 (1H, m, 9-H_{eq}), 3.45 (1H, dd, J = 5, 14.5 Hz, 4-H_{eq}), 3.50 (1H, m, 8-H_{eq}), 3.61 (1H, dt, J = 3, 11.5 Hz, 7-H_{eq}), 3.67 (3H, s, OCH_3), 7.11 (1H, d, J = 7 Hz, 12-H), 7.20 (1H, s, 2-H), 7.31 (1H, q, J = 7, 9 Hz, 13-H), 7.39 (1H, d, J = 9 Hz, 14-H), and 11.52 ppm (1H, bs, indole NH); ^{13}C-NMR (pyridine/d_5) δ 11.98 ($\underline{CH_3}CH_2$), 18.58 ($CH_3\underline{CH_2}$), 27.38 (C-4), 28.96 (C-9), 38.98 (C-8), 40.19 (C-10), 51.45 (OCH_3), 54.77 (C-7), 55.09 (NCH_2), 65.47 (C-5), 109.26 (C-15), 111.69 (C-3), 113.0 (C-12), 113.97 (C-2), 123.04 (C-13), 127.29 (C-16), 134.14 (C-11), 134.59 (C-15), 174.38 (C=O).

Anal. calc'd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; and N, 8.97. Found: C, 72.80; H, 7.81; and N, 8.72.

6-Propylergolinyl-8α-carboxyhydrazide, 21:

Anhydrous hydrazine (2 mL) and **20** (0.066 g, 0.21 mmol) were heated at 90-100°C for 3.5 hr, then allowed to cool to room temperature. The resulting mixture was diluted with water and extracted with chloroform (3 x 50 mL). The combined extracts were washed with saturated brine, dried and concentrated *in vacuo*. The residue was crystallized from methanol to yield **21** (0.061 g, 92%): 148-150°C (Literature 151-153°C)[27]; MS(FAB) $(M+1)^+$ 313.

8α-Carboxamido-6-propylergoline, 22:

A hydrochloric acid solution (0.2N x 3.5 mL, 0.7 mmol) of **21** (0.061 g, 0.195 mmol) was chilled and treated dropwise with an aqueous solution of sodium nitrite (0.0156g, 0.224 mmol in 1 mL of water) as described above in the preparation of **18.** After treatment of the acyl azide with ammonia in tetrahydrofuran, the crude product was purified by flash chromatography. The product was eluted with 10 mL fractions of 9:1 chloroform/methanol. Fractions 4-6 were combined and concentrated to yield **22** (0.0504 g, 87%); TLC (9:1 chloroform/methanol, $r_f = 0.40$ and 18:6:1 chloroform/methanol acetic acid, $r_f = 0.29$) showed a single component; NMR (pyridine/d_5) δ 0.74 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.38 (2H, m, $CH_3\underline{CH_2}$), 1.68 (1H, dt, J = 5, 12 Hz, 9-H_{ax}), 2.35 (3H, m), 2.65 (2H, m), 2.81 (1H, m), 3.20 (2H, m), 3.35 (2H, m, 4-H_{eq}, 7-H_{eq}), 6.92 (1H, d, J = 7 Hz, 12-H), 7.13 (1H, s, 2-H), 7.18 (1H, m, 13-H), 7.27 (1H, d, J = 9 Hz, 14-H), 7.71 (1H, bs, amide NH), 8.32 (1H, bs, amide NH), and 11.51 ppm (1H, bs, indole NH); MS(FAB) $(M+1)^+$ 298.

HR-MS(FAB) calc'd for $C_{18}H_{23}N_3O$ + H: 298.19967. Found: 298.19184.

8α-Cyano-6-propylergoline, 23:

A pyridine solution (1 mL) of **22** (0.047 g, 0.158 mmol) was treated portionwise with *p*-toluenesulfonyl chloride (0.060 g, 0.316 mmol), then heated at 68-70°C for 1 hr. Ice water was added and the mixture was extracted with chloroform (3 x 25 mL). The extracts were washed with saturated brine, dried, and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluted in 10 mL fractions with ethyl ether). Fractions 3-5 were combined, concentrated, and crystallized from ether to yield **23** (0.010 g, 23%), mp 200-202°C which was a single component by TLC (ether, $r_f = 0.76$). NMR (pyridine/d_5) δ 0.76 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.31 (2H, m, $CH_3\underline{CH_2}$), 1.56 (1H, dt, J = 5, 12 Hz, 9-H_{ax}), 2.27 (1H, dd, J = 3, 12 Hz, 7-H_{ax}), 2.37 (1H, m, 7-H_{eq}), 2.51 (1H, m, NCH_{ax}), 2.64-2.90 (3H, NCH_{eq}, 4-H_{ax}, 9-H_{eq}), 3.03-3.17 (2H, m, 8-H_{eq}), 3.30-3.45 (2H, m, 10-H_{ax}), the assignments for 5-H_{ax} and 4-H_{eq} are ambiguous from the 2D-COSY data, 6.87 (1H, d, J = 5 Hz, 12-H), 7.14 (1H,s, 2-H), 7.21 (1H, m, 13-H), 7.32 (1H, d, J = 7 Hz, 14-H), and 11.32 ppm (1H, bs, indole NH).

HR-MS(FAB) calc'd for $C_{18}H_{21}N_3$ + H: 280.18137. Found: 280.18111.

8β-Carboxy-6-propylergoline, 24a:

Method A:

8β-Carbomethoxy-6-propylergoline (**8**, 0.414 g, 1.33 mmol) was suspended in a 70% aqueous ethanol solution (35 mL) and potassium hydroxide (0.113 g, 2.02 mmol) was added. The mixture was warmed to 50°C until homogeneous, then stirred for 3 hours with stirring. (TLC 9:1 chloroform/methanol indicated that no ester remained). The mixture was concentrated *in vacuo* and the amorphous residue was washed into a beaker with 20 mL of water (pH = 13.3) and the pH was

adjusted to 5.5 by the dropwise addition of acetic acid. The white crystallization was collected by filtration, washed with water, and vacuum dried at 35°C to yield **24a** (0.40 g, 100%): mp 205-7°C (dec). TLC (18:6:1 chloroform/methanol/acetic acid) showed the material to be a single component (r_f = 0.40) migrating less than **8** (r_f = 0.84). NMR (pyridine/d_5) δ 0.78 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.45 (2H, m, $CH_3\underline{CH_2}$), 1.85 (1H, q, J = 12 Hz, 9-H_{ax}), 2.5-2.72 (3H, m, NCH_{ax}, 5-H_{ax}), 2.80 (2H, m, NCH_{eq}, 4-H_{ax}), 3.12 (1H, m, 8-H_{ax}), 3.25 (1H, m, 9-H_{eq}), 3.42 (1H, q_{AB}, J = 4, 11 Hz, 4-H_{eq}), 3.58 (1H, m, 7-H_{eq}), the signals for 7-H_{ax} and 10-H_{ax} are unassigned, 7.03 (1H, d, J = 7 Hz, 12-H), 7.19 (1H, s, 2-H), 7.24 (1H, m, 13-H), 7.34 (1H, d, J = 8 Hz, 14-H), and 11.51 ppm (1H, bs, indole NH); MS(EI) M^+ 298, (M-Et) 269.

Anal. calc'd for $C_{18}H_{22}N_2O_2 \cdot 0.5\ H_2O$: C, 70.33; H, 7.52; and N, 9.11. Found: C, 70.47; H, 7.41; and N, 9.35.

Method B:

A methanolic sodium hydroxide (1.23 mL x 5N sodium hydroxide in 10 mL of methanol) solution of **17a** (0.049 g, 0.176 mmol) was stirred under reflux for 48 hrs (no starting material remaining by TLC 18:6:1 chloroform/methanol/acetic acid). The mixture was allowed to cool to room temperature, then concentrated *in vacuo*. The residue was redissolved in water. The pH was adjusted to 5.5 by the dropwise addition of acetic acid, whereupon the product crystallized, to yield 0.036 g (69%) of **24a** which was identical to the **24a** prepared by Method A (*vida supra*).

8β-Carboxy-6-propylergoline-17-[^{14}C], 24b:

To a mixture of 5N sodium hydroxide (18.5 mL, 92.25 mmol) and methanol (50 mL) was added **17b** (0.742 g, 2.64 mmol) and the resulting mixture was stirred under gentle reflux for 48 hrs, then allowed to cool to room temperature. TLC (9:1 chloroform/methanol) showed that all of the nitrile **17b** was consumed and was all converted to **24b** (18:6:1 chloroform/methanol/acetic acid). The reaction was worked up as described above for **24a** to yield 0.680 g (86.4%) of **24b**, which was mixed with 0.380 g of **24a** and dissolved in 7.5 mL of 1N sodium hydroxide. Charcoal (0.050 g) was added and the mixture was stirred at room temperature for 10 min, then filtered and acidified to pH 5.5 with acetic acid. After crystallization, the mixture was chilled to 0°C and filtered. The solid was washed with water and vacuum dried at 40°C for 16 hrs, to yield **24b** (0.896 g, 84.5%). TLC (18:6:1 chloroform/methanol/acetic acid) showed **24b** to be one spot material co-migrating with **24a**; MS(DCI) $(M+1)^+$ 299/301.

8β-Hydroxymethyl-6-propylergoline, 25a:

Borane-tetrahydrofuran (1.13 mL x 1M, 1.13 mmol) was added to a stirred suspension of **24a** (0.168 g, 0.564 mmol) in tetrahydrofuran (5 mL) under argon. After stirring for 6 hrs, 1 mL of additional borane-tetrahydrofuran (1 mmol) was added and stirring was continued overnight. The excess borane was quenched by the dropwise addition of methanol (5 mL) and the resulting mixture was heated at 50°C for 4 hrs. The mixture was then concentrated to a white amorphous foam,

which was triturated with ether to crystallize. The white solid was collected by filtration, washed with cold ether and dried *in vacuo* to yield **25a** (0.109 g, 68%): mp 174-6°C; NMR (pyridine/d_5) δ 0.76 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.26 (1H, q, J = 12 Hz, 9-H_{ax}), 1.43 (2H, m, $CH_3\underline{CH_2}$), 2.13 (1H, t, J = 6 Hz, 7-H_{ax}), 2.30 (1H, m, 8-H_{ax}), 2.54 (2H, m, NCH_{ax}, 5-H_{ax}), 2.80 (3H, m, NCH_{eq}, 4-H_{ax}, 9-H_{eq}), 3.09 (1H, m, 10-H_{ax}), 3.45 (2H, m, 4-H_{eq}, 7-H_{eq}), 3.75 and 3.87 (2H, m, collapses to dd in D_2O, $HOCH_2$), 6.09 (1H, bs, OH), 7.05 (1H, d, J = 7 Hz, 12-H), 7.21 (1H, s, 2-H), 7.28 (1H, m, 13-H), 7.35 (1H, d, J = 9 Hz, 14-H), and 11.50 ppm (1H, bs, indole NH).
TLC (18:6:1 chloroform/methanol/acetic acid) showed the material to be pure and was identical to that prepared by the sodium borohydride reduction ($r_f = 0.53$).[21]

Anal. calc d for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; and N, 9.85. Found: C, 75.85; H, 8.33; and N, 9.72.

8β-Hydroxymethyl-6-propylergoline-17-[^{14}C], 25b:

Borane-tetrahydrofuran (4.5 mL x 1M, 4.5 mmol) was added to a suspension of **24b** (0.896 g, 3.01 mmol) in tetrahydrofuran (25 mL) under argon. Stirring was continued as the solid slowly dissolved and eventually re-precipitated. After stirring for 4 hrs, an additional 3 mL (3 mmol) of borane-tetrahydrofuran was added and stirring was continued overnight.

There was still unreacted **24b** remaining (TLC, 18:6:1 chloroform/methanol/acetic acid) and an additional 5 mL (5 mmol) of borane-tetrahydrofuran was added. After stirring an additional 2 hrs, the solids dissolved and TLC indicated that the mixture was free of **24b**). Methanol was added and the mixture was heated at 55°C for 2 hrs, then allowed to cool to room temperature.

The mixture was worked up as described for **25a** (*vida supra*) to yield **25b** (0.785 g, 92%). TLC (18:6:1 chcloroform/methanol/acetic acid) showed that the material was a single material co-eluting with **25a**. MS(DCI) $(M+1)^+$ 285/287.

8β-[(Mesyloxy)methyl]-6-propylergoline, 26a:

A pyridine solution (2 mL) of **25a** (0.109 g, 0.384 mmol), cooled to 0°C under argon was treated dropwise with methanesulfonyl chloride (0.090 mL, 1.15 mmol), then stirred for 2.5 hrs while allowing to warm to room temperature. The reaction mixture was added dropwise to 10 mL of water; the pH of the resulting mixture was adjusted to 9 with ammonium hydroxide. A crystalline precipitate formed and the mixture was stirred for 1 hr, then filtered. The solid was washed with water and dried under vacuum at room temperature for 16 hrs to yield **26a** (0.109g, 78%). TLC (9:1 chloroform/methanol) showed a single component ($r_f = 0.58$), different from starting material ($r_f = 0.18$); MS(DCI) M^+ 362, (M-Et) 333.

8β-[(Mesyloxy)methyl]-6-propylergoline-17-[^{14}C], 26b:

Methanesulfonyl chloride (1.9 mL, 24.87 mmol) was added dropwise to a pyridine solution (40

mL) of **25a** (1.57 g, 5.53 mmol) and **25b** (0.7845 g, 2.76 mmol) which was cooled to 0°C under argon. Stirring was continued for 2.5 hrs and the mixture was worked up as described above for **26a**, to yield 2.52 g (84%) of **26b**: TLC (9:1 chloroform/methanol) showed **26b** to co-migrate as a single spot with **26a**; MS(DCI) $(M+1)^+$ 363.

8β-[(Methylthio)methyl]-6-propylergoline, 2a:

To a suspension of sodium hydride (hexane washed from 60% mineral oil dispersion, 0.1 g, 2.5 mmol) in 1 mL of dimethylformamide, was added 3.5 mL of 1M methanethiol in dimethylformamide under argon. Subsequently, a dimethylformamide (9 mL) solution of **26a** (0.090 g, 0.25 mmol)was added dropwise and the resulting solution was stirred at room temperature overnight. The mixture was poured into water (35 mL) and extracted with ethyl acetate (2 x 25 mL). The organic extracts were washed with water (3 x 10 mL), dried, and concentrated to a slightly yellow solid. The solid was redissolved in ethyl acetate, treated with charcoal, filtered, and concentrated. The resulting white solid was partially dissolved in 5 mL of warm methanol and treated with 0.0175 mL (0.275 mmol) of methanesulfonic acid. The mixture was heated to reflux and allowed to cool. Addition of ether to the insipient cloud point induced crystallization. After chilling to 5°C, the white solid was collected by filtration, washed with ether, and dried at 40°C to yield **2a** (0.063 g, 61.5%): mp 255-7°C(dec); ^{1}H-NMR (DMSO/d_6) δ 0.99 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.37 (1H, q, J = 12 Hz, 9-H_{ax}) 1.72 (2H, m, $CH_3\underline{CH_2}$), 2.15 (3H, s, SCH_3), 2.31 (3H, s, $CH_3SO_3^-$), 2.38 (1H, m, 8-H_{ax}), 2.52 (1H, dd, J = 7.3, 18.9 Hz, $CH_3S\underline{CH}_{ax}$), 2.68 (1H, dd, J = 13.7, 18.9 Hz, $CH_3S\underline{CH}_{eq}$), 2.80 (1H, m, 9-H_{eq}), 2.88 (1H, m, 4-H_{ax}), 3.00 (1H, m, 7-H_{ax}), 3.32 (2H, m, NCH_2), 3.35 (1H, m, 10-H_{ax}), 3.38 (1H, m, 5-H_{ax}), 3.56 (1H, m, 4-H_{eq}), 3.66 (1H, m, 7-H_{eq}), 6.87 (1H, d, J = 7 Hz, H-12), 7.09 (1H, m, 13-H), 7.10 (1H, s, 2-H), 7.22 (1H, d, J = 9 Hz, 14-H), 9.65 (1H, bs, 6-NH^+), and 10.85 ppm (1H, bs, indole NH); ^{13}C-NMR (DMSO/d_6) δ 10.56 ($\underline{CH_3}CH_2$), 15.26 (SCH_3), 15.59 ($CH_3\underline{CH_2}$), 23.95 (C-4), 31.32 (C-9), 32.74 (C-8), 36.50 (CH_2S), 38.30 (C-10), 39.73 ($CH_3SO_3^-$), 53.86 (NCH_2), 55.60 (C-7), 63.87 (C-5), 107.12 (C-3), 109.54 (C-14), 112.54 (C-12), 119.46 (C-2), 122.30 (C-13), 125.25 (C-16), 129.58 (C-11), and 133.11 ppm (C-15); MS(DCI), M^+ 314, (M-29) 285.

TLC (9:1 chloroform/methanol) showed a major component which co-migrated with authentic pergolide mesylate[21] (r_f = 0.57) with a very minor impurity at a lower r_f (0.42).

8β-[(Methylthio)methyl]-6-propylergoline-17-[^{14}C], 2b:

Methanethiol (1M in dimethylformamide, 98 mL, 98 mmol) was added dropwise to a stirred mixture of sodium hydride (hexane washed from a 60% mineral oil dispersion, 2.8 g, 70 mmol) under argon at 0-5°C. After stirring for 0.5 hr, while allowing to warm to room temperature, a dimethylformamide solution (40 mL) of **26b** (2.52 g, 6.96 mmol) was added dropwise over 30-35 min. The resulting solution was stirred overnight at room temperature. TLC (63:27:7:2 chloroform/ acetone/methanol/ammonium hydroxide) showed that the reaction was complete with no starting material remaining.

The reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (3 x 450 mL). The combined extracts were washed with water (2 x 250 mL), dried, and concentrated *in vacuo* to yield **2b**(as the free base) as a semi-white crystalline residue. The solid was triturated with ether and collected by filtration (1.914 g, 87.6%). To a suspension of the free base was slowly added methanesulfonic acid (0.644 g, 0.435 mL). The resulting mixture was refluxed until dissolved, then allowed to cool to room temperature (the mesylate salt subsequently crystallized). After stirring at -10°C for 0.5 hr, filtration yielded **2b**. The solid was washed with cold methanol and dried under vacuum to yield 1.932 g (77%) of **2b**. Carrier pergolide mesylate (0.837 g) was mixed with **2b** and re-crystallized from methanol (40 mL). The solution was filtered through a glass wool plug and allowed to crystallize. The mixture was chilled to -10°C, stirred for 1 hr, and filtered. The white solid was washed with cold methanol and dried at 40°C under vacuum to yield **2b** (2.220 g, 80%); specific activity 15.7 μCi/mg (6.44 mCi/mmol); MS(DCI) $(M+1)^+$ 315, (M-29) 285. The radiochemical purity by TLC/autoradiography was a) 63:27:7:2 chloroform/ acetone/methanol ammonium hydroxide 99.3% b) 10:1 toluene/ethanol 97.7% c) 9:1 chloroform/ methanol 97.7%.

8α-Hydroxymethyl-6-propylergoline, 27:

To an anhydrous tetrahydrofuran solution (15 mL) of **20** (0.24 g, 0.77 mmol) was added lithium aluminum hydride (0.24 g). The resulting mixture was stirred under reflux for 16 hrs. After cooling to room temperature, the excess lithium aluminum hydride was destroyed by the careful addition of ethyl acetate. The crude product was purified by flash chromatography over silica gel, eluting with 10 mL fractions of 9:1 chloroform/methanol. Fractions 7-12 were concentrated to yield **27** (0.072 g, 33%). TLC (9:1 chloroform/methanol, r_f = 0.296); NMR (pyridine/d_5) δ 0.72 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.38 (2H, m, $CH_3\underline{CH_2}$), 1.68 (1H, dt, J = 5, 12 Hz, 9-H_{ax}), 2.15 (1H, m, 8-H_{eq}), 2.40 (3H, m), 2.71 (2H, m), 2.90 (1H, m), 3.23 (2H, m, 7-H_{eq}), 3.40 (1H, dd, J = 3.6, 7.5 Hz, 4-H_{eq}), 4.12 (1H, m, collapses to dd in D_2O, HO$\underline{CH}_{ax}$), 4.23 (1H, m, collapses to dd in D_2O, HO$\underline{CH}_{eq}$), 4.95 (1H, s, OH), 7.00 (1H, d, J = 7 Hz, H-12), 7.17 (1H, s, 2-H), 7.21 (1H, m, 13-H), 7.32 (1H, d, J = 9 Hz, 14-H), and 11.52 ppm (1H, bs, indole NH).
HR-MS(FAB) calc'd for $C_{18}H_{24}N_2O$ + H: 285.19669. Found: 285.19604.

8α-[(Mesyloxy)methyl]-6-propylergoline, 28:

8α-Hydroxymethyl-6-propylergoline (**27,** 0.072 g, 0.254 mmol) was dissolved in pyridine (2 mL) and treated dropwise with methanesulfonyl chloride (0.072 mL). After stirring at room temperature for 2.5 hrs, the mixture was diluted with water and made basic with ammonium hydroxide, then extracted with ethyl acetate (2 x 25 mL). The combined extracts were washed with water, brine, then dried, and concentrated to yield **28** in quantitative yield. DCI-MS, $(M+1)^+$ 363.

A small sample was crystallized from methanol to obtain a sample for microanalysis; mp 95°C(dec).

Anal. calc'd for $C_{19}H_{26}N_2O_3S$: C, 62.96; H, 7.23; N, 7.73; and S, 8.85. Found: C, 63.82; H, 7.24; N, 8.00; and S, 8.81.

8α-[(Methylthio)methyl]-6-propylergoline, 29:

A dimethylformamide solution (1 mL) of **28** (0.254 mmol) was added to a stirred solution of sodium methylmercaptide (prepared by the addition of a 1M dimethylformamide solution of methanethiol, 4 mL, to a suspension of NaH, 0.102 g, 0.254 mmol) in 2 mL of dimethylformamide. Stirring was continued for 2 hrs, and the reaction mixture was worked up as described previously for **2a** (*vida supra*)and crystallization from methanol/ether yielded **29** (0.0187 g, 19%) as a slightly violet colored solid: mp 206-8°C(dec). TLC (9:1 chloroform/methanol r_f = 0.88, 10:1 toluene/ethanol r_f = 0.37) indicated that **29** was a single component, migrating differently from **2a** (the β-isomer); NMR (pyridine/d_5) δ 0.77 (3H, t, J = 7.4 Hz, $\underline{CH_3}CH_2$), 1.63 (2H, m, $CH_3\underline{CH_2}$), 1.72 (1H, dt, J = 5, 12 Hz, 9-H_{ax}), 2.05 (3H, s, SCH_3), 2.18 (1H, m, 10-H_{ax}), 2.71 (1H, m, 8-H_{eq}), 2.85-3.05 (5H, m, $CH_3S\underline{CH_2}$, $CH_3SO_3^-$), 3.08 (1H, m, NCH_{ax}), 3.20 (1H, m, NCH_{eq}), 3.25-3.40 (2H, m, 5-H_{ax}, 7-H_{ax}), 3.45 (2H, m, 4-H_{ax}, 9-H_{eq}), 3.56 (2H, m, 4-H_{eq}, 7-H_{eq}), 6.72 (1H, bs, 6-NH^+), 7.09 (1H, d, J = 7 Hz, H-12), 7.16 (1H, s, 2-H), 7.19 (1H, m, 13-H), 7.34 (1H, d, J = 8 Hz, 14-H), and 11.65 ppm (1H, bs, indole NH).

Anal. calc'd for $C_{20}H_{30}N_2O_3S_2$: C, 58.50; H, 7.36; N, 6.82; and S, 15.62. Found: C, 58.75; H, 7.59; N, 6.67; and S, 15.37.

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ACKNOWLEDGEMENT

The authors are grateful to Mr. David Hunden of the Chemical Preparations Laboratory for the preparation of large quantities of 8β-carbomethoxy-6-propylergoline (**8**) for use in these studies. We are also especially grateful to Mr. Douglas O'Bannon for conducting the 2D-COSY NMR (QE-300) experiments. Our appreciation also should be expressed to members of the staff of the Physical Chemical Research Department for their support of our work.