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5(10→9)*Abeo*-ergoline derivatives: Synthesis, 5-HT_{1A}-receptor affinity and selectivity

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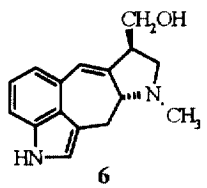
Abstract – The synthesis and the structure–affinity relationship (S.A.F.I.R.) study for the 5-HT_{1A} receptor sites of a novel series of 5(10→9)*abeo*-ergoline derivatives are presented. Most derivatives showed moderate to high affinity and selectivity for 5-HT_{1A} receptor sites. The structure–affinity relationship pointed out the role of the substituent at position 8, and the outstanding importance of the reduction of the indole 2,3-double bond for achieving the highest 5-HT_{1A} affinity and selectivity within the compounds presented. © Elsevier, Paris

ergoline derivative / 5(10→9)*abeo*-ergoline derivative / serotonin / 5-HT_{1A} receptor ligand / structure–affinity relationship

1. Introduction

Ergot alkaloids and their synthetic derivatives, having a wide spectrum of central and peripheral pharmacological activity, are used in the treatment of a variety of pathophysiological disturbances [1, 2]. All ergot compounds possess the tetracyclic ergoline skeleton as a common structural element that contains a structural relationship to indoleethylamines and catecholamines. It is therefore not surprising that ergot derivatives interact non-selectively with monoaminergic (adrenergic, dopaminergic and serotonergic) recognition sites [3]. As a consequence of these interactions, a major challenge in the development of therapeutic agents from this class is the identification of compounds that are sufficiently selective for a single neurotransmitter. Of particular importance to us was the identification of compounds possessing selectivity for the serotonergic system, which has been shown to be involved in psychiatric disorders such as anxiety and depression as well as in physiological processes such as sleep, regulation of mood and sexual behaviour [4–6]. Notwithstanding the receptorial non-selectivity of most ergolines, compounds such as the 5-HT_2 partial agonist LSD, or the 5-HT_{1A} agonist/5-$HT_{1C/2A}$ antagonist metergoline, or the 5-$HT_{1C/2A}$ antagonist mesulergine (*figure 1*) do show relative serotonergic selectivity. These compounds may be considered as serotonergic templates for their conformationally-constrained and stereochemically-defined serotonin framework embedded in the tetracyclic ergoline skeleton [7–11].

The 5-HT_{1A} receptor subfamily has attracted considerable attention as a target in the development of novel therapeutics for the treatment of depression and anxiety disorders [12–14]. Many compounds of different chemical classes, for example indoles, aminotetralines, benzodioxanes and arylpiperazines, are known to have a high affinity for the 5-HT_{1A} receptors and act as agonists, antagonists or partial agonists at this receptor site [15, 16]. In the process of screening different classes of ergolines as novel 5-HT_{1A} ligands, the 5(10→9)*abeo*-ergoline **6**:



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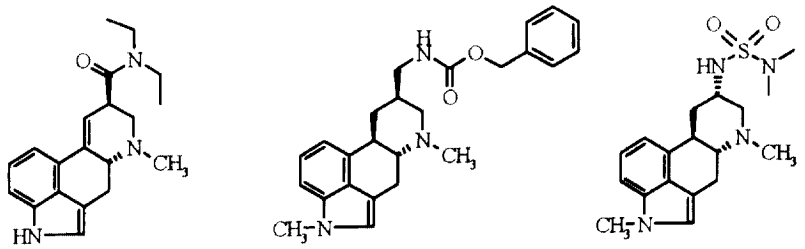


LSD **metergoline** **mesulergine**

Figure 1. Serotonergic ergoline derivatives.

was identified on the basis of its reasonable 5-HT_{1A} affinity and selectivity [17].

The identification of this compound prompted the preparation and evaluation of a new series of analogues with a view of identifying compounds with a higher affinity and selectivity for the 5-HT_{1A} receptors than **6**. In this paper, we report on the preparation of several analogues of **6** and their receptor affinities as determined by receptor binding assays.

2. Chemistry

The majority of the compounds described in this study were prepared starting from **6** and its diastereoisomer **7**. The corresponding acetates **4** and **5** were unexpectedly obtained by treatment of the monoacetyl derivative **3** with phosphoryl chloride in pyridine in presence of pyridine hydrochloride, in an attempt to replace the hydroxy by chlorine atom. The structure and the stereochemical relationship were proved by ^{1}H-NMR and reverse heterocorrelated ^{13}C–^{1}H-long range (HMBC) experiments. The intermediate **3** was obtained in high yield and with a high degree of diastereoselectivity by oxidative hydroboration of methyl lysergate **1**, followed by careful acetylation of the diol **2**, according to *figure 2* [18].

A Wagner–Meerwein rearrangement favoured by the antiperiplanarity of the 5-10 and C9-OH bonds was initially proposed as a mechanism of the transposition reaction leading to the 5(10→9)*abeo*-ergoline skeleton. Such mechanism did not account for the formation of **7** having an opposite chirality at C-5 with respect to **3**. Experiments pointed out that a Grob fragmentation, *via* an internal cleavage through an azecine intermediate, followed by an aza-Cope rearrangement, *via* a transannular cyclization rather than a simple Wagner–Meerwein rearrangement, complies better with the formation of the two diastereoisomers **6** and **7**, as illustrated in *figure 3* [19, 20].

The compounds reported in *tables I* and *II* were prepared by structural modification of **6** and **7**, except **8** prepared from 6-propyl-lysergic acid methyl ester. This intermediate was obtained by demethylation at the nitrogen in position 6 by the von Braun degradation. The 6-nor-6-cyano-lysergic acid methyl ester provided by action of cyanogen bromide on the parent compound was reduced directly with zinc in acetic acid to the 6-nor compound [21]. The alkylation of the 6-nor derivative was carried out by treating with propyl iodide in the presence of potassium carbonate in dimethylformamide [22]. Catalytic hydrogenation of **6** and **12** afforded **10**, **11** and **21**. In both cases, the *trans* isomer was formed preferentially. NOESY spectra were acquired for both **10** and **11**. The crosspeaks most relevant for the determination of the configurations of the two diastereoisomers are for **10**: H-7A/H-8, H-8/H-9, H-4Aax/H-9, H-5/H-10B, H-4Beq/H-5, instead for **11** are: H-4Beq/H-5, H-4Beq/CH_3N, H-5/H-9, H-5/CH_3N, H-5/H-7B, H-9/CH_2, H-9/H-7B. Both spectra contain the crosspeaks of H-9 with H-10A and H-10B, but for **11** the intensity of the crosspeak H-9/H-10B is greater than of H-9/H-10A, while for **10** the opposite is true. It is thus likely that only NOE between H-9 and H-10eq (H-10eq is H-10A in **11**, but H-10eq is H-10B in **10** is real, while the crosspeak H-9H-/H-10ax is mainly due to spin diffusion. Also the lack of some crosspeaks confirms the proposed structures: in **11** the NOEs H-4Aax/H-9 and H-8/H-9, and in **10** the NOEs H-9/CH_2, H-9/H-7A, and H-9/H-7B are absent. The ether derivative **9** was obtained by photochemical ring-closure of **6** in isopropanol containing methanesulphonic acid. The preparations of the deoxy **12**, **13** and **16** were accomplished by conversion of **6**, **7** and **8** into the corresponding chlorides by reaction with phosphoryl chloride in pyridine, followed by reduction with sodium borohydride in dimethylsulphoxide at low temperature [23]. The dienes **14** and **15** were obtained by treatment of the corresponding chlorides with

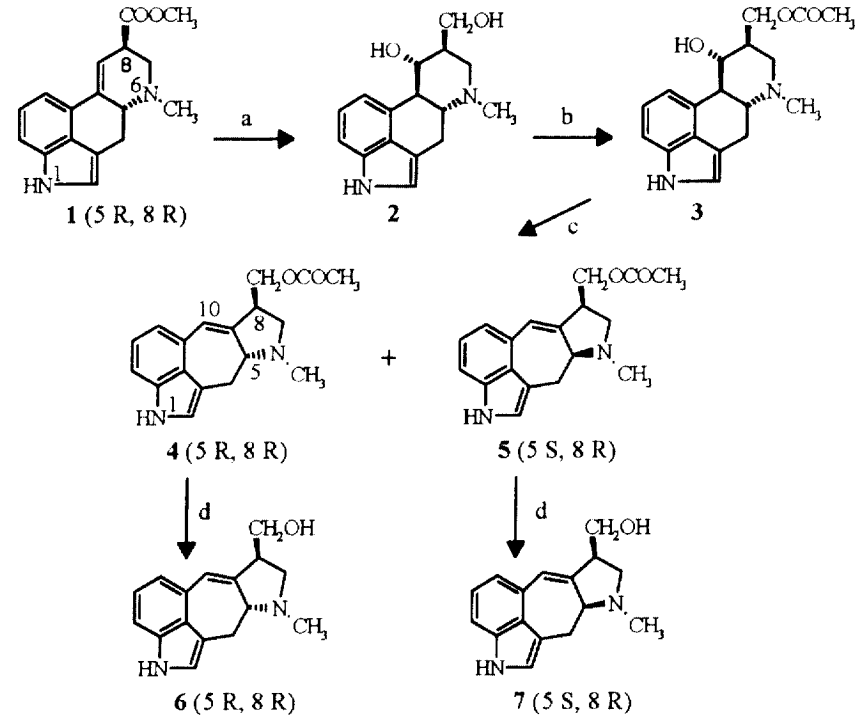


Figure 2. Synthesis of the key compounds **6** and **7**.

1,8-diazabicyclo[5.4.0]-undec-7-ene in dimethylformamide at low temperature. The conversion of **12** into the corresponding 1-methyl derivative **17** was performed by reaction with methyl iodide in dimethylsulphoxide in presence of potassium hydroxide [24, 25]. The introduction of the 2-substituent on **12** was achieved by direct substitution with the appropriate electrophilic reagent in all cases, as shown in *figure 4*.

Action of *N*-bromosuccinimide in tetrahydrofuran afforded **18**, whilst bromine in acetic acid gave access to the 2, 12-dibromo derivative **20** [26]. The thioether **19** was provided by employing methylsulphenyl

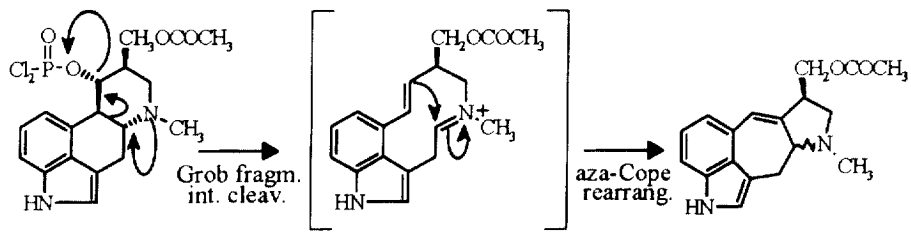


Figure 3. Proposed mechanism for the formation of the *abeo*-diastereoisomers.

Table I. Chemical data of the 5(10→9)*abeo*-ergolines **6–16**.

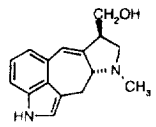
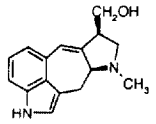
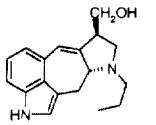
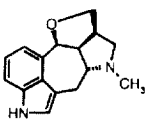
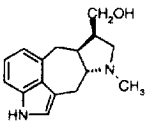
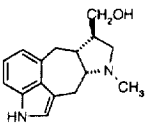
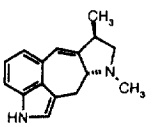
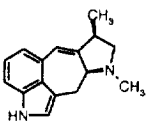
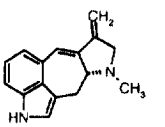
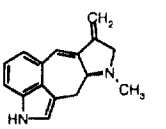
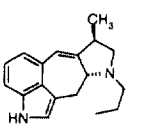
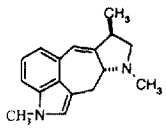
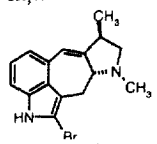
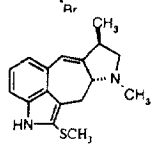
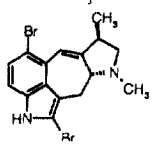
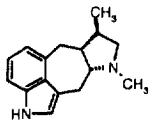
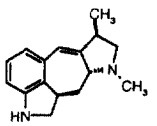
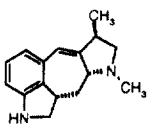
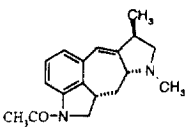
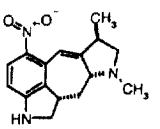
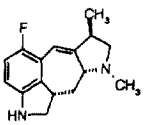
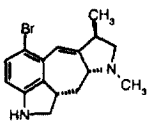
Compound	Structure	Formula	M.p. (°C)
6		$C_{16}H_{18}N_2O$	251–253
7		$C_{16}H_{18}N_2O$	215–218
8		$C_{18}H_{22}N_2O$	209–211
9		$C_{16}H_{18}N_2O$	235–237
10		$C_{16}H_{20}N_2O$	231–233
11		$C_{16}H_{20}N_2O$	190–192
12		$C_{16}H_{18}N_2$	218–220
13		$C_{16}H_{18}N_2$	146–148
14		$C_{16}H_{16}N_2$	230–232
15		$C_{16}H_{16}N_2$	229–231
16		$C_{18}H_{22}N_2$	147–149

Table II. Chemical data of the 5(10→9)*abeo*-ergolines **17–27**.

Compound	Structure	Formula	M.p. (°C)
17		$C_{17}H_{20}N_2$	187–189
18		$C_{16}H_{17}BrN_2$	201–203
19		$C_{17}H_{20}N_2S$	195–198
20		$C_{16}H_{16}Br_2N_2$	120–123
21		$C_{16}H_{20}N_2$	265–268
22		$C_{16}H_{20}N_2$	157–160
23		$C_{16}H_{20}N_2$	179–181
24		$C_{18}H_{22}N_2O$	142–145
25		$C_{16}H_{19}N_3O_2$	165–169
26		$C_{16}H_{19}FN_2$	152–154
27		$C_{16}H_{19}BrN_2$	148–151

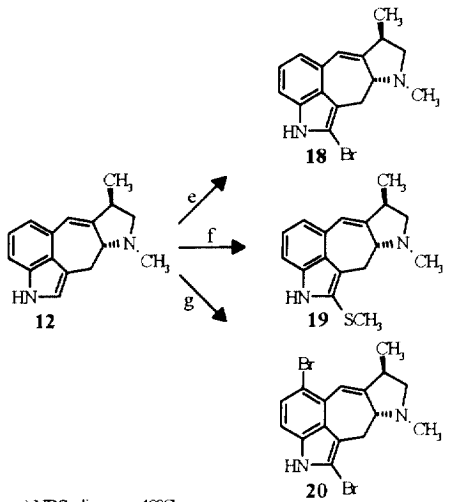


Figure 4. Preparation of the substituted aromatic derivatives **18**, **19**, **20**.

chloride, generated by action of sulphuryl chloride on dimethyldisulphide in dichloromethane [27]. Regioselective reduction of the 2,3-double bond was achieved by reaction of **12** with sodium borohydride in trifluoroacetic acid at low temperature. The reduction provided the diastereoisomers **22** and **23** as the major product [28]. The structure proposed for **22** (H-3A, H-5B) is confirmed by the NOESY crosspeaks between the protons: H-2B/H-4B, H-2A/H-3A, H-3A/H-4A, H-4B/H-5B, H-4B/CH_3N, H-7A/H-8, H-7B/CH_3-8, H-5/CH_3N, which are all consistent. No NOE data are available for **23**, but under the assumption that the stereochemistry of C-5 and C-8 cannot have changed, the only possible structure is the diastereoisomer **23** with H-3B. The coupling constants in the ^{1}H-NMR are consistent with the hypothesis, but are not sufficient by themselves to demonstrate it. Besides, NOE data exist for the N-1-acetyl derivatives of both products, and they confirm the structures. Action of acetic anhydride in pyridine on **23** led to **24**. Compound **25** was provided following nitration of **24** with fuming nitric acid in acetic acid at low temperature and subsequent hydrolysis with diluted sulphuric acid solution. The nitration occurs in highly regioselective manner. Indeed, only a small amount of 14-nitro isomer was formed. Selective reduction of the nitro group of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-nitro-9,10-didehydroergoline by means of stannous chloride in ethanol, furnished the (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-amino-9,10-[29]. This compound was subsequently converted into the corresponding diazonium tetrafluoroborate by reaction with nitrosonium tetrafluoroborate in dichloromethane at room temperature. Pyrolysis of this salt in *o*-dichlorobenzene at 120 °C and subsequent saponification with diluted ethanolic potassium hydroxide solution, afforded the 12-fluoro derivative **26** [30]. Bromination of **24** with bromine in acetic acid afforded regioselectively the 12-bromo derivative. After removal of the acetyl group by diluted ethanolic potassium hydroxide solution, **27** was provided, as depicted in *figure 5*.

3. Results and discussion

The compounds described in this study were evaluated for their α_1, α_2, D_1, D_2, 5-HT_{1A} and 5-HT_2 receptor binding affinities assessed by measuring the displacement of [^{3}H]-prazosin binding in rat frontal cortex [31], [^{3}H]-yohimbine binding in rat frontal cortex [32], [^{3}H]-SCH-23390 binding in rat striatum [33], [^{3}H]-spiroperidol binding in rat striatum [34], [^{3}H]-8-OH-DPAT binding in rat hippocampus [35] and [^{3}H]-ketanserin binding in rat pre-frontal cortex [36], respectively.

The influence of different structural modifications on 5-HT_{1A} affinity, expressed as IC_{50} in μM, and selectivity are reported in *table III*. The diastereoisomer (5S, 8R) **7** was devoid of receptor affinity in similar manner to (5S, 8R)-ergolines [37]. Conversely, the deoxy **13** and particularly the diene analogue **15**, showed an appreciable 5-HT_{1A} affinity. Replacement of the *N*-methyl group of **6** and **12** with the *N*-propyl group as in **8** and **16** led to a noticeable drop in 5-HT_{1A} affinity. 5-HT_{1A} versus α_2 selectivity was increased approximately ten fold by the ring closure of **6** to **9**. Reduction of the 9,10-double bond of **6** provided the *trans* **10** and the *cis* **11**. The former retained the 5-HT_{1A} affinity, but its 5-HT_2 component was doubled. The latter was devoid of receptor affinity. This result mirrors that of 9,10-*cis*-ergolines [38]. An appreciable enhancement of 5-HT_{1A} affinity was observed by conversion of **6** into the deoxy **12**. However, this was accompanied by an increased α_2 component. N-indole methylation of **6** provided **17**, that displayed a significant lower 5-HT_{1A} component than the parent. Similarly, aromatic substitution as in **18**, **19** and **20** was highly detrimental in terms of 5-HT_{1A} affinity and selectivity. Selective reduction of the 2,3-double bond of **12** furnished the 3α-H **22** and the 3β-H **23**. As demonstrated by comparison of the binding profile of **22** and **23**, the nature of the stereochemistry at C-3 was most important in order to achieve high affinity and selectivity. The latter displayed the highest 5-HT_{1A} selectivity so far reported for an ergoline deri-

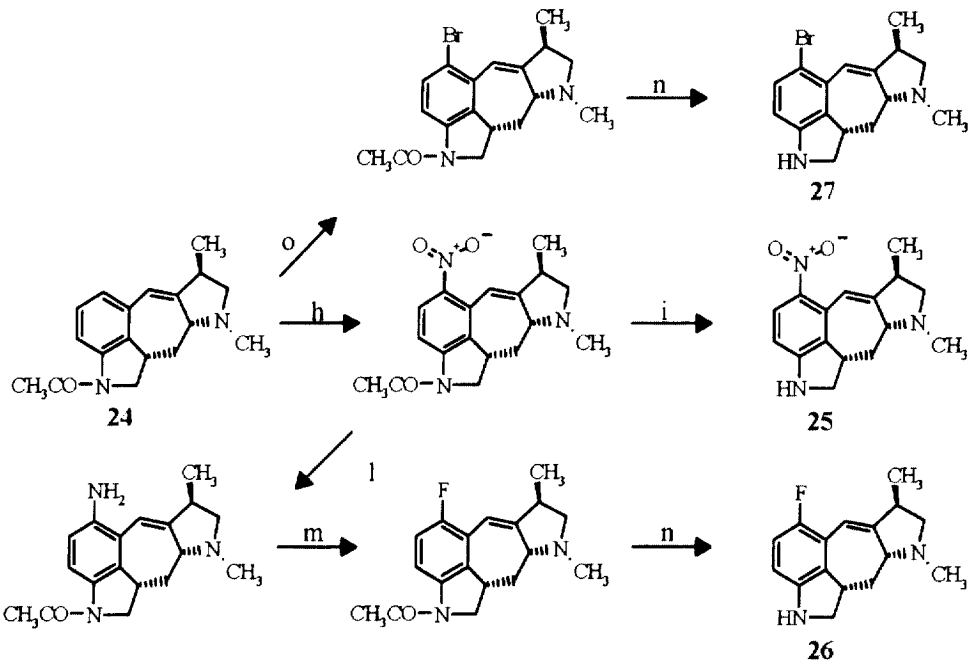


Figure 5. Preparation of the substituted aromatic derivatives **25**, **26**, **27**.

vative. 5-HT_{1A} affinity was lost by acetylation of the indoline nitrogen as in **24**. Aromatic substitution of **23** with nitro, fluoro and bromo group as in **25**, **26** and **27**, strongly altered 5-HT_{1A} selectivity; whilst affinity was preserved. The reappearance of a significant D_2 component in **25** is noteworthy.

In summary, this structure–affinity relationship (SAR) study revealed several 5(10→9)*abeo*-ergoline derivatives with high 5-HT_{1A} affinity and selectivity over α_1, α_2, D_1, 5-HT_2 receptor sites. Within this class of compounds, the receptor binding profile indicated that 5-HT_{1A} affinity was generally enhanced by conversion of the 8β-hydroxymethyl group into a methyl group. On the other hand, the highest affinity was associated with 2,3-double bond reduction. In fact, the indoline **23** displayed an astounding 5-HT_{1A} selectivity for a compound of this class. These results illustrate the subtle structure–affinity relationship of the ergoline derivatives and highlight the richness of this class as a source of potential therapeutic agents.

4. Experimental protocols

4.1. Chemistry

Analytical and spectroscopic data were consistent with the structure of the corresponding compounds. ^{1}H-NMR were recorded on a Bruker AC 200 spectrometer at 200 MHz and Varian VXR 400 S MHz. Chemical shifts are reported as δ values in part per million (ppm) relative to tetramethylsilane (δ 0.00) used as internal standard. Microanalyses were performed on a Carlo Erba autoanalyser and were within 0.4% of the calculated values.

4.2. (5R, 8R)-6-Methyl-8β-hydroxymethyl-9α-hydroxyergoline **2**

To a stirred solution of methyl lysergate **1** (35.7 g, 125 mmol) containing sodium borohydride (24.2 g, 638 mmol) in tetrahydrofuran (600 mL) was added dropwise etherate borotrifluoride (23 mL, 210 mmol) at –30 °C under nitrogen. After stirring overnight at room temperature, water (25 mL) in tetrahydrofuran (150 mL) was carefully added maintaining the temperature between –25 and –15 °C by cooling. The mixture

Table III. Binding profile to adrenergic, dopaminergic and serotonergic receptors for the 5(10→9)*abeo*-ergoline derivatives **6–27**. Affinities are expressed as IC_{50} in μM, standard errors are ± 10% of the mean reported values.

Compound	α_1	α_2	D_1	D_2	5-HT_{1A}	5-HT_2
6	>10	0.23	2.14	1.02	0.02	0.19
7	>10	>10	>10	>10	>10	>10
8	>10	0.54	>10	0.73	0.034	0.15
9	2.07	3.98	3.76	1.16	0.03	0.19
10	>10	0.26	>10	1.92	0.029	0.076
11	>10	5.97	>10	>10	1.36	1.24
12	2.33	0.09	1.85	0.94	0.006	0.11
13	7.46	0.78	>10	2.68	0.033	1.63
14	4.39	0.16	6.56	0.52	0.02	0.08
15	4.09	0.21	5.81	0.49	0.015	0.14
16	6.69	0.94	8.72	0.34	0.035	0.048
17	1.34	0.19	0.92	0.42	0.086	0.054
18	0.07	0.21	1.93	0.62	0.33	0.95
19	0.18	0.84	2.54	0.85	0.82	1.12
20	0.16	0.33	1.18	0.32	0.95	4.39
21	4.77	0.27	>10	0.21	0.025	0.23
22	7.46	0.78	>10	2.68	0.033	1.63
23	>10	1.36	>10	>10	0.004	>10
24	>10	5.67	>10	5.67	0.73	>10
25	2.75	0.25	4.87	0.06	0.003	1.24
26	3.87	0.32	5.71	0.62	0.018	0.98
27	8.03	0.69	7.12	0.13	0.006	2.08

was then gradually warmed up at room temperature followed by concomitant addition of 120 vol. hydrogen peroxide solution (100 mL) and a solution of potassium hydroxide (50 g, 877 mmol) in water (350 mL). Afterwards, the resulting suspension was heated at 45 °C for 4 h. The solvents were then removed and the residue taken up in methanol (250 mL) was refluxed for 5 h. After removal of the solvent, the crude reaction mixture was dissolved in boiling water (500 mL) and set aside at room temperature. The precipitate was collected, washed with water, then crystallised twice from boiling methanol to give, after drying, compound **2** (22.5 g, 65% yield), as white needles, m.p. 278–281 °C. $[\alpha]_D^{20}$ –25.3 (*c* = 0.124, 1 N HCl). MS *m/z*: 272 ($C_{16}H_{20}N_2O_2$, 100, $[M]^{+\bullet}$), 255 (84, $[M - OH]^+$), 223 (32, $[M - CH_2OH - H_2O]^+$), 167 (11), 154 (91), 144 (32), 127 (40). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.92 (m, 2H, H-8, H-7ax), 2.01 (ddd, *J* = 4.0, 10.0, 11.0 Hz, 1 H, H-5), 2.29 (s, 3 H, NCH_3), 2.54 (ddd, *J* = 1.0, 11.0, 14.0 Hz, 1 H, H-4ax), 2.80 (dd, *J* = 10.0, 10.0 Hz, 1 H, H-10), 2.92 (m, 1 H, H-7eq), 3.24 (dd, *J* = 4.0, 14.0 Hz, 1H, H-4eq), 3.41 (m, 1H, CH(*H*)OH), 3.51 (m, 1 H, H-9), 3.73 (m, 1 H, C*H*(H)OH), 4.52 (t, *J* = 5.1 Hz, 1 H, CH_2OH), 4.82 (d, *J* = 7.7 Hz, 1 H, OH-9), 6.91 (m, 1 H, H-2), 6.94 (m, 1 H, H-13), 7.08 (d, *J* = 8.0 Hz, 1 H, H-12), 7.54 (d, *J* = 7.0 Hz, 1 H, H-14), 10.53 (br s, 1 H, NH-1).

4.3. (5R, 8R)-6-Methyl-8β-acetyloxymethyl-9α-hydroxyergoline ***3***

Acetyl chloride (19.5 mL, 275 mmol) was added dropwise to a stirred suspension of **2** (41 g, 150 mmol) in pyridine (750 mL) at 0 °C and the mixture was stirred at room temperature for 5 h. Ice water (1500 mL) was added to the solution and the mixture was extracted with ethylacetate. The extract was subsequently washed with water, saturated aqueous sodium hydrogencarbonate solution and brine, then dried over sodium sulphate. Concentration of the solvent in vacuo gave nearly pure **3** that was crystallised from ethylacetate affording **3** (39 g, 83% yield) as white crystals, m.p. 205–207 °C. $[\alpha]_D^{20}$ – 67 (*c* = 0.147, pyridine). MS *m/z*: 314 ($C_{18}H_{22}N_2O_3$, 100, $[M]^{+\bullet}$), 297 (44, $[M - OH]^+$), 254 (27, $[M - OH - CH_3CO]^+$), 238 (53, $[M - OH - CH_3COO]^+$), 223 (20, $[M - H_2O - CH_3COOCH_2]^+$), 154 (72), 144 (17), 127 (27). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3 H, $OCOCH_3$), 2.1–2.4 (m, 3 H, H-5, H-7ax, H-8), 2.45 (s, 3 H, NCH_3), 2.74 (ddd, *J* = 1.6, 11.0, 14.5 Hz, 1 H, H-4ax), 2.96 (m, 1 H, H-7eq), 3.00 (dd, *J* = 9.8, 9.8 Hz, 1 H, H-10), 3.36 (dd, *J* = 4.1, 14.5 Hz, 1 H, H-4eq), 3.78 (dd, *J* = 9.8, 9.8 Hz, 1 H, H-9ax), 4.20 (dd, *J* = 2.9, 11.5 Hz, 1 H, C*H*(H)$OCOCH_3$), 4.47 (dd, *J* = 4.8, 11.5 Hz, 1 H, CH(*H*)-$OCOCH_3$), 6.86 (m, 1 H, H-2), 7.1–7.7 (m, 3 H, H-12, H-13, H-14), 7.94 (br s, 1 H, NH-1).

4.4. (5R, 8R)-5(10→9)abeo-6-Methyl-8β-acetyloxymethyl-9,10-didehydroergoline ***4*** *and (5S, 8R)-5(10→9)abeo-6-Methyl-8β-acetyloxymethyl-9,10-didehydroergoline* ***5***

Phosphoryl chloride (50.2 g, 330 mmol) was slowly added dropwise to a stirred solution of **3** (80 g, 254 mmol) and pyridine hydrochloride (58.4 g, 508 mmol) in pyridine (500 mL) at 45 °C. After heating for 3 h, the solvent was removed in vacuo, and the residue taken up in ethylacetate was partitioned with 0.1 M ammonium hydroxide solution. The organic phase was thoroughly washed with brine, then dried over sodium sulphate. The solvent was removed, and the residue was chromatographed on silica gel eluting with ethylacetate/cyclohexane 1:3 to furnish, after crystallisation from ethylacetate, 49.2 g of **4** (65.3% yield), m.p. 129–131 °C. $[\alpha]_D^{20}$+185 (*c* = 0.098, pyridine). MS *m/z*: 296 ($C_{18}H_{20}N_2O_2$, 20, $[M]^{+\bullet}$), 235 (12, $[M - CH_3COO - 2H]^+$), 223 (100, $[M - CH_3COOCH_2]^+$), 221 (13, $[M - CH_3COOCH_2 - 2H]^+$), 192 (8), 180 (6), 167 (11), 154 (9), 117 (9), 111 (12), 110 (10). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.06 (s, 3 H, $OCOCH_3$), 2.44 (s, 3 H, NCH_3), 2.49 (dd, *J* = 6.0, 9.4 Hz, 1 H, H-7β), 2.75 (ddd, *J* = 1.6, 10.5, 14.0 Hz, 1 H, H-4β), 3.00 (m, 2H, H-5, H-8), 3.12 (d, *J* = 9.4 Hz, 1 H, H-7α), 3.32 (dd, *J* = 2.7, 14.0 Hz, 1 H, H-4α), 4.10 (dd, *J* = 10.6, 10.6 Hz, 1 H, C*H*(H)$OCOCH_3$), 4.22 (dd, *J* = 6.3, 10.6 Hz, 1 H, CH(*H*)$OCOCH_3$), 6.55 (dd, *J* = 1.6, 1.6 Hz, 1 H, H-10), 6.90 (d, *J* = 7.0 Hz, 1 H, H-12), 6.97 (dd, *J* = 1.6, 1.6 Hz, 1 H, H-2), 7.11 (dd, *J* = 7.0, 7.1 Hz, 1 H, H-13), 7.19 (dd, *J* = 1.3, 8.1 Hz, 1 H, H-14), 7.99 (br s, 1 H, NH-1). The mixed fractions containing **4** and **5** were pooled, and after removal of the solvent the residue was carefully fractionated by flash chromatography eluting with ethylacetate/cyclohexane 1:5 to provide, after crystallisation from ethylacetate, 5.7 g of **5** (7.6% yield) as the less polar product, m.p. 147–150 °C. $[\alpha]_D^{20}$ – 223 (*c* = 0.102, pyridine). MS *m/z*: 296 ($C_{18}H_{20}N_2O_2$, 18, $[M]^{+\bullet}$), 235 (11, $[M - CH_3COO - 2H]^+$), 223 (100, $[M - CH_3COOCH_2]^+$), 221 (18, $[M - CH_3COO - 2H]^+$), 192 (13), 180 (10), 167 (12), 154 (18), 117 (16), 111 (23), 110 (24). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.09 (s, 3 H, $OCOCH_3$), 2.24 (m, 1 H, H-7β), 2.50 (s, 3 H, NCH_3), 2.85 (ddd, *J* = 1.5, 10.5, 13.8 Hz, 1 H, H-4α), 3.28 (m, 1 H, H-8), 3.35 (m, 2H, H-4β, H-7α), 4.16 (dd, *J* = 7.8, 11.0 Hz, 1 H, C*H*(H)$OCOCH_3$), 4.51 (dd, *J* = 4.8, 11.0 Hz, CH(*H*)$OCOCH_3$), 6.46 (dd, *J* = 2.4, 2.4 Hz, 1 H, H-10), 6.91 (m, 1 H, H-12), 6.98 (dd, *J* = 1.9 Hz, 1 H, H-2), 7.0–7.2 (m, 2H, H-13, H-14), 8.17 (br s, 1 H, NH-1).

4.5. (5R, 8R)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-9,10-didehydroergoline ***6***

A stirred solution of **4** (12.5 g, 42 mmol) in methanol (150 mL) was treated with 1 M sodium hydroxide solution (50 mL, 50 mmol) at room temperature for 1 h. The solvent was removed in vacuo and the residue dissolved in chloroform/methanol 9.5:1 was washed with water, then brine and dried over sodium sulphate. The solvent was evaporated and the residue, crystallised from methanol, furnished **6** (9.2 g, 85% yield) as white crystal. $[\alpha]_D^{20}$– 274 (*c* = 0.168; pyridine). MS *m/z*: 254 ($C_{16}H_{18}N_2O$, 23, $[M]^{+\bullet}$), 223 (100, $[M - CH_2OH]^+$), 221 (15, $[M - CH_2OH - 2H]^+$), 192 (14), 180 (13), 167 (15), 154 (20), 117 (8), 111 (42), 110 (31), 103 (18). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.08 (dd, *J* = 8.8, 10.6 Hz, 1 H, H-7β), 2.35 (s, 3 H, NCH_3), 2.59 (ddd, *J* = 1.5, 10.2, 12.0 Hz, 1 H, H-4α), 2.85 (m, 1 H, H-5), 2.92 (m, 1 H, H-8), 3.21 (dd, *J* = 7.3, 8.5 Hz, 1 H, H-7α), 3.30 (dd, *J* = 2.6, 12.0 Hz, 1 H, H-4β), 3.44 (m, 1 H, C*H*(H)OH), 3.82 (m, 1 H, CH(*H*)OH), 4.62 (dd, *J* = 5.0, 5.0 Hz, 1 H, CH_2OH), 6.42 (dd, *J* = 2.3, 2.3 Hz, 1 H, H-10), 6.75 (d, *J* = 7.0 Hz, H-12), 6.98 (dd, *J* = 7.0, 7.9 Hz, 1 H, H-13), 7.09 (dd, *J* = 1.5, 2.0 Hz, 1 H, H-2), 7.15 (d, *J* = 7.9 Hz, 1 H, H-14), 10.81 (br s, 1 H, NH-1).

4.6. (5S, 8R)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-9,10-didehydroergoline ***7***

The same treatment of **5** (2.5 g, 8.4 mmol) as described for the preparation of **6** from **4**, gave after crystallisation from acetone, 1.8 g of **7** (84% yield). $[\alpha]_D^{20}$+188 (*c* = 0.178; pyridine). MS *m/z*: 254 ($C_{16}H_{18}N_2O$, 23, $[M]^{+\bullet}$), 223 (100, $[M - CH_2OH]^+$), 221 (17, $[M - CH_2OH - 2H]^+$), 192 (15), 180 (12), 167 (14), 154 (14), 117 (3), 111 (16), 110 (11). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.46 (s, 3 H, NCH_3), 2.67 (ddd, *J* = 0.9, 5.9, 9.1 Hz, 1 H, H-7α), 2.84 (m, 1 H, H-8), 2.90 (ddd, *J* = 1.7, 10.5, 14.1 Hz, 1 H, H-4β), 3.08 (m, 1 H, H-5), 3.16 (d, *J* =

9.1 Hz, 1 H, H-7β), 3.31 (dd, J = 2.9, 14.1 Hz, 1 H, H-4α), 3.79 (ddd, J = 0.9, 4.7, 9.7 Hz, 1 H, C*H*(H)OH), 3.89 (dd, J = 4.4, 9.7 Hz, CH(*H*)OH), 6.59 (dd, J = 1.5, 2.6 Hz, 1 H, H-10), 6.91 (d, J = 7.0 Hz, 1 H, H-12), 6.99 (dd, J = 1.7, 1.7 Hz, 1 H, H-2), 7.13 (dd, J = 7.0, 8.2 Hz, 1 H, H-13), 7.20 (dd, J = 0.9, 8.2 Hz, 1 H, H-14), 8.02 (br s, 1 H, NH-1).

4.7. (5R, 8R)-5(10→9)abeo-6-Propyl-8β-hydroxymethyl-ergoline ***8***

The same treatment of 6-propyl-lysergic acid methyl ester as described for the preparation of **2** from **1**, afforded (5R, 8R)-6-propyl-8β-hydroxymethyl-9α-hydroxyergoline, m.p. 246–249 °C. MS *m/z*: 300 ($C_{16}H_{20}N_2O_2$, 100, $[M]^{+\bullet}$), 283 (74, $[M - OH]^+$), 251 (29, $[M - CH_2OH - H_2O]^+$), 167 (21), 154 (96). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 0.11 (t, 3 H, $NCH_2CH_2CH_3$), 1.4–1.6 (m, 2H, $NCH_2CH_2CH_3$), 2.0–2.3 (m, 1 H, $NCHHCH_2CH_3$)), 2.68 (ddd, J = H, 1 H, H-4ax), 2.7–3.1 (m, 4 H, H-4eq, H-5, H-8, $NCHHCH_2CH_3$), 3.2–3.9 (m, 3 H, H-7eq, CH_2OH), 4.71 (t, 1 H; CH_2OH), 4.87 (d, J = 7.7 Hz, 1 H, OH-9), 6.46 (t, 1 H, H-10), 6.74 (d, 1 H, H-12), 6.91 (m, 1 H, H-2), 6.94 (m, 1 H, H-13), 7.05 (d, J = 8.0 Hz,1 H, H-12), 7.44 (d, J = 7.0 Hz, 1 H, H-14), 10.58 (br s, 1 H, NH-1).

The same treatment of (5R, 8R)-6-propyl-8β-hydroxymethyl-9α-hydroxyergoline as described for the preparation of **3** from **2**, afforded (5R, 8R)-6-propyl-8β-acetyloxymethyl-9α-hydroxyergoline, m.p. 156–159 °C. MS *m/z*: 342 ($C_{20}H_{26}N_2O_3$, 100, $[M]^{+\bullet}$), 325 (51, $[M - OH]^+$), 282 (22, $[M - OH - CH_3CO]^+$), 266 (47, $[M - OH - CH_3COO]^+$), 251 (17, $[M - H_2O - CH_3COOCH_2]^+$), 154 (66), 144 (19), 127 (17). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 0.12 (t, 3 H, $NCH_2CH_2CH_3$), 1.4–1.7 (m, 2H, $NCH_2CH_2CH_3$), 2.0–2.3 (m, 1 H, $NCHHCH_2CH_3$)), δ 2.08 (s, 3 H, $OCOCH_3$), 2.1–2.4 (m, 3 H, H-5, H-7ax, H-8), 2.75 (ddd, J = 1.6, 11.0, 14.6 Hz, 1 H, H-4ax), 2.86 (m, 1 H, H-7eq), 3.10 (dd, J = 9.8, 9.8 Hz, 1 H, H-10), 3.46 (dd, J = 4.1, 14.5 Hz, 1 H, H-4eq), 3.79 (dd, J = 9.8, 9.8 Hz, 1 H, H-9ax), 4.21 (dd, J = 2.9, 11.5 Hz, 1 H, C*H*(H)OCOCH$_3$), 4.57 (dd, J = 4.8, 11.5 Hz, 1 H, CH(*H*)OCOCH$_3$), 6.87 (m, 1 H, H-2), 7.1–7.8 (m, 3 H, H-12, H-13, H-14), 7.94 (br s, 1 H, NH-1).

The same treatment of (5R, 8R)-6-propyl-8β-acetyloxymethyl-9α-hydroxyergoline as described for the preparation of **4** from **3**, afforded (5R, 8R)-5(10→9)abeo-6-propyl-8β-acetyloxymethyl-9,10-didehydroergoline, m.p. 104–107 °C. MS *m/z*: 324 ($C_{20}H_{24}N_2O_2$, 24, $[M]^{+\bullet}$), 263 (17, $[M - CH_3COO - 2H]^+$), 249 (100, $[M - CH_3COOCH_2]^+$), 245 (15, $[M - CH_3COOCH_2 - 2H]^+$), 192 (10), 180 (7), 167 (18), 154 (5), 117 (11), 111 (15), 110 (7). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.15 (t, 3 H, $NCH_2CH_2CH_3$), 1.4–1.8 (m, 2H, $NCH_2CH_2CH_3$), 2.1–2.3 (m, 1 H, $NCHHCH_2CH_3$)), 2.16 (s, 3 H, $OCOCH_3$), 2.51 (dd, J = 6.0, 9.4 Hz, 1 H, H-7β), 2.73 (ddd, J = 1.6, 10.5, 14.0 Hz, 1 H, H-4β), 3.05 (m, 2H, H-5, H-8), 3.17 (d, J = 9.4 Hz, 1 H, H-7α), 3.38 (dd, J = 2.7, 14.0 Hz, 1 H, H-4α), 4.14 (dd, J = 10.6, 10.6 Hz, 1 H, C*H*(H)OCOCH$_3$), 4.24 (dd, J = 6.3, 10.6 Hz, 1 H, CH(*H*)OCOCH$_3$), 6.58 (dd, J = 1.6, 1.6 Hz, 1 H, H-10), 6.94 (d, J = 7.0 Hz, 1 H, H-12), 6.93 (dd, J = 1.6, 1.6 Hz, 1 H, H-2), 7.15 (dd, J = 7.0, 7.1 Hz, 1 H, H-13), 7.21 (dd, J = 1.3, 8.1 Hz, 1 H, H-14), 7.81 (br s, 1 H, NH-1).

The same treatment of (5R, 8R)-5(10→9)abeo-6-propyl-8β-acetyloxymethyl-9,10-didehydroergoline as described for the preparation of **6** from **4**, afforded **8**. MS *m/z*: 282 ($C_{18}H_{22}N_2O$, 24, $[M]^{+\bullet}$), 251 (100, $[M - CH_2OH]^+$), 207 (11), 192 (13), 180 (14), 167 (17), 154 (17), 127 (10), 115 (11), 111 (16). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 0.91 (t, 3 H, $NCH_2CH_2CH_3$), 1.4–1.6 (m, 2H, $NCH_2CH_2CH_3$), 2.0–2.2 (m, 1 H, $NCHHCH_2CH_3$)), 2.58 (ddd, J = H, 1 H, H-4ax), 2.7–3.0 (m, 4 H, H-4eq, H-5, H-8, $NCHHCH_2CH_3$), 3.2–3.9 (m, 3 H, H-7eq, CH_2OH), 4.65 (t, 1 H; CH_2OH), 6.42 (t, 1 H, H-10), 6.74 (d, 1 H, hH-12), 6.98 (dd, 1 H, H-13), 7.08 (s, 1 H, H-2), 7.14 (d, 1 H, H-14), 10.81 (bs, 1 H, NH-1).

4.8. (5R, 8R, 9 S, 10 S)-5(10→9)abeo-6-Methyl-8β-methylen-ergoline-10β, 17-epoxide ***9***

A solution of **6** (2.2 g, 8.6 mmol) and methanesulphonic acid (5 g, 52 mmol) in isopropanol (30 mL) was irradiated (Hanovia PCR) under nitrogen for 2 h at 0 °C. After dilution with ethyl acetate, the solution was washed with 0.1 M ammonium hydroxide solution, then with brine and dried over sodium sulphate. The solvent was removed, and the residue chromatographed on silica gel eluting with ethylacetate/cyclohexane to afford, after crystallisation from ethanol 1.3 g of **9** (56% yield). MS *m/z*: 254 ($C_{16}H_{18}N_2O$, 92, $[M]^{+\bullet}$), 224 (39, $[M - CH_2O]^{+\bullet}$), 233 (100, $[M - CH_2O - H]^+$), 183 (22), 180 (10), 167 (20), 154 (24), 130 (32), 96 (45), 94 (28). ^{1}H-NMR (200 MHz, $CDCl_3$)): δ 2.10 (dd, 1 H, H-7β), 2.34 (s, 3 H, NCH_3), 2.47 (m, 1 H, H-5), 2.68 (ddd, 1 H, H-4ax), 2.94 (ddd, 1 H, H-9), 3.0–3.2 (m, 1 H, H-8), 3.35 (dd, 1 H, H-9), 3.56 (dd, 1 H, H-7α), 3.8–4.0 (m, 2H, CH_2OCH), 4.97 (d, 1 H, H-10), 7.02 (s, 1 H, H-2), 7.2–7.6 (m, 3 H, H-12, H-13, H-14), 8.24 (bs, 1 H, NH-1).

4.9. (5R, 8R, 9 S)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-ergoline ***10*** *and (5R, 8R, 9 R)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-ergoline* ***11***

A solution of **6** (25 g, 98 mmol) in acetic acid (159 mL) was hydrogenated at atmospheric pressure over 2.5 g of 10% Pd/C. The calculated amount of H_2 was taken up in 3 h. The catalyst was removed by filtration and the solvent was evaporated off. The residue dissolved in chloroform was washed with dilute ammonium hydroxide solution, then the organic phase was dried and evaporated. The mixture of **10** and **11** was chromatographed on silica gel eluting with acetone/cyclohexane 3:1, to afford after crystallisation from acetone, 7.4 g of **11** (33.6% yield) as the less polar compound. MS *m/z*: 256 ($C_{16}H_{20}N_2O$, 40, $[M]^{+\bullet}$), 225 (12, $[M - CH_2OH]^+$), 197 (3), 180 (3), 167 (7), 154 (5), 144 (100), 115 (10), 94 (7), 82 (10). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.24 (dd, 1 H, H-7β), 2.36 (s, 3 H, NCH_3), 2.4–2.6 (m, 1 H, H-8), 2.6–2.7 (m, 1 H, H-9), 2.80, (ddd, J = 4.4, 9.6, 9.6 Hz, 1 H, H-5), 3.05 (dd, J = 2.4, 14.4 Hz, 1 H, H-10β), 3.2–3.4 (m, 3 H, CH_2-4, H-7α), 3.66 (dd, J = 10.6, 14.4 Hz, 1 H, H-10α), 3.85 (dd, 1 H, C*H*HOH), 4.04 (dd, 1 H, C*H*HOH), 6.18 (bs, 1 H, CH_2OH), 6.90 (d, 1 H, H-12), 7.15 (dd, 1 H, H-13), 7.23 (s, 1 H, H-2), 7.38 (d, 1 H, H-14), 11.56 (bs, 1 H, NH-1).

Continuing the elution with acetone/cyclohexane 2:1, 13.7 g of **10** (54.8% yield) were obtained after crystallisation from ethanol. MS *m/z*: 256 ($C_{16}H_{20}N_2O$, 39, $[M]^{+\bullet}$), 225 (39, $[M - CH_2OH]^+$), 180 (3), 167 (7), 154 (5), 127 (3), 144 (100), 115 (8), 94 (7), 82 (7). ^{1}H-NMR (200 MHz, Pyridine-d_5)): δ 2.39 (s, 3 H, NCH_3), 2.3–2.5 (m, 2H, H-5, H-7β), 2.5–2.8 (m, 1 H, H-9), 2.8 3.0 (m, 2H, H-4α, H-8), 3.32 (dd, J = 12.8, 16.4, Hz, 1 H, H-10β), 3.44 (dd, J = 6.8, 8.8 Hz, 1 H, H-7α), 3.61 (dd, J = 3.1, 15.0 Hz, 1 H, H-4β), 3.79 (dd, J = 2.5, 16.4 Hz, 1H, H-10α), 3.96 (ddd, 1 H, C*H*HOH), 4.16 (ddd, 1 H, CH*H*OH), 6.14 (t, 1 H, CH_2OH), 7.09 (d, 1 H, H-12), 7.20 (dd, 1 H, H-13), 7.34 (s, 1 H, H-2), 7.46 (d, 1 H, H-14), 11.86 (bs, 1 H, NH-1).

4.10. (5R, 8R)-5(10→9)abeo-6-Methyl-8β-methyl-9,10-didehydroergoline ***12***

To a stirred solution of **6** (3.25 g, 12.5 mmol) in pyridine (50 mL) was slowly added dropwise phosphoryl chloride (2.5 g, 16 mmol) at room temperature. After stirring for 2 h, the

solvent was removed in vacuo and the residue taken up in ethylacetate was washed with 10% ammonium hydroxide solution, then with brine and dried over sodium sulphate. Removal of the solvent, treating with charcoal and crystallisation from a small volume of acetone, afforded 2.65 g of (5R, 8R)-5(10→9)abeo-6-methyl-8β-chloromethyl-9,10-didehydroergoline (77% yield), m.p. 183–185 °C. $[\alpha]_D^{20}$–153 (*c* = 0.076; pyridine). MS *m/z*: 272 ($C_{16}H_{17}N_2Cl$, 43, $[M]^{+\bullet}$), 237 (32, $[M - Cl]^+$), 223 (100, $[M - CH_2Cl]^+$), 221 (11, $[M - CH_2Cl - 2H]^+$), 192 (8), 180 (9), 167 (7), 154 (14), 117 (6), 111 (13), 110 (15). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.23 (m, 1 H, H-7β), 2.38 (s, 3 H, NCH_3), 2.60 (dd, *J* = 10.7, 13.4 Hz, 1 H, H-4α), 2.94 (m, 1 H, H-5), 3.20 (m, 1 H, H-8), 3.30 (m, 2H, H-4β, H-7α), 3.70 (dd, *J* = 8.6, 10.7 Hz, 1 H, C*H*(H)Cl), 4.12 (dd, *J* = 3.8, 10.7 Hz, 1 H, C*H*(H)Cl), 6.46 (dd, *J* = 2.6, 2.6 Hz, 1 H, H-10), 6.79 (d, *J* = 7.3, 1 H, H-12), 7.00 (dd, *J* = 7.3, 8.1 Hz, 1 H, H-13), 7.11 (s, 1 H, H-2), 7.18 (d, *J* = 8.1 Hz, 1 H, H-14), 10.88 (br s, 1 H, NH-1).

To a stirred solution of (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline (22.1 g, 81 mmol) was slowly added portionwise sodium borohydride (6 g, 162 mmol) in dimethylsulphoxide (150 mL). After heating for 2 h at 45 °C, the solution was diluted with brine and thoroughly extracted with ethylacetate. After drying, the solvent was removed in vacuo and the residue filtered on a small pad of silica gel eluting with ethylacetate/cyclohexane 3:5 to afford, after crystallisation from acetone 14.3 g of **12** (74% yield). MS *m/z*: 238 ($C_{16}H_{18}N_2$, 92, $[M]^{+\bullet}$), 237 (39, $[M - H]^{+\bullet}$), 223 (100, $[M - CH_3]^+$), 192 (8), 180 (18), 167 (11), 154 (22), 111 (19), 110 (11), 103 (16). ^{1}H-NMR (200 MHz, $CDCl_3$): δ ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.27 (d, 3 H, CH_3-8), 2.08 (dd, *J* = 8.5, 11.1 Hz, 1 H, H-7ax), 2.50 (s, 3 H, NCH_3), 2.86 (ddd, *J* = 1.6, 10.4, 13.7 Hz, 1 H, H-4ax), 2.9–3.3 (m, 2H, H-5, H-8), 3.31 (m, 1 H, H-7eq), 3.37 (dd, *J* = 2.2, 13.7 Hz, 1 H, H-4eq), 6.41 (dd, *J* = 2.5, 2.5 Hz, 1 H, H-10), 6.9–7.3 (m, 4 H, H-2, H-12, H-13, H-14), 8.20 (bs, 1 H, NH-1).

4.11. (5S, 8R)-5(10→9)abeo-6-Methyl-8β-methyl-9,10-didehydroergoline ***13***

The same treatment of **7** as described for the preparation of (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline from **4**, afforded (5S, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline, m.p. 152–157 °C. MS *m/z*: 272 ($C_{16}H_{17}N_2Cl$, 47, $[M]^{+\bullet}$), 237 (39, $[M - Cl]^+$), 223 (100, $[M - CH_2Cl]^+$), 221 (13, $[M - CH_2Cl - 2H]^+$), 192 (11), 180 (15), 167 (9), 154 (17), 117 (11), 111 (17), 110 (13). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.48 (s, 3 H, NCH_3), 2.58 (m, 1 H, H-7ax), 2.7–2.9 (m, 2H, H-4ax, H-8), 2.90 (d, *J* = 9.3 Hz, 1 H, H-7eq), 3.22 (ddd, *J* = 2.5, 2.5, 10.6 Hz, 1 H, H-5), 3.37 (dd, *J* = 2.5, 13.6 Hz, 1 H, H-4eq), 3.73 (dd, *J* = 8.6, 10.7 Hz, 1 H, C*H*(H)Cl), 4.14 (dd, *J* = 3.8, 10.7 Hz, 1 H, C*H*(H)Cl), 6.42 (s, 1 H, H-10), 6.84 (dd, 1 H, H-12), 7.1–7.32 (m, 2H, H-13, H-14), 8.12 (bs, 1 H, NH-1).

The same treatment of (5S, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline as described for the preparation of **12** from (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline, gave **13**. MS *m/z*: 238 ($C_{16}H_{18}N_2$, 92, $[M]^{+\bullet}$), 237 (41, $[M - H]^{+\bullet}$), 223 (100, $[M - CH_3]^+$), 192 (12), 180 (16), 167 (13), 154 (32), 111 (23), 110 (9), 103 (18). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.32 (d, 3 H, CH_3-8), 2.48 (s, 3 H, NCH_3), 2.58 (m, 1 H, H-7ax), 2.7–2.9 (m, 2H, H-4ax, H-8), 2.90 (d, *J* = 9.3 Hz, 1 H, H-7eq), 3.06 (ddd, *J* = 2.5, 2.5, 10.6 Hz, 1 H, H-5), 3.39 (dd, *J* = 2.5, 13.6 Hz, 1 H, H-4eq), 6.48 (s, 1 H, H-10), 6.88 (dd, 1 H, H-12), 7.1–7.2 (m, 2H, H-13, H-14), 8.09 (bs, 1 H, NH-1).

4.12. (5R)-5(10→9)abeo-6-Methyl-8-methylene-9,10-didehydroergoline ***14***

To a solution of (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline (0.5 g, 1.3 mmol) in dimethylformamide (5 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (0.59 g, 5 mmol) at 10 °C. After stirring for 2 h at 10 °C, the solution was diluted with water and extracted with ethylacetate. The extract was washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the residue was filtered on a small pad of silica gel eluting with acetone/cyclohexane 1:3, to give after crystallisation from acetone 0.36 g of **14** (83% yield)), m.p. 230–232 °C. $[\alpha]_D^{20}$–87.4 (*c* = 0.134; Pyridine). MS *m/z*: 236 ($C_{16}H_{16}N_2$, 93, $[M]^{+\bullet}$), 235 (100, $[M - H]^+$), 221 (20, $[M - CH_3]^+$), 220 (15, $[M - CH_3 - H]^+$), 192 (11), 180 (4), 167 (4), 154 (15), 117 (23), 111 (17), 110 (18). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.41 (s, 3 H, NCH_3), 3.0–3.2 (m, 2H, C*H*(H)-7, CH(*H*)-4), 3.35 (m, 1 H, H-5), 3.60 (dd, *J* = 2.8, 13.9 Hz, 1 H, CH(*H*)-4), 3.75 (d, *J* = 12.1 Hz, 1 H, CH(*H*)-7), 4.98 (m, 1 H, CH(*H*)=), 5.54 (d, *J* = 2.2 Hz, 1H,C*H*(H)=), 7.2–7.5 (m, 4 H, H-12, H-13, H-14, H-2), 12.10 (br s, 1 H, NH-1).

4.13. (5S)-5(10→9)abeo-6-Methyl-8-methylene-9,10-didehydroergoline ***15***

The same treatment of (5S, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline as described for the preparation of **14** from (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline, gave **15** (79% yield), m.p. 229–233 °C. $[\alpha]_D^{20}$+ 88.7 (*c* = 0.162; pyridine). MS *m/z*: 236 ($C_{16}H_{16}N_2$, 95, $[M]^{+\bullet}$), 235 (100, $[M - H]^+$), 221 (23, $[M - CH_3]^+$), 220 (25, $[M - CH_3 - H]^+$), 192 (22), 180 (7), 167 (8), 154 (28), 117 (4), 111 (12), 110 (20). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.42 (s, 3 H, NCH_3), 3.0–3.2 (m, 2H, C*H*(H)-7, CH(*H*)-4), 3.35 (m, 1 H, H-5), 3.61 (dd, *J* = 2.8, 13.9 Hz, 1 H, CH(*H*)-4), 3.74 (d, *J* = 12.1 Hz, 1 H, CH(*H*)-7), 4.98 (m, 1 H, CH(*H*)=), 5.54 (d, *J* = 2.2 Hz, 1 H, C*H*(H)=), 7.2–7.5 (m, 4 H, H-12, H-13, H-14, H-2), 12.00 (br s, 1 H, NH-1).

4.14. (5R, 8R)-5(10→9)abeo-6-Propyl-8β-methyl-9,10-didehydroergoline ***16***

The same treatment of **8** as described for the preparation of (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline from **6**, afforded (5R, 8R)-5(10→9)*abeo*-6-propyl-8β-chloromethyl-9,10-didehydroergoline, m.p. 113–116 °C. MS *m/z*: 300 ($C_{18}H_{21}N_2Cl$, 51, $[M]^{+\bullet}$), 265 (38, $[M - Cl]^+$), 251 (100, $[M - CH_2Cl]^+$), 249 (13, $[M - CH_2Cl - 2H]^+$), 192 (6), 180 (12), 167 (88), 154 (23), 117 (11), 111 (17), 110 (13). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.98 (t, 3 H, $NCH_2CH_2CH_3$), 1.5–1.7 (m, 2H, $NCH_2CH_2CH_3$), 1.93 (dd, *J* = 8.4, 11.2 Hz, 1 H, H-7ax), 2.1–2.2 (dd, 1 H, $NCHHCH_2CH_3$), 2.8–3.10 (m, 3 H, H-4ax, H-8, $NCHHCH_2CH_3$), 3.22 (m, 1 H, H-8), 3.34 (m, 2H, H-4β, H-7α), 3.72 (dd, *J* = 8.6, 10.7 Hz, 1 H, C*H*(H)Cl), 4.12 (dd, *J* = 3.8, 10.7 Hz, 1 H, C*H*(H)Cl), 6.46 (dd, *J* = 2.6, 2.6 Hz, 1 H, H-10), 6.79 (d, *J* = 7.3, 1 H, H-12), 7.05 (dd, *J* = 7.3, 8.1 Hz, 1 H, H-13), 7.21 (s, 1 H, H-2), 7.28 (d, *J* = 8.1 Hz, 1 H, H-14), 10.98 (br s, 1 H, NH-1).

The same treatment of (5R, 8R)-5(10→9)*abeo*-6-propyl-8β-chloromethyl-9,10-didehydroergoline as described for the preparation of 12 from (5R, 8R)-5(10→9)*abeo*-6-methyl-8β-chloromethyl-9,10-didehydroergoline, afforded **16**. MS *m/z*: 266 ($C_{18}H_{22}N_2$, 100, $[M]^{+\bullet}$), 251 (95, $[M - CH_3]^{+\bullet}$), 237 (32, $[M - CH_2CH_2]^+$), 192 (14), 180 (21), 167 (14), 154 (25), 127 (11), 118 (10), 111 (10). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.98

(t, 3 H, $NCH_2CH_2CH_3$), 1.26 (d, 1 H, CH_3-8), 1.5–1.7 (m, 2H, $NCH_2CH_2CH_3$), 1.93 (dd, J = 8.4, 11.2 Hz, 1 H, H-7ax), 2.1–2.2 (dd, 1 H, $NCHHCH_2CH_3$), 2.8–3.0 (m, 3 H, H-4az, H-8, $NCHHCH_2CH_3$), 3.21 (m, 1 H, H-5), 3.34 (dd, J = 2.6, 13.8 Hz, 1 H, H-4eq), 3.43 (dd, 1 H, H-7eq), 6.40 (dd, J = 2.5, 2.5 Hz, 1 H, H-10), 96.96 (s, 1 H, H-2), 7.1–7.2 (m, 3 H, H-12, H-13, H-14), 8.14 (bs, 1 H, NH-1).

4.15. (5R, 8R)-5(10→9)abeo-1,6-Dimethyl-8β-methyl-9,10-didehydroergoline ***17***

To a stirred solution of **12** (0.7 g, 3 mmol) and potassium hydroxide (0.81 g, 8.8 mmol) was added methyl iodide (0.56 g, 4 mmol) in dimethylsulphoxide at room temperature. After stirring 1 h, the solution was diluted with ethylacetate and washed thoroughly with brine and dried over sodium sulphate. The solvent was removed, then the residue was chromatographed on silica gel eluting with ethylacetate/cyclohexane 1:3 to provide, after crystallisation from acetone 0.46 g of **17** (62% yield). MS *m/z*: 252 ($C_{17}H_{20}N_2$, 71, $[M]^{+\bullet}$), 251 (31, $[M - H]^+$), 237 (100, $[M - CH_3]^+$), 208 (10), 194 (20), 181 (11), 168 (24), 118 (24), 118 (12), 110 (15), 108 (25). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (d, 1 H, CH_3-8), 2.05 (dd, 1 H, H-7ax), 2.47 (s, 3 H, NCH_3), 2.83 (ddd, 1 H, H-4ax), 2.9–3.1 (m, 2H, H-5, H-8), 3.2–3.4 (m, 2H, H-4eq, H-7eq), 3.74 (s, 3 H, NCH_3-1), 6.38 (dd, 1 H, H-10), 6.83 (d, 1 H, H-2), 6.9–7.2 (m, 3 H, H-12, H-13, H-14).

4.16. (5R , 8R)-5(10→9)abeo-2-Bromo-6-methyl-8β-methyl-9,10-didehydroergoline ***18***

A solution of *N*-bromosuccinimide (0.8 g, 4.5 mmol) in dioxane (15 mL) was added dropwise to a stirred solution of **12** (0.8 g, 3.4 mmol) in dioxane (40 mL) at 40 °C. After stirring 2 h, the solvent was removed and the residue taken up in chloroform was washed with 0.1 M of ammonium hydroxide solution, then with brine and dried over sodium sulphate. The residue was chromatographed on silica gel eluting with ethylacetate to afford after crystallisation from acetone 0.65 g of **18** (63% yield). MS *m/z*: 216 ($C_{17}H_{17}BrN_2$, 94, $[M]^{+\bullet}$), 303 (100), 301 (95, $[M - CH_3]^+$), 258 (20), 232 (19), 221 (84, $[M - CH3 - HBr]^+$), 205 (18), 152 (23), 126 (16), 118 (22), 110 (41), 103 (16). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.24 (d, 1 H, CH_3-8), 2.09 (dd, 1 H, H-7ax), 2.55 (s, 3 H, NCH_3), 2.76 (m, 1 H, H-4ax), 2.9–3.2 (m, 2H, H-5, H-8), 3.3–3.4 (m, 2H, H-4eq, H-7eq), 6.37 (dd, 1 H, H-10), 6.92 (m, 1 H, H-13), 7.11 (m, 2H, H-12, H-14), 9.11 (bs, 1 H, NH-1).

4.17. (5R, 8R)-5(10→9)abeo-2-Thiomethyl-6-methyl-8β-methyl-9,10-didehydroergoline ***19***

A solution of sulphurylchloride (1.1 g, 7.5 mmol)) in dichloromethane (25 mL) was slowly added dropwise to a stirred solution of dimethyldisulphide (0.4 g, 11 mmol) in dichloromethane (25 mL) at –20 °C. The yellow solution was set aside at room temperature for 1 h, then added dropwise to a stirred solution of **12** (1.25 g, 5.3 mmol) in dichloromethane (30 mL) at –35 °C. After being kept for 1 h at this temperature, the solution was slowly warmed to room temperature and partitioned with 0.1 M ammonium hydroxide. The organic phase was washed with brine and then dried. After removal of the solvent, the residue was crystallised twice from ethylacetate to give 0.8 g of **19** (53% yield). MS *m/z*: 284 ($C_{17}H_{20}N_2S$, 89, $[M]^{+\bullet}$), 283 (12, $[M - H]^+$), 269 8100, $[M - CH_3]^+$), 236 (20), 222 (12), 221 (16), 194 (4), 127 (4), 110 (8). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.23 (d, 1 H, CH_3-8), 2.06 (dd, J = 8.5, 11.0 Hz, 1 H, H-7ax), 2.36 (s, 3 H, NCH_3), 2.51 (s, 3 H, SCH_3)), 2.72 (dd, J = 10.6, 14.3 Hz, 1 H, H-4ax), 2.9–3.1 (m, 2H, H-5, H-8), 3.30 (dd, J = 6.2, 8.5 Hz, 1 H, H-7eq), 3.58 (dd, J = 2.6, 14.3 Hz, 1 H, H-4eq), 6.36 (dd, J = 2.6, 2.6 Hz, 1 H, H-10), 6.91 (m, 1 H, H-13), 7.14 (m, 2H, H-12, H-14), 8.07 (bs, 1 H, NH-1).

4.18. (5R, 8R)-5(10→9)abeo-2,12-Dibromo-6-methyl-8β-methyl-9,10-didehydroergoline ***20***

A solution of bromine (1.7 g, 10.6 mmol) in acetic acid (30 mL) was added dropwise to a stirred solution of **12** (1.5, 6.3 mmol) in acetic acid (50 mL) at room temperature. After stirring for 2 h, the solvent was removed and the residue dissolved in water was extracted with chloroform after basification with 0.1 ammonium hydroxide. The organic phase was dried over sodium sulphate, then the solvent was removed and the residue crystallised twice from ethanol, to furnish 1.3 g of **20** (52% yield). MS *m/z*: 396 (80), 394 ($C_{16}H_{16}Br_2N_2$, 37, $[M]^{+\bullet}$), 381 (100), 316 (31), 301 (75), 258 85), 233 (14), 221 (52), 152 (18), 118 815), 110 (46). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.29 (d, 1 H, CH_3-8), 2.09 (dd, J = 8.5, 11.1 Hz, 1 H, H-7ax), 2.50 (s, 3 H, NCH_3), 2.64 (dd, J = 10.6, 14.3 Hz, 1 H, H-4ax), 2.9–3.1 (m, 2H, H-5, H-8), 3.2–3.4 (m, 2H, H-4eq, H-7eq), 6.76 (dd, J = 2.4, 2.4 Hz, 1 H, H-10), 6.96 (d, 1 J = 8.6 Hz, H, H-14), 7.33 (d, J = 8.6 Hz, 1 H, H-13), 8.43 (bs, 1 H, NH-1).

4.19. (5R, 8R, 9 S)-5(10→9)abeo-6-Methyl-8β-methyl-ergoline ***21***

A solution of **12** (2.5 g, 9.8 mmol) in ethanol (50 mL) was hydrogenated at atmospheric pressure over 1.5 g of 10% Pd/C. The calculated amount of H_2 was taken up in 0.5 h. The catalyst was removed by filtration and the solvent was evaporated off. The residue was twice crystallised from acetone to provide 1.4 g of **21** (56% yield). MS *m/z*: 240 ($C_{16}H_{20}N_2$, 59, $[M]^{+\bullet}$), 225 (4, $[M - CH_3]^+$), 197 (6), 167 (7), 154 (6), 144 (100), 115 (12), 110 (7), 96 (34), 94 (14), 82 (15). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.96 (d, 1 H, CH_3-8), 1.90 (dd, 1 H, H-7ax), 2.2–2.3 (m, 1 H, H-5), 2.35 (s, 3 H, NCH_3), 2.4–2.6 (m, 2H, H-8, H-9), 2.82 (ddd, 1 H, H-4ax), 2.9–3.28 (m, 2H, CH_2-10), 3.28 (dd, 1 H, H-7eq), 3.60 (dd, 1 H, H-4eq), 7.1–7.5 (m, 4 H, H-2, H-12, H-13, H-14), 11.9 (bs, 1 H, NH-1).

4.20. (3R, 5R, 8R)-5(10→9)abeo-2,3α-Dihydro-6-methyl-8β-methyl-9,10-didehydroergoline ***22*** *and (3S, 5R, 8R)-5(10→9)abeo-2,3β-Dihydro-6-methyl-8β-methyl-9,10-didehydroergoline* ***23***

Sodium borohydride (0.45 g, 13 mmol) was cautiously added portionwise to a stirred solution of **12** (1.6 g, 6.7 mmol) in trifluoroacetic acid (50 mL) at 10 °C under nitrogen. After 1 h, the solvent was removed in vacuo and the residue taken up in water was extracted with ethylacetate after basification with 0.1 M ammonium hydroxide solution. The organic phase was washed with brine, then dried over sodium sulphate. The solvent was removed and the residue carefully chromatographed on silica gel eluting with ethylacetate/cyclohexane 2:3, to give after crystallisation from acetone 0.15 g of **22** (9% yield). MS *m/z*: 240 ($C_{16}H_{20}N_2$, 100, $[M]^{+\bullet}$), 239 (59, $[M - H]^+$), 197 (24), 180 (19), 167 (27), 154 (25), 144 (26), 130 (69), 118 (25), 110 (33), 108 (74), 94 (32). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 1 H, CH_3-8), 2.19 (m, 1 H, H-7β), 2.39 (ddd, 1 H, H-4β), 2.65 (s, 3 H, NCH_3), 2.73 (m, 1 H, H-4α), 3.20 (m, 1 H, H-8), 3.26 (dd, 1 H, H-2β), 3.4–3.5(m, 2H, H-3, H-5β), 3.70 (m, 1 H, H-7α), 3.75 (dd, 1 H, H-2α), 6.29 (dd, 1 H, H-10), 6.51 (m, 2H, H-12, H-14), 7.03 (bs, 1 H, NH-1).

Continuing the elution with ethylacetate/cyclohexane 1:1, followed by crystallisation from ethanol 0.75 g of **23** (47% yield) was obtained. MS *m/z*: 240 ($C_{16}H_{20}N_2$, 75, $[M]^{+\bullet}$), 239 (48, $[M - H]^+$), 225 (100), 197 (18), 167 (22), 154 (16), 144 (16), 130 (83), 115 (17), 108 (70), 94 (41). ^{1}H-NMR (400 MHz, 1H-NMR (400 MHz, $CDCl_3$): δ 1.19 (d, 1 H, CH_3-8), 1.62 (dd, 1 H, H-4α), 1.92 (dd, 1 H, H-7β), 2.25 (ddd, 1 H, H-4), 2.41 (s, 3 H, NCH_3), 2.81 (m, 1 H, H-8), 2.91 (m, 1 H, H-5), 3.19 (dd, 1 H, H-2α), 3.28 (dd, 1 H, H-7α), 3.48 (m, 1 H, H-3), 3.65 (dd, 1 H, H-2β), 3.71 (bs, 1 H, NH-1), 6.08 (dd, 1 H, H-10), 6.53 (m, 2H, H-12, H-14), 6.99 (dd, 1 H, H-13).

4.21. (3S, 5R, 8R)-5(10→9)abeo-1-Acetyl-2,3β-Dihydro-6-methyl-8β-methyl-9,10-didehydroergoline ***24***

A solution of **23** (5 g, 21 mmol) and acetic anhydride (3.2 g, 31 mmol) in pyridine (50 mL) was heated at 50 °C for 1 h. The solvent was removed in vacuo and the residue taken up in chloroform was washed with 0.1 M of ammonium hydroxide solution, then brine and dried over sodium sulphate. Removal of the solvent and crystallisation from acetone, provided 4.2 g of **24** (71% yield). MS *m/z*: 282 ($C_{18}H_{22}N_2O$, 68, $[M]^{+\bullet}$), 267 (100, $[M - CH_3]^+$), 239 (13, $[M - CH_3CO]^+$), 197 (16), 180 (10), 167 (15), 154 (11), 130 (18), 115 (13), 108 (53), 94 (42). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.20 (d, 1 H, CH_3-8), 1.65 (dd, 1 H, H-4α), 1.93 (dd, 1 H, H-7β), 2.23 (s, 1 3 H, CH_3CON), 2.25 (m, 1 H, H-4β), 2.40 (s, 3 H, NCH_3), 2.81 (m, 1 H, H-8), 2.91 (m, 1 H, H-5), 3.30 (dd, 1 H, H-7α), 3.4–3.8 (m, 2H, H-2α, H-3), 4.23 (m, 1 H, H-2β), 6.12 (dd, 1 H, H-10), 6.81 (d, 1 H, H-12), 7.13 (dd, 1 H, H-13), 8.03 (d, 1 H, H-14).

4.22. (3S, 5R, 8R)-5(10→9)abeo-2,3β-Dihydro-6-methyl-8β-methyl-12-nitro-9,10-didehydroergoline ***25***

To a stirred solution of **24** (2.25 g, 8 mmol) in acetic acid was added dropwise fuming nitric acid (15 mL) at 15 °C. After 2 h, the solution was diluted with ice water, basified with 0.1 M ammonium hydroxide solution and extracted with ethylacetate. The organic phase was washed with brine and dried over sodium sulphate. After removal of the solvent, the residue was chromatographed on a small pad of silica gel eluting with acetone/cyclohexane 1:2, to furnish after crystallisation from ethanol 1.6 g of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-nitro-9,10-didehydroergoline (61% yield), m.p. 187–189 °C. MS *m/z*: 327 ($C_{18}H_{22}N_3O_3$, 57, $[M]^{+\bullet}$), 312 (100, $[M - CH_3]^+$), 284 (17, $[M - CH_3CO]^+$), 197 (11), 180 (6), 167 (25), 154 (11), 130 (11), 115 (13), 108 (29), 94 (51). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.22 (d, 1 H, CH_3-8), 1.67 (dd, 1 H, H-4α), 1.97 (dd, 1 H, H-7β), 2.23 (s, 1 3 H, CH_3CON), 2.22 (m, 1 H, H-4β), 2.40 (s, 3 H, NCH_3), 2.81 (m, 1 H, H-8), 2.91 (m, 1 H, H-5), 3.30 (dd, 1 H, H-7α), 3.4–3.8 (m, 2H, H-2α, H-3), 4.23 (m, 1 H, H-2β), 6.38 (dd, 1 H, H-10), 7.42 (d, 1 H, H-14), 8.13 (d, 1 H, H-13).

A solution of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-nitro-9,10-didehydroergoline (0.8 g, 2.4 mmol) in 0.1 M sulphuric acid solution (50 mmol) was refluxed for 3 h. The resulting solution was subsequently basified with 0.1 M ammonium hydroxide solution and extracted with chloroform. The organic phase was dried over sodium sulphate and evaporated to dryness. The residue was twice crystallised from ethanol to provide 0.45 g of **25** (65% yield). MS *m/z*: 285 ($C_{16}H_{19}N_3O_2$, 46, $[M]^{+\bullet}$), 284 (27, $[M - H]^+$), 268 (41, $[M - CH_3]^+$), 238 (35), 237 (30), 167 (14), 127 (20), 111(100), 96 (29), 94 (29). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 1 H, CH_3-8), 1.66 (m, 1 H, H-4α), 1.24 (dd, 1 H, H-7β), 2.23 (ddd, 1 H, H-4β), 2.46 (s, 3 H, NCH_3), 2.8–3.0 (m, 2H, H-5, H-8), 3.23 (dd, 1 H, H-2α), 3.32 (dd, 1 H, H-7α), 3.50 (m, 1 H, H-3), 3.66 (dd, 1 H, H-2β), 6.71 (dd, 1 H, H-10), 7.36 (d, 1 H, H-14), 8.02 (d, 1 H, H-13).

4.23. (3S, 5R, 8R)-5(10→9)abeo-2,3β-Dihydro-6-methyl-8β-methyl-12-fluoro-9,10-didehydroergoline ***26***

A solution of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-nitro-9,10-didehydroergoline (2.3 g, 7 mmol) and dihydrate stannous chloride (7.9 g, 35 mmol) in ethanol (100 mL) was heated at 70 °C under nitrogen. After stirring 0.5 h, the solvent was removed and the residue taken up in 0.05 M ammonium hydroxide and extracted with ethylacetate. The organic phase was thoroughly washed with brine, treated with charcoal and dried over sodium sulphate. Evaporation of the solvent and crystallisation from ethanol, furnished 1.9 g (86% yield) of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-amino-9,10-didehydroergoline, m.p. 145–148 °C. MS *m/z*: 297 ($C_{18}H_{22}N_3O$, 47, $[M]^{+\bullet}$), 282 (100, $[M - CH_3]^+$), 254 (27, $[M - CH_3CO]^+$), 197 (26), 180 (4), 167 (15), 154 (19), 130 (10), 115 (23), 108 (26), 94 (21). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (d, 1 H, CH_3-8), 1.63 (dd, 1 H, H-4α), 1.94 (dd, 1 H, H-7β), 2.21 (s, 1 3 H, CH_3CON), 2.20 (m, 1 H, H-4β), 2.47 (s, 3 H, NCH_3), 2.80 (m, 1 H, H-8), 2.93 (m, 1 H, H-5), 3.25 (dd, 1 H, H-7α), 3.4–3.9 (m, 2H, H-2α, H-3), 4.12 (br s, 2H, NH_2), 4.23 (m, 1 H, H-2β), 6.34 (dd, 1 H, H-10), 7.32 (d, 1 H, H-14), 8.04 (d, 1 H, H-13).

A solution of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8 β-methyl-12-amino-9,10-didehydroergoline (3.4 g, 11.4 mmol) in dichloromethane (50 mL) was added dropwise to a suspension of nitrosonium tetrafluoroborate (2.1 g, 12.5 mmol) at 0 °C and the resulting suspension was stirred for 7 h, afterward set aside overnight at room temperature. After dilution with *o*-dichlorobenzene (150 mL), the dichloromethane was distilled off by heating, then the suspension was slowly heated at 150 °C and maintained for 0.5 h. After removal of the solvent in vacuo, the residue was dissolved in chloroform and the solution washed with 0.1 M ammonium hydroxide solution and dried over sodium sulphate. The solvent was removed and the residue chromatographed on silica gel eluting with acetone /cyclohexane 2:3 to furnish, after crystallisation from isopropanol 1.3 g (38% yield) of (3S, 5R, 8R)-5(10→9)*abeo*-2,3β-dihydro-1-acetyl-6-methyl-8β-methyl-12-fluoro-9,10-didehydroergoline, m.p. 164–166 °C. MS *m/z*: 300 ($C_{18}H_{21}FN_2O$, 51, $[M]^{+\bullet}$), 285 (100, $[M - CH_3]^+$), 257 (23, $[M - CH_3CO]^+$), 167 (32), 154 (17), 130 (8), 115 (27), 94 (11). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.20 (d, 1 H, CH_3-8), 1.62 (dd, 1 H, H-4α), 1.89 (dd, 1 H, H-7β), 2.23 (s, 1 3 H, CH_3CON), 2.20 (m, 1 H, H-4β), 2.47 (s, 3 H, NCH_3), 2.80 (m, 1 H, H-8), 2.91 (m, 1 H, H-5), 3.35 (dd, 1 H, H-7α), 3.5–3.9 (m, 2H, H-2α, H-3), 4.11 (m, 1 H, H-2β), 6.28 (dd, 1 H, H-10), 7.14 (d, 1 H, H-14), 7.78 (d, 1 H, H-13).

A solution of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-fluoro-9,10-didehydroergoline (0.7 g, 2.3 mmol) in 0.05 M ethanolic potassium hydroxide solution (30 mmol) was refluxed for 5 h. The solvent was removed and the residue taken up in ethylacetate was washed with brine. The organic phase was dried over sodium sulphate and evaporated to dryness. The residue was crystallised from ethanol to provide 0.35 g of **26** (58% yield). MS *m/z*: 258 ($C_{16}H_{19}FN_2$, 67, $[M]^{+\bullet}$), 243 (100, $[M - CH_3]^+$), 225 (14), 185 (17), 163 (14), 148 (68), 130 (16), 108 (60), 94 (73), 84 (42). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.22 (d, 1 H, CH_3-8), 1.59 (m, 1 H, H-4α), 1.93 (dd, 1 H, H-7β), 2.23 (ddd, 1 H, H-4β), 2.40 (s, 3 H, NCH_3), 2.7–3.0 (m, 2H, H-5, H-8), 3.20 (dd, 1 H,

H-2α), 3.29 (dd, 1 H, H-7α), 3.47 (m, 1 H, H-3), 3.65 (dd, 1 H, H-2β), 6.41 (dd, 1 H, H-14), 6.45 (dd, 1 H, H-10), 6.71 (ddd, 1 H, H-13).

4.24. (3S, 5R, 8R)-5(10→9)abeo-2,3β-Dihydro-6-methyl-8β-methyl-12-bromo-9,10-didehydroergoline **27**

To a stirred solution of **24** (0.7 g, 2.5 mmol) in acetic acid (30 mL) was added dropwise a solution of bromine (0.45 g, 2.8 mmol) in acetic acid (10 mL) at room temperature. After stirring for 3 h, the solution was diluted with ethylacetate and thoroughly washed with ammonium hydroxide 0.1 M, then dried over sodium sulphate. Removal of the solvent and crystallisation from methanol, furnished 0.65 g of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-bromo-9,10-didehydroergoline (72% yield), m.p. 163–165 °C. MS *m/z*: 360 ($C_{18}H_{21}BrN_2O$, 59, $[M]^{+\bullet}$), 345 (100, $[M - CH_3]^+$), 317 (11, $[M - CH_3CO]^+$), 197 (26), 180 (17), 154 (19), 130 (17), 115 (15), 108 (33), 94 (22). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (d, 1 H, CH_3-8), 1.64 (dd, 1 H, H-4α), 1.97 (dd, 1 H, H-7β), 2.24 (s, 1 3 H, CH_3CON), 2.23 (m, 1 H, H-4β), 2.42 (s, 3 H, NCH_3), 2.81 (m, 1 H, H-8), 3.23 (dd, 1 H, H-2α), 3.30 (dd, 1 H, H-7α), 3.50 (m, 1 H, H-3), 3.65 (dd, 1 H, H-2β), 6.71 (dd, 1 H, H-10) 6.92 (d, 1 H, H-14), 7.27 (d, 1 H, H-13).

A solution of (3S, 5R, 8R)-5(10→9)*abeo*-1-acetyl-2,3β-dihydro-6-methyl-8β-methyl-12-bromo-9,10-didehydroergoline (0.4 g, 1.1 mmol) in 0.05 M ethanolic potassium hydroxide (30 mmol) was refluxed for 7 h. The solvent was removed and the residue taken up in ethylacetate was washed with brine. The organic phase was dried over sodium sulphate and evaporated to dryness. The residue was crystallised from acetone to afford 0.18 g of **27** (51% yield). MS *m/z*: 318 ($C_{16}H_{19}BrN_2$, 53, $[M]^{+\bullet}$), 305 (100), 303 (94, $[M - CH_3]^+$]), 223 (16), 208 (15), 182 (15), 167 (16), 152 (12), 130 (10), 111 (11), 108 (21), 94 (34). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 1 H, CH_3-8), 1.62 (m, 1 H, H-4α), 1.94 (dd, 1 H, H-7β), 2.23 (ddd, 1 H, H-4β), 2.40 (s, 3 H, NCH_3), 2.8–3.0 (m, 2H, H-5, H-8), 3.23 (dd, 1 H, H-2α), 3.30 (dd, 1 H, H-7α), 3.50 (m, 1 H, H-3), 3.65 (dd, 1 H, H-2β), 6.36 (d, 1 H, H-14), 6.71 (dd, 1 H, H-10), 7.22 (d, 1 H, H-13).

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