Dehydrogenation with Benzeneseleninic Anhydride in the Total Synthesis of Ergot Alkaloids[1,2]

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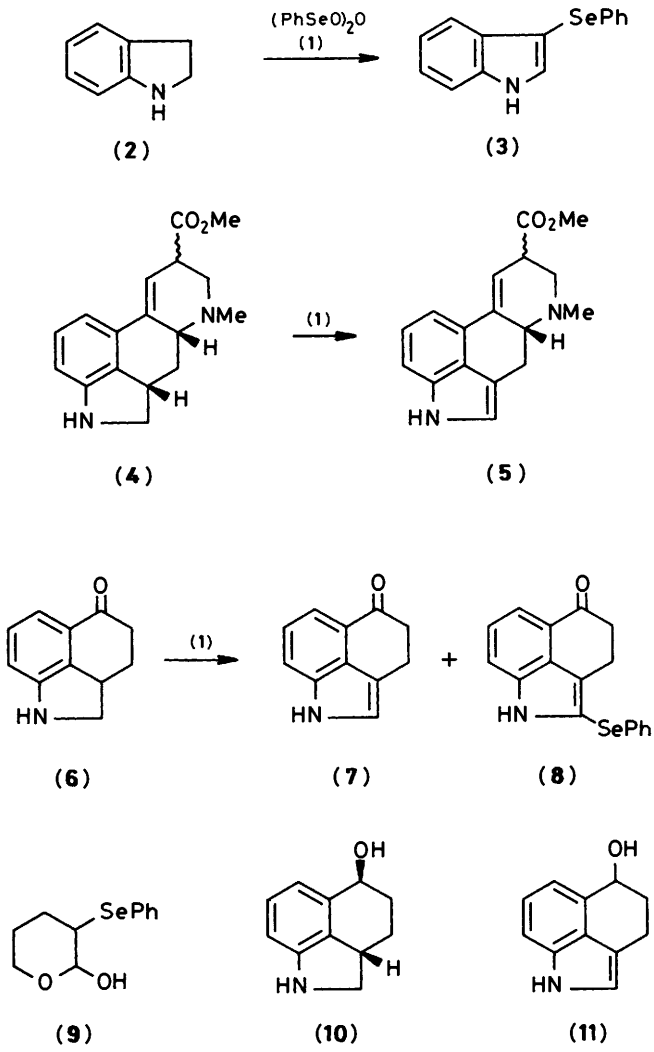
Investigation of the dehydrogenative conversion of indolines into indoles with benzeneseleninic anhydride (**1**) resulted in the development of an efficient standardised procedure, which was successfully applied to the final steps in first total synthesis of (±)-lysergol (**18**), (±)-isolysergol (**27**), and (±)-elymoclavine (**29**).

The total synthesis of ergot alkaloids remains a major topic of current importance and interest.[3] Often the route adopted in the syntheses of ergot alkaloids involves finally the dehydrogenation of an indoline moiety into the corresponding indole. In the previous total syntheses of ergot alkaloids, manganese dioxide[4] or disodium arsenate–Raney nickel[5] was used for this dehydrogenation. However the yields were often mediocre. In view of the necessity of establishing a practical procedure, an extensive investigation with benzeneseleninic anhydride (**1**) has been carried out on the tricyclic compounds (**6**) and (**10**) and has resulted in the development of an efficient standardised procedure for the conversion of indolines to indoles, which was then successfully applied to the total synthesis of (±)-lysergol (**18**), (±)-isolysergol (**27**), and (±)-elymoclavine (**29**).

Establishment of an Improved Procedure for the Conversion of Indolines into Indoles.—The use of benzeneseleninic anhydride (**1**) for the dehydrogenation of secondary amines was thoroughly investigated by Barton *et al.*,[6] who reported that the 3-substituted indolines gave the corresponding indoles in good yields, while indoline itself (**2**) gave the 3-phenylselenylated indole (**3**) in quantitative yield. As reported previously,[7] we also applied this dehydrogenation to the ester (**4**), but the yield of methyl (±)-lysergate (**5**) did not exceed 60%. Thus it seemed that benzeneseleninic anhydride (**1**) was an effective dehydrogenation reagent but that a Se^{II} species, such as benzeneselenenic acid which would be formed during the reaction, was responsible for these unsatisfactory results. Thus we chose the benz[*cd*]indoline (**6**) as a model compound for the reinvestigation of the reaction aiming at establishment of a convenient procedure for the dehydrogenation reaction applicable to the total synthesis of ergot alkaloids. The results obtained are shown in the Table.

The reaction of the benz[*cd*]indoline (**6**) with 0.5 mol equiv. of benzeneseleninic anhydride (**1**) in tetrahydrofuran (THF) at room temperature was carried out to afford Uhle's ketone (**7**)[8] in 57% yield together with small amount of the starting compound (**6**) after 2 h. Similar treatment at 50–60 °C for 5.5 h decreased the yield of (**7**) to 42%, but increased the yield of the 2-selenide (**8**) to 20%. The structure of (**8**) was established from its spectral data [*m/z* 325 (M^+) and 327 ($M^+ + 2$)]; the formation of (**8**) appears to be the result of benzeneselenenation on the indole (**7**) with a Se^{II} species as in the case of indoline (**2**). Clearly the addition of a sacrificial enamine as scavenger to trap the Se^{II} reagent would be expected to increase the yield of the desired indole drastically. Indole itself was the compound of choice for preferential selenenation over the more complicated indole derivatives present in the synthetic reaction mixture. The



results shown in the Table demonstrate that this expectation is correct. In the presence of indole, only Uhle's ketone (**7**) and the 3-selenide (**3**) were isolated in almost quantitative yields respectively as shown in entries 3–6. Reaction at 50–60 °C in

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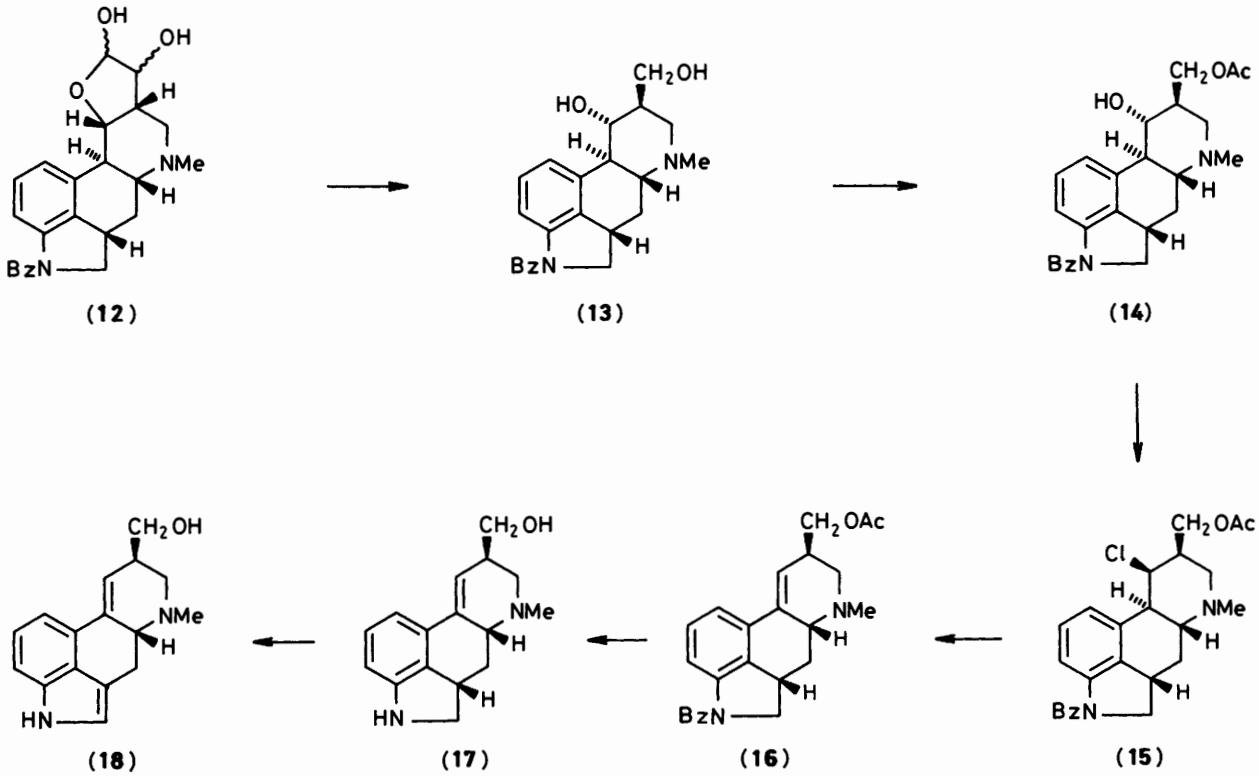
Table. Dehydrogenation of the benz[*cd*]indoline (**6**) with benzeneseleninic anhydride (**1**)

Entry	Conditions: Scavenger (mol equiv.)	Temp. (°C)	Time (h)	Products, % yield: (7)	(8)	(3)	(9)
1	None	R.t.[a]	2	57			
2	None	50–60	5.5	42	20		
3	Indole (1)	R.t.	23	90		Quant.	
4	Indole (2)	R.t.	23	95		Quant.	
5	Indole (3)	R.t.	23	92		Quant.	
6	Indole (3)	50–60	2	98		Quant.	
7	Dihydropyran (3)	R.t.	23	96	3		25
8	Dihydropyran (3)	50–60	3	91	4		34

[a] R.t. = room temperature.

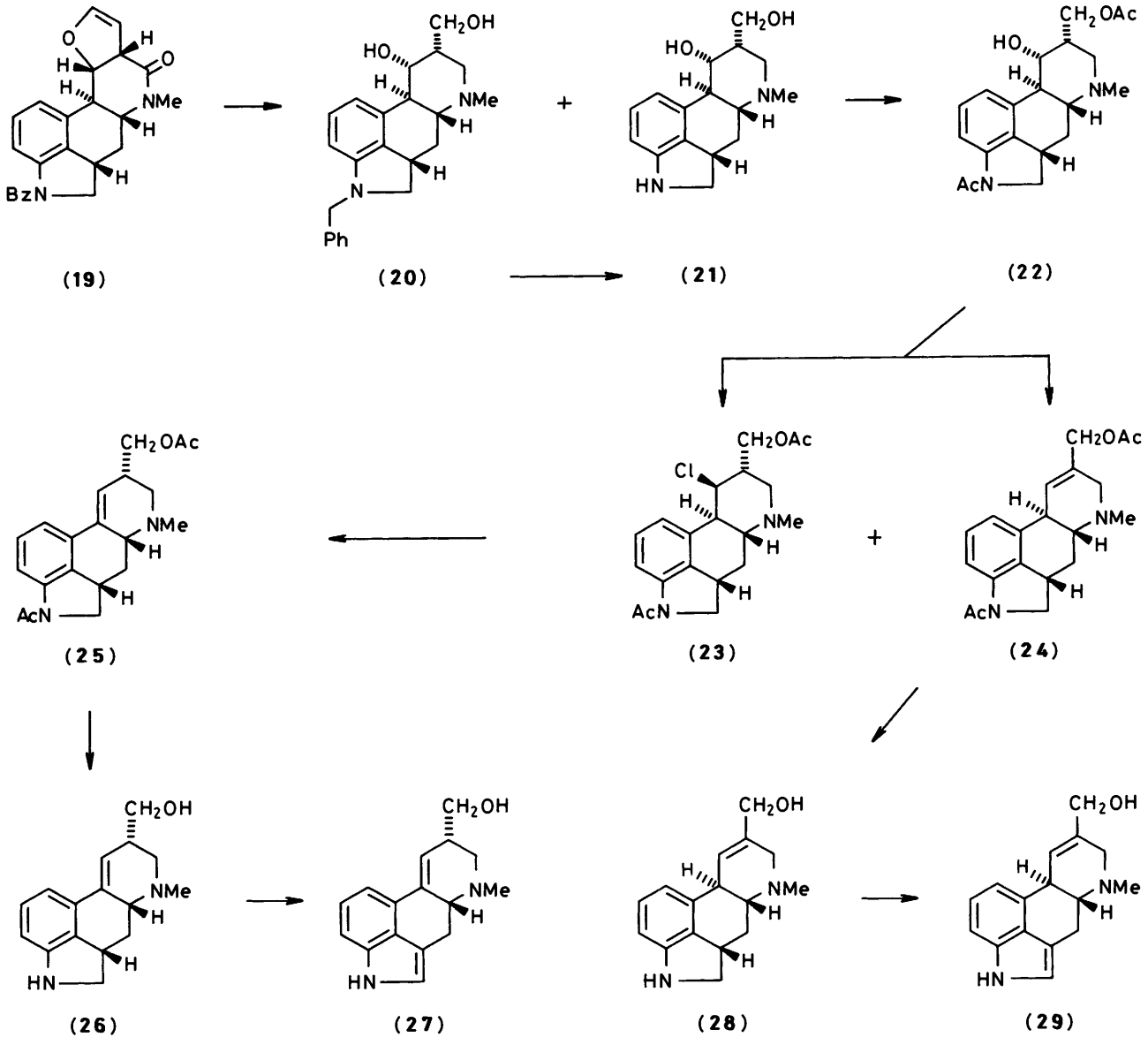


Bz = PhCO–

the presence of 3 mol equiv. of indole gave the best result by shortening the reaction time to 2 h as shown in entry 6. Dihydropyran, which is known to be an effective reagent for trapping sulphenic acid[9] can equally well be used as scavenger in this case, but it is slightly less efficient than indole and gives a trace amount of (**8**) and 25–34% of the 3-selenide (**9**) as shown in entries 7 and 8.

Similarly, satisfactory results were also obtained using the indoline (**10**) which has a hydroxy group at the benzylic position. At room temperature with (**1**) in the presence of 3 mol equiv. of indole, a 96% yield of (**11**) was obtained after 23 h with quantitative formation of (**3**) along with a small amount (1.7%) of (**7**). Similarly at 50–60 °C in 2 h the yield of (**11**) decreased to 64%, while 13% of (**7**) was obtained. It has been reported that the dehydrogenation of (**10**) with other agents such as manganese dioxide[10] gave exclusively Uhle's ketone (**7**) as a result of concomitant oxidation of the hydroxy group. Although the relatively facile oxidation of benzylic alcohols by benzeneseleninic anhydride (**1**) is known[11] to afford the corresponding ketone, oxidation of (**10**) with (**1**) at room temperature proceeded selectively to form the indole (**11**) as the major product. This method was therefore applied to the dehydrogenation of (**4**) to give methyl (±)-lysergate (**5**) in 88% yield. Thus we have succeeded in the development of an efficient standardised procedure for dehydrogenation of indolines into indoles, and the first total syntheses of (±)-lysergol (**18**), (±)-isolysergol (**27**), and (±)-elymoclavine (**29**) were completed using this dehydrogenation procedure in the final step as described in the next section.

Total Synthesis of (±)-*Lysergol* (**18**).—According to the synthetic route reported previously[12] and also by applying the above oxidation, the total synthesis of the ergot alkaloid (±)-lysergol (**18**) was carried out starting from the key intermediate (**12**). The glycol (**12**) had been prepared from the photocyclised lactam (**19**) and successfully used as the starting compound in the total synthesis of (±)-lysergic acid.[7] Glycol cleavage of (**12**) with sodium metaperiodate followed



by isomerisation of the resulting aldehyde by treatment with sodium carbonate, and sodium borohydride reduction of the 8β-aldehyde gave the 8β-hydroxymethyl compound (**13**) in 52% yield, which was then acetylated in pyridine with ice-cooling to give the monoacetate (**14**) in 91% yield. The stereochemistry of the monoacetate (**14**) was deduced from its ^{1}H NMR spectrum [δ 3.56 (td, *J* 10 and 5 Hz, 9-H) and 2.89 (t, *J* 10 Hz, 10-H)]. Treatment of the monoacetate (**14**) with thionyl chloride in benzene at 50 °C for 1 h afforded the 9β-chloride (**15**) in 72% yield, whose stereochemistry, particularly the 9β-configuration of the chloride, was confirmed from the ^{1}H NMR spectrum [δ 5.06 (br s, 9-H) and 3.14 (br d, *J* 10 Hz, 10-H)]. Treatment of the 9β-chloride (**15**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene under reflux for 2 h yielded the unsaturated compound (**16**) in 97% yield which was then hydrolysed with 10% hydrochloric acid under reflux for 1 h to yield the 1,2-dihydrolysergol (**17**) in 94% yield. In the ^{1}H NMR spectrum, the presence of an olefinic proton signal at δ 6.37 as a broad singlet firmly established its structure (**17**).

Conversion of the indoline (**17**) into the alkaloid (**18**) was carried out by applying the procedure established. Treatment of the indoline (**17**) with 0.5 mol equiv. of benzeneseleninic anhydride (**1**) in the presence of 3 mol equiv. of indole at 40 °C in THF for 1.5 h gave (±)-lysergol (**18**) in 97% yield. The comparison of the ^{1}H NMR and IR spectra, and TLC of the synthetic compound (**18**) with those of natural lysergol[13] established their identity. Thus, we completed the first total synthesis of (±)-lysergol.

Total Synthesis of (±)-*Isolysergol* (**27**) *and* (±)-*Elymoclavine* (**29**).—According to the previous synthetic route,[12] the total synthesis of (±)-lysergol (**27**) and (±)-elymoclavine (**29**) was carried out starting from the 8α-hydroxymethyl compound (**21**). Oxidative ring opening of the dihydrofuran ring of the photocyclised lactam (**19**) was achieved first by ozonolysis followed by lithium aluminium hydride reduction to give the *N*-benzyl-1,3-diol (**20**) in 56% yield and the 1,3-diol (**21**) in 5% yield. The *N*-benzyl-1,3-diol (**20**) was treated with palladium on carbon in a stream of hydrogen, hydrogenolysis giving the debenzylated amine (**21**) in 90% yield, which was acetylated in pyridine with ice-cooling to afford the corresponding *N*,*O*-diacetyl derivative (**22**) in 89% yield. The stereochemistry of (**22**) was deduced from its ^{1}H NMR spectrum [δ 4.01 (dd, *J* 10 and 5 Hz, 9-H), 2.84 (t, *J* 10 Hz, 10-H), and 1.39 (q, *J* 12 Hz, 4-H$_{ax}$)].

Treatment of this *N,O*-diacetyl derivative (**22**) with thionyl chloride in benzene under reflux for 1 h afforded a mixture of the 9β-chloride (**23**) and the dehydrated compound (**24**) which was separated by preparative thin layer chromatography (PLC) to give (**23**) and (**24**) in 65 and 18% yield respectively. The structures of these products were firmly established from the ^{1}H NMR signals at δ 4.96 (br s, 9-H) for (**23**) and at δ 6.31 (br s, 9-H) for the other product (**24**). Treatment of the 9β-chloride (**23**) with DBU in benzene under reflux for 9 h afforded the unsaturated acetate (**25**) in 97% yield, which was characterised by the broad ^{1}H NMR signal ($w_{\frac{1}{2}}$ 10 Hz) at δ 6.38 assignable to the olefinic proton. Removal of the two acetyl groups on both nitrogen and oxygen in (**25**) and (**24**) was readily achieved by treatment with a small amount of hydrochloric acid in methanol to give (**26**) and (**28**) in 94 and 66% yields respectively. The ^{1}H NMR spectrum of the amine (**26**) exhibited signals at δ 6.41 (br d, *J* 5 Hz, 9-H) and 1.34 (q, *J* 12 Hz, 4-H$_{ax}$) and that of the amine (**28**) at δ 6.30 (br s, 9-H) and 1.55 (q, *J* 12 Hz, 4-H$_{ax}$) respectively. The indolines (**26**) and (**28**) thus obtained were dehydrogenated by the procedure established [0.5 mol equiv. of benzenenseleninic anhydride (**1**) and 3 mol equiv. of indole in THF at 40 °C for 1.5 h] to give (±)-isolysergol (**27**) and (±)-elymoclavine (**29**) in 95 and 94% yields respectively. Despite the presence of a reactive allylic hydroxy group in the amine (**28**), no other product was detected. This result clearly shows the superiority of this newly developed procedure.

The final products (**27**) and (**29**) were found to be completely identical by direct comparison with authentic samples of the natural alkaloids isolysergol[14] and elymoclavine.[15] Thus we have completed the first total synthesis of two ergot alkaloids.

Experimental

M.p.s were measured on a micro hot-stage apparatus (Yanagimoto) and are uncorrected. ^{1}H NMR spectra were measured with Varian XL-200 (200 MHz) instrument for solutions in deuteriochloroform unless otherwise stated using tetramethylsilane as an internal reference, and IR spectra with Hitachi 215 and 270-30 machines for solutions in chloroform unless otherwise stated. Mass spectra were taken with Hitachi M-80 spectrometer. PLC was carried out on precoated plates of silica gel (Kieselgel 60F$_{254}$, Merck). Reactions were performed under nitrogen atmosphere. Extracts from the reaction mixture were washed with water, dried over anhydrous sodium sulphate, and evaporated under reduced pressure. Ether refers to diethyl ether.

1,2,2a,3-*Tetrahydrobenz*[cd]*indol*-5(4H)-*one* (**6**).—A solution of *N*-benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indol-5(4*H*)-one[5] (2.5 g) in methanol (180 ml) containing conc. hydrochloric acid (18 ml) was refluxed for 9 h. The reaction mixture was concentrated to a small volume and then diluted with water, and washed with benzene. The aqueous layer was made alkaline with 10% aqueous sodium carbonate and extracted with benzene. The extract was washed, dried, and evaporated to give a solid, which was recrystallised from methanol to afford the *indolone* (**6**) (1.48 g, 95%) as colourless plates, m.p. 126–127 °C; ν$_{max}$ 3 330 (NH) and 1 670 cm^{-1} (CO); δ 7.26 (1 H, d, *J* 8 Hz, 6-H), 7.16 (1 H, t, *J* 8 Hz, 7-H), 6.82 (1 H, d, *J* 8 Hz, 8-H), 3.88 (1 H, br, NH), 3.84 (1 H, t, *J* 8 Hz, 2-H$_β$), 3.48 (1 H, m, 2a-H), 3.27 (1 H, dd, *J* 12 and 8 Hz, 2-H$_α$), 2.76 (1 H, ddd, *J* 17, 5, and 2.5 Hz, 4-H$_{eq}$), 2.60 (1 H, ddd, *J* 17, 13, and 5 Hz, 4-H$_{ax}$), 2.38 (1 H, dtd, *J* 12, 5, and 2.5 Hz, 3-H$_{eq}$), and 1.96 (1 H, dtd, *J* 13, 12, and 5 Hz, 3-H$_{ax}$) (Found: C, 76.0; H, 6.2; N, 8.1. C$_{11}$H$_{11}$NO requires C, 76.3; H, 6.4; N, 8.1%).

(2aα,5α)-1,2,2a,3,4,5-*Hexahydrobenz*[cd]*indol*-5-*ol* (**10**).—Following the procedure given for (**6**), hydrolysis of *N*-benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-5-ol[16] (1.4 g) in methanol (100 ml) containing conc. hydrochloric acid (10 ml) gave the *indolol* (**10**) (0.76 g, 88%) as colourless needles, m.p. 212–215 °C (from methanol); ν$_{max}$ 3 250 cm^{-1} (OH and NH); δ(CDCl$_3$–CD$_3$OD) 7.08 (1 H, t, *J* 8 Hz, 7-H), 6.94 (1 H, d, *J* 8 Hz, 6-H), 6.61 (1 H, d, *J* 8 Hz, 8-H), 4.85 (1 H, dd, *J* 10 and 7 Hz, 5-H), 3.62 (1 H, br s, 2-H$_β$), 3.22–3.00 (2 H, m, 2-H$_α$ and 2a-H), 2.38 (1 H, m, 4-H$_{eq}$), 2.14 (1 H, m, 3-H$_{eq}$), 1.74 (1 H, ddd, *J* 13, 10, and 3 Hz, 4-H$_{ax}$), and 1.53 (1 H, m, 3-H$_{ax}$) (Found: C, 75.6; H, 7.5; N, 7.9. C$_{11}$H$_{13}$NO requires C, 75.4; H, 7.5; N, 8.0%).

General Procedure for Dehydrogenation of (**6**) *with Benzeneseleninic Anhydride* (**1**).—A mixture of the indoline (**6**) (30 mg, 0.17 mmol) and benzeneseleninic anhydride (**1**) (34.7 mg, 0.5 mol equiv.) in tetrahydrofuran (THF) (3 ml) was treated in the presence of indole or dihydropyran (0–3 mol equiv.) at the temperature and time described for each particular entry in the Table. The solvent was partially evaporated off, and 10% aqueous sodium carbonate was added to the residue. The mixture was extracted with ethyl acetate. The extract was washed, dried, and evaporated to give a residue which was purified by PLC (n-hexane–ether, 2:8). The following three products were isolated: 1,3-dihydrobenz[*cd*]indol-5(4*H*)-one (Uhle's ketone) (**7**), yellow needles, m.p. 162–165 °C (from n-hexane–ether) (lit.,[8] 159–162 °C); ν$_{max}$ 3 490 (NH) and 1 675 cm^{-1} (CO); δ 8.38 (1 H, br s, NH), 7.65 (1 H, d, *J* 8 Hz, 6-H), 7.59 (1 H, d, *J* 8 Hz, 8-H), 7.32 (1 H, t, *J* 8 Hz, 7-H), 7.14 (1 H, br s, 2-H), 3.29 (2 H, br t, *J* 7 Hz, 4-H$_2$), and 2.96 (2 H, br t, *J* 7 Hz, 3-H$_2$). 1,3-*Dihydro*-2-(*phenylseleno*)*benz*[cd]*indol*-5(4H)-*one* (**8**), pale brown crystals, m.p. 190–192 °C (from chloroform–methanol); ν$_{max}$ 3 480 (NH) and 1 680 cm^{-1} (CO); δ 8.24 (1 H, br s, NH), 7.64 (1 H, br d, *J* 8 Hz, 6-H), 7.52 (1 H, br d, *J* 8 Hz, 8-H), 7.36–7.22 (6 H, m, ArH), 3.26 (2 H, t, *J* 7 Hz, 4-H$_2$), and 2.96 (2 H, t, *J* 7 Hz, 3-H$_2$); *m/z* 325 (*M*$^+$) and 327 (*M*$^+$ + 2) (Found: C, 62.5; H, 3.7; N, 4.2. C$_{17}$H$_{13}$NOSe requires C, 62.6; H, 4.0; N, 4.3%). 3,4,5,6-*Tetrahydro*-2-*hydroxy*-3-*phenylseleno*-2H-*pyran* (**9**), colourless oil; ν$_{max}$ 3 600 and 3 400 cm^{-1} (OH); δ 7.72–7.26 (5 H, m, ArH), 4.95 (2/3 H, dd, *J* 7 and 2 Hz, 2-H), 4.82 (1/3 H, dd, *J* 7 and 5 Hz, 2-H), 4.03 (1 H, m, 6-H), 3.64–3.46 (5/3 H, m, 6-H and OH), 3.44–3.32 (1 H, m, 3-H and OH), 3.06 (1/3 H, m, 3-H), 2.22 (1 H, m, 4-H), 2.08 (1 H, m, 4-H), and 1.86–1.50 (2 H, m, 5-H$_2$) (Found: *M*$^+$, 256.016. C$_{11}$H$_{14}$O$_2$^{78}Se requires *M*, 256.017) (Found: *M*$^+$ + 2, 258.018. C$_{11}$H$_{14}$O$_2$^{80}Se requires *M*, 258.016).

Dehydrogenation of (**10**) *with Benzeneseleninic Anhydride* (**1**).—(a) *At room temperature*. Following the procedure given for (**6**), dehydrogenation of (**10**) (30 mg) with benzeneseleninic anhydride (**1**) (31 mg, 0.5 mol equiv.) in the presence of indole (60 mg, 3 mol equiv.) in THF (4 ml) at room temperature for 23 h followed by purification of the crude product by PLC (chloroform–methanol, 98:2) gave the alcohol (**11**) (28.5 mg, 96%) and Uhle's ketone (**7**) (0.5 mg, 1.7%); 1,3,4,5-*tetrahydrobenz*[cd]*indol*-5-*ol* (**11**), m.p. 125–126 °C (from n-hexane–ether); ν$_{max}$ 3 610, 3 530 (OH), and 3 500 cm^{-1} (NH); δ 8.00 (1 H, br s, NH), 7.32–7.07 (3 H, m, 6–8-H), 6.91 (1 H, q, *J* 1.5 Hz, 2-H), 5.14 (1 H, t, *J* 5 Hz, 5-H), 3.02 (1 H, dtd, *J* 15, 6, and 1.5 Hz, 3-H$_{eq}$), 2.90 (1 H, dtd, *J* 15, 6, and 1.5 Hz, 3-H$_{ax}$), and 2.17 (2 H, td, *J* 6 and 5 Hz, 4-H$_2$) (Found: *M*$^+$, 173.083. C$_{11}$H$_{11}$NO requires *M*, 173.090).

(b) *At* 50–60 °C. A mixture of (**10**) (30 mg), benzeneseleninic anhydride (**1**) (32 mg, 0.5 mol equiv.), and indole (60 mg, 3 mol equiv.) in THF (4 ml) was heated at 50–60 °C for 2 h. The same work-up as above gave the alcohol (**11**) (19 mg, 64%) and Uhle's ketone (**7**) (3.7 mg, 13%).

Dehydrogenation of (**4**) *with Benzeneseleninic Anhydride* (**1**).—A solution of an epimeric mixture of the 8α- and 8β-esters (**4**)

(5:2; 16 mg), benzeneseleninic anhydride (**1**) (12 mg), and indole (24 mg) in THF (3 ml) was heated at 40 °C for 1.5 h. The solvent was partially evaporated off, and 10% aqueous sodium carbonate was added to the residue. The mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated, and the residue was purified by PLC (chloroform–methanol, 97:3) to afford a 3:2 epimeric mixture of methyl (±)-lysergate and methyl (±)-isolysergate (**5**) (14 mg, 88%), which was identical with the sample reported previously.[7]

(3β,8β,9α)-1-*Benzoyl*-2,2a-*dihydro*-8-*hydroxymethyl*-6-*methylergolin*-9-*ol* (**13**).—A mixture of the glycol (**12**)[7] (838 mg) and sodium metaperiodate (838 mg) in methanol–water (1:1; 680 ml) was stirred at room temperature for 1 h, and then sodium carbonate (840 mg) was added to the reaction mixture which was then stirred for an additional hour. Then sodium borohydride (840 mg) was added and the mixture stirred for 1 h. The mixture was concentrated to half volume and then repeatedly extracted with methylene dichloride. The combined extracts were washed, dried, and evaporated to give a solid, which was recrystallised from methanol to give the *diol* (**13**) (403 mg, 52%) as a colourless powder, m.p. 252–254 °C (decomp.); ν_{max}(Nujol) 3 350 (OH) and 1 650 cm^{-1} (NCO); δ($CDCl_3$–CD_3OD) 7.88 (1 H, m, 12-H), 7.70–7.43 (6 H, m, ArH), 7.12 (1 H, br, 14-H), 4.19 (1 H, br, 2-H_β), 3.76 (2 H, m, CH_2OH), 3.68 (1 H, t, *J* 10 Hz, 9-H), 3.50–3.28 (2 H, m, 2-H_α and 3-H), 3.04 (1 H, dd, *J* 12 and 4 Hz, 7-H_{eq}), 2.88 (1 H, t, *J* 10 Hz, 10-H), 2.58–2.18 (2 H, m, 4-H_{eq} and 5-H), 2.43 (3 H, s, NMe), 2.28 (1 H, t, *J* 12 Hz, 7-H_{ax}), 2.08 (1 H, m, 8-H), and 1.44 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 73.0; H, 6.8; N, 7.45. $C_{23}H_{26}N_2O_3$ requires C, 73.0; H, 6.9; N, 7.4%).

(3β,8β,9α)-8-*Acetoxymethyl*-1-*benzoyl*-2,3-*dihydro*-6-*methylergolin*-9-*ol* (**14**).—Acetic anhydride (0.1 ml) was added dropwise to a stirred solution of the diol (**13**) (115 mg) in pyridine (2 ml) with ice-cooling, and the mixture was stirred at 0 °C for additional 3.5 h. Then 10% aqueous sodium carbonate was added and the mixture was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid which was recrystallised from ethyl acetate to afford the *acetate* (**14**) (116 mg, 91%) as colourless crystals, m.p. 215–218 °C; ν_{max} 3 450 (OH), 1 730 (OAc), and 1 635 cm^{-1} (NCO); δ 7.85 (1 H, m, 12-H), 7.78–7.42 (6 H, m, ArH), 7.10 (1 H, br, 14-H), 4.58 (1 H, dd, *J* 12 and 5 Hz, CH_2OAc), 4.36 (1 H, br, 2-H_β), 4.11 (1 H, dd, *J* 12 and 4 Hz, CH_2OAc), 3.68 (1 H, t, *J* 11 Hz, 2-H_α), 3.56 (1 H, td, *J* 10 and 5 Hz, 9-H), 3.37 (1 H, m, 3-H), 3.14 (1 H, d, *J* 5 Hz, OH), 3.06 (1 H, dd, *J* 12 and 4 Hz, 7-H_{eq}), 2.89 (1 H, t, *J* 10 Hz, 10-H), 2.43 (3 H, s, NMe), 2.36 (1 H, t, *J* 12 Hz, 7-H_{ax}), 2.28–2.14 (2 H, m, 4-H_{eq} and 5-H), 2.20 (1 H, m, 8-H), 2.12 (3 H, s, OAc), and 1.45 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 71.2; H, 6.5; N, 6.5. $C_{25}H_{28}N_2O_4$ requires C, 71.4; H, 6.7; N, 6.7%).

(3β,8β,9β)-8-*Acetoxymethyl*-1-*benzoyl*-9-*chloro*-2,3-*dihydro*-6-*methylergoline* (**15**).—Thionyl chloride (4.5 ml) was added dropwise to a stirred, ice-cooled solution of the acetate (**14**) (61 mg) in benzene (18 ml), and the mixture was then warmed at 50 °C for 1 h. The excess of thionyl chloride and the solvent were removed. 10% Aqueous sodium carbonate was then added to the residue, and the solution was extracted with methylene dichloride. The organic layer was washed, dried, and evaporated to give the crude product, which was purified by TLC (chloroform–methanol, 40:3) to afford the *chloride* (**15**) (45 mg, 71%) as colourless crystals, m.p. 192–194 °C (from ethyl acetate); ν_{max} 1 740 (OAc) and 1 640 cm^{-1} (NCO); δ 7.70–7.40 (6 H, m, ArH), 7.28–6.90 (2 H, m, ArH), 5.06 (1 H, br, s, 9-H), 4.40 (1 H, br, 2-H_β), 4.18 (2 H, m, CH_2OAc), 3.70 (1 H, t, *J* 11 Hz, 2-H_α), 3.40 (1 H, m, 3-H), 3.14 (1 H, br d, *J* 10 Hz, 10-H), 2.83 (1 H, br d, *J* 10 Hz, 7-H_{eq}), 2.81 (1 H, m, 5-H), 2.70–2.40 (3 H, m, 4-H_{eq}, 7-H_{ax}, and 8-H), 2.45 (3 H, s, NMe), 2.13 (3 H, s, OAc), and 1.40 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 68.5; H, 5.9; N, 6.3. $C_{25}H_{27}ClN_2O_3$ requires C, 68.4; H, 6.2; N, 6.4%).

(3β,8β)-8-*Acetoxymethyl*-1-*benzoyl*-2,3-*dihydro*-9,10-*didehydro*-6-*methylergoline* (**16**).—A solution of the chloride (**15**) (53 mg) and DBU (0.9 ml) in benzene (25 ml) was heated under reflux for 2 h. The mixture was washed, dried, and evaporated to give the residue which was purified by PLC (methylene dichloride–methanol, 94:6) to afford the *unsaturated compound* (**16**) (47 mg, 97%) as colourless needles, m.p. 149–150 °C (from ether); ν_{max} 1 730 (OAc) and 1 635 cm^{-1} (NCO); δ 7.68–7.42 (6 H, m, ArH), 7.28 (1 H, m, 13-H), 7.12 (1 H, br, 14-H), 6.34 (1 H, br s, 9-H), 4.39 (1 H, br, 2-H_β), 4.13 (1 H, dd, *J* 11 and 5 Hz, CH_2OAc), 4.06 (1 H, dd, *J* 11 and 6 Hz, CH_2OAc), 3.72 (1 H, t, *J* 12 Hz, 2-H_α), 3.42 (1 H, m, 3-H), 3.16–2.96 (2 H, m, 7-H_{eq} and 8-H), 2.97 (1 H, br d, *J* 10 Hz, 5-H), 2.60 (1 H, m, 4-H_{eq}), 2.52 (3 H, s, NMe), 2.27 (1 H, t, *J* 11 Hz, 7-H_{ax}), 2.12 (3 H, s, OAc), and 1.39 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 73.0; H, 6.2; N, 6.7. $C_{25}H_{26}N_2O_3 \cdot 2/5H_2O$ requires C, 73.3; H, 6.6; N, 6.8%).

(3β)-2,3-*Dihydrolysergol* (**17**).—A solution of (**16**) (40 mg) in 10% hydrochloric acid (5 ml) was gently refluxed for 2 h. The reaction mixture was diluted with water, made alkaline with 20% aqueous sodium hydroxide, and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid, which was recrystallised from methanol to afford (**17**) (24 mg, 94%) as colourless crystals, m.p. 223–226 °C (decomp.); δ($CDCl_3$–CD_3OD) 7.05 (2 H, m, 12- and 13-H), 6.58 (1 H, m, 14-H), 6.37 (1 H, br s, 9-H), 3.72 (1 H, br, 2-H_β), 3.60 (2 H, m, CH_2OAc), 3.46–3.08 (3 H, m, 2-H_α, 3-H, and 7-H_{eq}), 3.01 (1 H, m, 5-H), 2.82 (1 H, m, 8-H), 2.57 (1 H, dt, *J* 12 and 3 Hz, 4-H_{eq}), 2.52 (3 H, s, NMe), 2.29 (1 H, t, *J* 11 Hz, 7-H_{ax}), and 1.39 (1 H, q, *J* 12 Hz, 4-H_{ax}) (Found: C, 73.4; H, 7.8; N, 10.6. $C_{16}H_{20}N_2O \cdot 1/3H_2O$ requires C, 73.25; H, 7.9; N, 10.7%).

(±)-*Lysergol* (**18**).—Following the dehydrogenation procedure given for (**4**), treatment of (**17**) (5 mg) with benzeneseleninic anhydride (**1**) (3.5 mg) in the presence of indole (6.9 mg) in THF (2 ml) gave (±)-lysergol (**18**) (4.8 mg, 97%), m.p. 222–224 °C (decomp.) (from ethanol) (lit.,[13] 253–255 °C); δ($CDCl_3$–CD_3OD) 7.36–7.10 (3 H, m, ArH), 7.00 (1 H, d, *J* 1.5 Hz, 2-H), 6.47 (1 H, br s, 9-H), 3.66 (2 H, m, CH_2OH), 3.59 (1 H, dd, *J* 14 and 6 Hz, 4-H_{eq}), 3.30 (1 H, m, 5-H), 3.20 (1 H, br dd, *J* 11 and 5 Hz, 7-H_{eq}), 2.92 (1 H, m, 8-H), 2.74 (1 H, ddd, *J* 14, 12 and 1.5 Hz, 4-H_{ax}), 2.64 (3 H, s, NMe), and 2.39 (1 H, t, *J* 11 Hz, 7-H_{ax}). The IR and ^1H NMR spectra and R_f values of (±)-(**18**) were found to be identical with those of natural lysergol[13] (Found: M^+, 254.141. Calc. for $C_{16}H_{18}N_2O$: *M*, 254.142).

Ozonolysis of the Lactam (**19**).—Into a solution of the lactam (**19**) (350 mg) in chloroform (30 ml) was slowly bubbled ozone gas at −60 °C for 5 min. Removal of the solvent at room temperature gave a residue which was dissolved in anhydrous ether–THF (2:3; 50 ml), and lithium aluminium hydride (300 mg) was added in small portions to the cooled solution. The mixture was refluxed for 2 h, and treatment in the usual way gave a solid, which was purified by PLC (chloroform–methanol, 5:1) to afford the diols (**20**) (185 mg, 56%) and (**21**) (12 mg, 5%); (3β,8α,9α)-1-*benzyl*-2,3-*dihydro*-8-*hydroxymethyl*-6-*methylergolin*-9-*ol* (**20**) formed colourless crystals, m.p. 224–227 °C (decomp.) (from chloroform–methanol); ν_{max}(Nujol) 3 350 cm^{-1} (OH); δ($CDCl_3$–CD_3OD) 7.48–7.20 (6 H, m, ArH), 7.04 (1 H, t, *J* 8 Hz, 13-H), 6.40 (1 H, d, *J* 8 Hz, 14-H), 4.45 and 3.86 (2 H, ABq, *J* 14.5 Hz,

NCH_2Ph), 4.20 (1 H, dd, J 11 and 7 Hz, CH_2OH), 4.02 (1 H, dd, J 10 and 5 Hz, 9-H), 3.97 (1 H, dd, J 11 and 5 Hz, CH_2OH), 3.50 (1 H, t, J 8 Hz, 2-H$_\beta$), 3.16 (1 H, m, 3-H), 3.10 (1 H, t, J 10 Hz, 10-H), 3.03 (1 H, dd, J 12 and 2 Hz, 7-H$_{eq}$), 2.69 (1 H, dd, J 12 and 8 Hz, 2-H$_\alpha$), 2.46 (1 H, dd, J 12 and 3 Hz, 7-H$_{ax}$), 2.39 (1 H, m, 4-H$_{eq}$), 2.31 (3 H, s, NMe), 2.20 (1 H, m, 8-H), 2.10 (1 H, ddd, J 12, 10, and 2 Hz, 5-H), and 1.36 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: M^+, 364.215. $C_{23}H_{28}N_2O_2$ requires M, 364.215). (3β,8α,9α)-2,3-*Dihydro*-8-*hydroxymethyl*-6-*methylergolin*-9-*ol* (**21**) formed colourless crystals, m.p. 218.5–220 °C (decomp.) (from methanol); ν_{max}(Nujol) 3 330 cm^{-1} (NH and OH); δ(CDCl$_3$–CD$_3$OD) 7.50 (1 H, d, J 8 Hz, 12-H), 7.00 (1 H, t, J 8 Hz, 13-H), 6.62 (1 H, d, J 8 Hz, 14-H), 4.20 (1 H, dd, J 10.5 and 7 Hz, CH_2OH), 4.02 (1 H, dd, J 10.5 and 5 Hz, 9-H), 3.93 (1 H, dd, J 10.5 and 5 Hz, CH_2OH), 3.62 (1 H, m, 2-H$_\beta$), 3.30–3.02 (3 H, m, 2-H$_\alpha$, 3-H, and 7-H$_{eq}$), 3.00 (1 H, t, J 10 Hz, 10-H), 2.54–2.40 (2 H, m, 4-H$_{eq}$ and 7-H$_{ax}$), 2.38 (3 H, s, NMe), 2.20 (1 H, m, 8-H), 2.15 (1 H, ddd, J 12, 10, and 2 Hz, 5-H), and 1.37 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: C, 67.75; H, 8.2; N, 9.5. $C_{16}H_{22}N_2O_2$·3/5H_2O requires C, 67.9; H, 8,4; N, 9.5%).

Debenzylation of the N-*Benzyl Diol* (**20**).—A solution of the *N*-benzyl diol (**20**) (700 mg) in 10% hydrochloric acid (80 ml) containing 70% perchloric acid (1.5 ml) was catalytically hydrogenated over 40% palladium on carbon (700 mg) under 4.5 atom at 50 °C for 4 h. The catalyst was filtered off, and the filtrate was made alkaline with potassium carbonate and extracted repeatedly with chloroform. The combined organic layer was washed, dried, and evaporated to give a solid which was recrystallised from methanol to afford the diol (**21**) (477 mg, 90%) which was identical with the sample obtained from (**19**).

(3β,8α,9α)-1-*Acetyl*-8-*acetoxymethyl*-2,3-*dihydro*-6-*methylergolin*-9-*ol* (**22**).—A solution of the diol (**21**) (160 mg) and acetic anhydride (0.5 ml) in pyridine (20 ml) was worked-up in the same manner as described for the acetylation of (**13**) to afford the *acetate* (**22**) (185 mg, 89%) as colourless crystals, m.p. 258–260 °C (from chloroform–ether); ν_{max} 1 730 (OAc) and 1 650 cm^{-1} (NCO); δ 7.89 (1 H, d, J 8 Hz, 14-H), 7.72 (1 H, d, J 8 Hz, 12-H), 7.17 (1 H, t, J 8 Hz, 13-H), 4.70 (1 H, br dd, J 11 and 5 Hz, CH_2OAc), 4.40 (1 H, dd, J 11 and 7.5 Hz, CH_2OAc), 4.20 (1 H, t, J 9 Hz, 2-H$_\beta$), 4.01 (1 H, dd, J 10 and 5 Hz, 9-H), 3.58 (1 H, t, J 9 Hz, 2-H$_\alpha$), 3.36 (1 H, m, 3-H), 3.06 (1 H, dd, J 12 and 2.5 Hz, 7-H$_{eq}$), 2.84 (1 H, t, J 10 Hz, 10-H), 2.72 (1 H, m, 8-H), 2.50–2.20 (2 H, m, 4-H$_{eq}$ and 7-H$_{ax}$), 2.36 (3 H, s, NMe), 2.24 (3 H, s, NAc), 2.12 (3 H, s, OAc), 2.06 (1 H, ddd, J 12, 10, and 2 Hz, 5-H), and 1.39 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: M^+, 358.190. $C_{20}H_{26}N_2O_4$ requires M, 358.189).

Reaction of the Acetate (**22**) *with Thionyl Chloride*.—According to the procedure given for the preparation of (**15**), the reaction of the acetate (**22**) (100 mg) with thionyl chloride (10 ml) in benzene (60 ml) under reflux for 1 h, followed by separation of the crude product by PLC (chloroform–methanol, 10:1) afforded the chloride (**23**) (68 mg, 65%) and the unsaturated acetate (**24**) (17 mg, 18%). (3β,8α,9β)-1-*Acetyl*-8-*acetoxymethyl*-9-*chloro*-2,3-*dihydro*-6-*methylergoline* (**23**) formed pale yellow crystals, m.p. 166.5–167.5 °C (from ethyl acetate); ν_{max} 1 740 (OAc) and 1 660 cm^{-1} (NCO); δ 7.90 (1 H, d, J 8 Hz, 14-H), 7.24 (1 H, t, J 8 Hz, 13-H), 6.92 (1 H, d, J 8 Hz, 12-H), 4.96 (1 H, br s, 9-H), 4.40 (2 H, m, CH_2OAc), 4.22 (1 H, br t, J 8 Hz, 2-H$_\beta$), 3.62 (1 H, m, 2-H$_\alpha$), 3.40 (1 H, m, 3-H), 3.25 (1 H, br d, J 10 Hz, 10-H), 2.91 (1 H, dd, J 12 and 4 Hz, 7-H$_{ax}$), 2.78 (1 H, br d, J 12 Hz, 7-H$_{eq}$), 2.70 (1 H, br d, J 12 Hz, 5-H), 2.60–2.30 (2 H, m, 4-H$_{eq}$ and 8-H), 2.38 (3 H, s, NMe), 2.24 (3 H, s, NAc), 2.14 (3 H, s, OAc), and 1.41 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: C, 63.2; H, 6.7; N, 7.25. $C_{20}H_{25}N_2O_3Cl$·1/4H_2O requires C, 63.0; H, 6.75; N, 7.35%). (3β)-1-*Acetyl*-8-*acetoxymethyl*-2,3-*dihydro*-8,9-*didehydro*-6-*methylergoline* (**24**) was an oil, ν_{max} 1 730 (OAc) and 1 650 cm^{-1} (NCO); δ 7.84 (1 H, d, J 8 Hz, 14-H), 7.19 (1 H, t, J 8 Hz, 13-H), 7.01 (1 H, d, J 8 Hz, 12-H), 6.31 (1 H, br s, 9-H), 4.52 (2 H, m, CH_2OAc), 4.17 (1 H, br t, J 8 Hz, 2-H$_\beta$), 3.64–3.20 (4 H, m, 2-H$_\alpha$, 3-H, 7-H$_{eq}$, and 10-H), 3.08 (1 H, br d, J 17 Hz, 7-H$_{ax}$), 2.60–2.30 (2 H, m, 4-H$_{eq}$ and 5-H), 2.40 (3 H, s, NMe), 2.19 (3 H, s, NAc), 2.01 (3 H, s, OAc), and 1.51 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: M^+, 340.181. $C_{20}H_{24}N_2O_3$ requires M, 340.179).

(3β,8α)-1-*Acetyl*-8-*acetoxymethyl*-2,3-*dihydro*-9,10-*didehydro*-6-*methylergoline* (**25**).—According to the procedure given for the preparation of (**16**), treatment of the chloride (**23**) (65 mg) with DBU (1.5 ml) in benzene (40 ml) under reflux for 9 h, followed by purification of the crude product by PLC (chloroform–methanol, 93:7) afforded the N-*acetoxy compound* (**25**) (57 mg, 97%) as colourless crystals, m.p. 167–168 °C (decomp.) (from methylene dichloride–ether); ν_{max} 1 740 (OAc) and 1 660 cm^{-1} (NCO); δ 7.89 (1 H, d, J 8 Hz, 14-H), 7.24 (2 H, m, 12- and 13-H), 6.38 (1 H, br, $w_{\frac{1}{2}}$ 10 Hz, 9-H), 4.24 (2 H, m, 2-H$_\beta$ and CH_2OAc), 4.10 (1 H, dd, J 11 and 9 Hz, CH_2OAc), 3.63 (1 H, br t, J 8 Hz, 2-H$_\alpha$), 3.44 (1 H, m, 3-H), 2.92 (1 H, d, J 11 Hz, 7-H$_{eq}$), 2.84 (1 H, br d, J 12 Hz, 5-H), 2.70–2.40 (3 H, m, 4-H$_{eq}$, 7-H$_{ax}$, and 8-H), 2.48 (3 H, s, NMe), 2.24 (3 H, s, NAc), 2.10 (3 H, s, OAc), and 1.36 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: C, 70.7; H, 7.2; N, 8.3. $C_{22}H_{24}N_2O_3$ requires C, 70.6; H, 7.1; N, 8.2%).

(3β)-2,3-*Dihydroisolysergol* (**26**).—A solution of the acetate (**25**) (34 mg) in methanol (4 ml) containing conc. hydrochloric acid (0.35 ml) was refluxed for 2 h. The reaction mixture was concentrated to a small volume and then diluted with water, and washed with benzene. The aqueous layer was made alkaline with 10% aqueous sodium carbonate and extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid, which was purified by PLC (chloroform–methanol, 87:13) to afford the 2,3-*dihydroisolysergol* (**26**) (24 mg, 94%) as colourless crystals, m.p. 234–235 °C (decomp.) (from chloroform–methanol); ν_{max} 3 680 (NH) and 3 400 cm^{-1} (OH); δ(CDCl$_3$–CD$_3$OD) 7.02 (2 H, m, 12- and 13-H), 6.58 (1 H, d, J 8 Hz, 14-H), 6.41 (1 H, br d, J 5 Hz, 9-H), 3.81 (1 H, dd, J 10 and 4.5 Hz, CH_2OH), 3.70 (1 H, dd, J 11 and 6 Hz, CH_2OH), 3.68 (1 H, t, J 7 Hz, 2-H$_\beta$), 3.22 (1 H, m, 3-H), 3.12 (2 H, m, 2-H$_\alpha$ and 7-H$_{eq}$), 2.97 (1 H, br d, J 12 Hz, 5-H), 2.68 (2 H, m, 4-H$_{eq}$ and 7-H$_{ax}$), 2.57 (3 H, s, NMe), 2.48 (1 H, m, 8-H), and 1.34 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: C, 74.2; H, 7.8; N, 10.9. $C_{16}H_{20}N_2O$·1/5-CH_3OH requires C, 74.05; H, 8.0; N, 10.7%).

(3β)-2,3-*Dihydroelymoclavine* (**28**).—Following the procedure given for the preparation of (**26**), hydrolysis of the acetate (**24**) (14 mg) in methanol (2 ml) containing conc. hydrochloric acid (0.15 ml) gave the 2,3-dihydroelymoclavine (**28**) (7 mg, 66%) as colourless crystals, m.p. 180 °C (decomp.) (from chloroform–methanol); ν_{max} 3 670 (NH) and 3 400 cm^{-1} (OH); δ 7.07 (1 H, t, J 8 Hz, 13-H), 6.77 (1 H, d, J 8 Hz, 12-H), 6.56 (1 H, d, J 8 Hz, 14-H), 6.30 (1 H, br s, 9-H), 4.13 (2 H, br s, CH_2OH), 3.68 (1 H, m, 2-H$_\beta$), 3.60–3.42 (2 H, m, 2-H$_\alpha$ and 7-H$_{eq}$), 3.36–3.00 (3 H, m, 3-H, 7-H$_{ax}$, and 10-H), 2.64–2.40 (2 H, m, 4-H$_{eq}$ and 5-H), 2.46 (3 H, s, NMe), and 1.55 (1 H, q, J 12 Hz, 4-H$_{ax}$) (Found: M^+, 256.157. $C_{16}H_{20}N_2O$ requires M, 256.157).

(±)-*Isolysergol* (**27**).—A mixture of (**26**) (9 mg), benzeneseleninic anhydride (**1**) (7.3 mg), and indole (13.7 mg) in THF (5 ml) was heated at 40 °C for 1.5 h. Following the work-up as given for (**5**) (±)-isolysergol (**27**) (8.5 mg, 95%) was obtained

as colourless crystals, m.p. 137–140 °C (decomp.) (from chloroform–methanol) (lit.,[14] 139.5–140 °C); ν_{max} 3 500 (NH) and 3 250 cm^{-1} (OH); δ 7.94 (1 H, br s, NH), 7.20 (3 H, m, 12–14-H), 6.90 (1 H, d, *J* 2 Hz, 2-H), 6.50 (1 H, br d, *J* 6 Hz, 9-H), 4.02 (1 H, dd, *J* 10 and 3 Hz, CH_2OH), 3.86 (1 H, ddd, *J* 10, 3, and 2 Hz, CH_2OH), 3.54 (1 H, dd, *J* 15 and 5.5 Hz, 4-H_{eq}), 3.18 (1 H, m, 5-H), 3.07 (1 H, br d, *J* 11 Hz, 7-H_{eq}), 2.87 (1 H, ddd, *J* 11, 3.5, and 2 Hz, 7-H_{ax}), 2.68 (1 H, ddd, *J* 15, 12, and 2 Hz, 4-H_{ax}), 2.56 (3 H, s, NMe), and 2.46 (1 H, m, 8-H). The IR and ^1H NMR spectra and R_f values of (±)-(**27**) were found to be identical with those of natural isolysergol[14] (Found: M^+, 254.141. Calc. for $C_{16}H_{18}N_2O$: *M*, 254.142).

(±)-*Elymoclavine* (**29**).—Following the dehydrogenation procedure given for (**4**), treatment of (**28**) (7 mg) with benzeneseleninic anhydride (**1**) (5 mg) and indole (9.6 mg) in THF (2 ml) gave (±)-elymoclavine (**29**) (6.5 mg, 94%) as colourless crystals, m.p. 207–210 °C (decomp.) (from chloroform–methanol) (lit.,[15] 247–248 °C); ν_{max}(Nujol) 3 330 cm^{-1} (NH and OH); δ($CDCl_3$–CD_3OD) 7.26–7.12 (2 H, m, 12- and 13-H), 7.01 (1 H, d, *J* 8 Hz, 14-H), 6.96 (1 H, d, *J* 1.5 Hz, 2-H), 6.50 (1 H, br s, 9-H), 4.14 (2 H, m, CH_2OH), 3.83 (1 H, br d, *J* 9 Hz, 10-H), 3.46 (1 H, br d, *J* 16 Hz, 7-H_{eq}), 3.38 (1 H, m, 4-H_{eq}), 3.05 (1 H, br d, *J* 16 Hz, 7-H_{ax}), 2.82 (1 H, ddd, *J* 14, 12, and 1.5 Hz, 4-H_{ax}), 2.64 (1 H, ddd, *J* 12, 9, and 4 Hz, 5-H), and 2.56 (3 H, s, NMe). The IR and ^1H NMR spectra and R_f values of (±)-(**29**) were found to be identical with those of natural elymoclavine[15] (Found: M^+, 254.143. $C_{16}H_{18}N_2O$ requires *M*, 254.142).

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