SYNTHESIS OF 5(10→9)abeo-ERGOLINES

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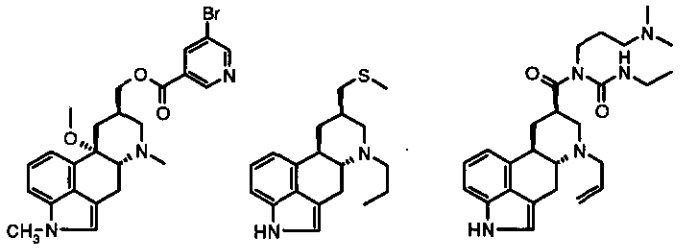
Abstract-Reaction of the (5 R, 8 R)-ergoline derivative (**6**) with the couple $CCl_4/(Ph)_3P$ unexpectedly resulted in the formation of the novel (5 S, 8 R)-5 (10→9)abeo-ergoline derivative. A mechanism of this transposition process is proposed.

Ergoline derivatives exhibit marked central and peripheral pharmacological effects.[1] These include adrenergic, serotonergic/antiserotonergic and dopaminergic/antidopaminergic activities generally due to non selective interaction with the receptors for these neurotransmitters. The diverse pharmacological actions of ergolines have generated considerable interest in their use as research tools in neuropsychopharmacology (eg. LSD) and as potential therapeutic agents in the treatment of various neuroendocrine and neuropsychiatric disorders.[2]

Of particular importance is the dopamine agonist activity of ergot compounds, which has many important research and clinical implications in the treatment of Parkinsonism, the galactorrhea-amenorrhea syndrome, acromegaly, and several neuropsychiatric disturbances associated with aging.[3]

Extensive efforts to discover novel therapeutically active ergoline derivatives have been centred on structural modifications of natural ergot alkaloids and the simpler clavines with the aim to improve the potency and selectivity of action.[4]

From works in this field, some semisynthetic ergoline derivatives have become valuable drugs, for example, nicergoline (Sermion®) (**1**) is clinically used for the treatment for senile mental impairment, whilst pergolide (Permax®) (**2**) and cabergoline (Dostinex®) (**3**) have been developed as effective agents for the treatment of hyperprolactinemic states and Parkinson's disease.[5]



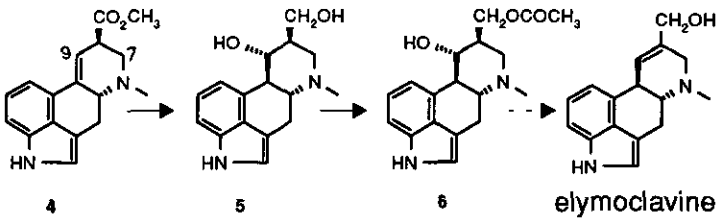
1 nicergoline **2** pergolide **3** cabergoline

From this background, a preparation of the elymoclavine, to be used as a highly amenable intermediate, was explored starting from stereochemically pure lysergic acid easily provided by fermentation.[6]

The synthetic strategy was based on the use of the key intermediate (**6**) obtained by controlled monoacetylation of the diol (**5**) prepared in highly diastereoselective manner and in high yield by treatment of methyl lysergate (**4**) with diborane followed by action of hydrogen peroxide.[7]

Compound (**6**) can presumably be converted into elymoclavine by the action of a suitable dehydrating agent. However, the *cis* stereochemical relationship between the 9α-OH and 8α-H in **6** makes this conversion unlikely.

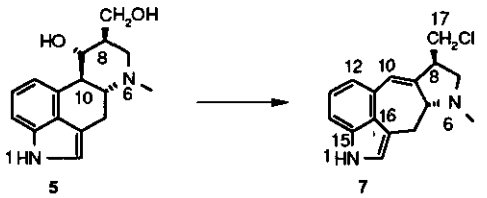
Scheme I



4 **5** **6** elymoclavine

Ninomiya has previously demonstrated that analogues of **6** under solvolytic conditions follow different reaction outcomes leading to an elimination, or substitution, or fragmentation reaction.[8] The probabilities of occurrence of these reactions are significantly affected either by the C/D ring junction or by the stereochemical relationship between the 8 and 9 substituents. Moreover, Bernardi showed that the 9α-hydroxy-dihydrolysergol (**5**) underwent a molecular rearrangement yielding 5(10→9)abeo-6-methyl-9,10-didehydro-8β-chloromethylergoline (**7**) (85% yield), when submitted to the action of $POCl_3$/Py.HCl in pyridine at 70°C.[9]

Scheme II



The attribution of the structure to the rearranged product (**7**) was established on the basis of spectroscopic data. However, no substantial proof of the stereochemical relationship of the chiral centres C-5 and C-8 was reported.

The formation of the 5(10→9)abeo-ergoline skeleton was explained assuming the occurrence of a Wagner-Meerwein rearrangement favoured by the antiperiplanar relationship between C-9α-OH and C-5-C-10 bonds. The structure of the rearranged olefin (**7**) was supported by mechanistic consideration.

In fact, for a Wagner-Meerwein rearrangement, the coplanarity of migrating groups in the rearranging species is an essential geometrical requirement for the occurrence of such reaction mechanism.

This antiparallel relationship of departing and migrating groups fulfils the requirements for a concerted bond-breaking and bond-forming process.

Based on this considerations, the condition required for ring C expansion-ring D contraction are satisfied for the hydroxy compound (**5**). It was taken for granted that the absolute configuration at both C-5 and C-8 was the same as in the starting material, (5 R, 8 R), since these chiral centres were assumed not involved in the mechanism considered.

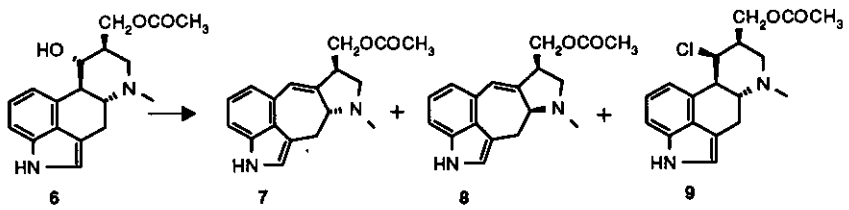
Following this precedent, the conversion of **6** into elymoclavine was attempted using the couple $CCl_4/(Ph)_3P$ in acetonitrile, which has been reported to dehydrate secondary alcohols.[10]

When compound (**6**) was submitted to the reaction conditions referred to by Appel, three compounds (**7**) (12% yield), (**8**) (68% yield), and (**9**) (7% yield) were formed.

None was similar to *O*-acetylelymoclavine or to *O*-acetyllysergol when compared to sample prepared either by acetylation of the natural occurring elymoclavine, or lysergol prepared by $LiAlH_4$ reduction of methyl lysergate.

Factors such as the structure and conformation of the chiral transition state could account for the different proportion of compounds (**7**) and (**8**).

Scheme III



The formation of **9** can be explained by nucleophilic displacement of the triphenyloxyphosphonio group by chloride ion under the Walden inversion condition.

The structures and diastereomeric relationship of (**7**) (5 R, 8 R) and the unnatural (**8**) (5 S, 8 R) were demonstrated by NMR experiments conducted on the hydroxy derivatives (**10**) and (**11**) deriving respectively from the saponification of **7** and **8**.

A reverse heterocorrelated ^{13}C-^{1}H long range experiment (HMBC) confirmed the proposed structure of **10**. The correlations of C-12 and C-16 with the vinylic proton H-10, and the correlation of the vinylic carbon C-10 with H-12, define the connection between the indolic and vinylic fragment.

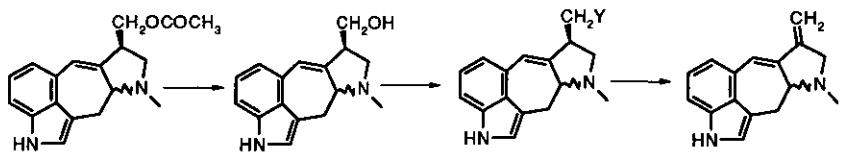
The three bond correlations of C-5 with H-10 and C-9 with CH_2-4, define the seven-membered ring. Moreover, the correlations of C-8 with H-10, C-5 and C-9 with CH_2-7, define the five-membered ring and its junction with the seven-membered one. As far as the diastereomeric relationship of compounds (**10**) and (**11**) is concerned, considering (R) the stereochemistry at C-8, the absolute configuration at C-5 is assigned by comparison of the NOESY spectra of the two compounds.

In the case of the stereochemistry at C-8 was (S), this should reasonably imply the involvement of C-8 in the reaction mechanism leading to the formation of two racemates,(5 R, 8 R), (5 S, 8 S) and (5 R, 8 S), (5 S, 8 R), whereas the optically pure diastereomers (**10**) and (**11**) were formed. In compound (**10**), a correlation in the bidimensional map between H-8 and H-7 at 3.34 ppm assigns this resonance to H-7α. A correlation between H-7β at 2.40 ppm and H-5, and no correlation between H-7α and H-5, assigns to C-5 the absolute stereochemistry (R).

In compound (**11**), a correlation between H-8 and H-7 at 2.66 ppm, assigns this resonance to H-7α and, consequently, a correlation between H-7α and H-5 assignes to C-5 the absolute stereochemistry (S). The stereochemical relationship was further demonstrated by the conversion of (**7**) and (**8**) into the two corresponding diene enantiomers (**14**) and (**15**).

This was achieved respectively by the conversion of **7** into the corresponding chloride (**12**) by reaction with $POCl_3$ in pyridine at room temperature, and **8** into the corresponding iodide (**13**) by reaction with $(Ph)_3P/I_2$ and imidazole.[11] The transformation of **7**, differently from **8**, into the corresponding iodide analogue occurred in low yield, this may be caused by the steric effect of the H-5β on the formation of the activated species (triphenyloxyphosphonium group) necessary for the conversion. Two halo derivatives (**12**) and (**13**) were subsequently treated with DBU in DMF at low temperature thus affording the diene analogues (**14**) and (**15**).

Scheme IV

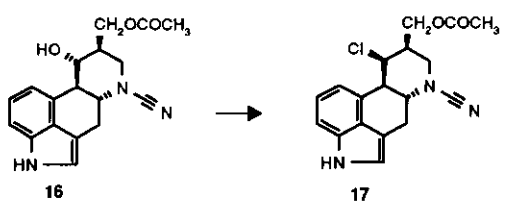


As far as the mechanism of the formation of **7** and **8** is concerned, a Wagner-Meerwein rearrangement previously considered as a conceivable mechanism for the transposition of 9α-hydroxyergolines to 5(9→10)abeo-ergolines does not account completely for the formation of compound (**8**) with an opposite chirality of C-5 with respect to the starting material.

Two analogues of **6**, bearing a modification either in position 6 (piperidine's nitrogen) **17**, or in the indole moiety **18**, were designed as a suitable marker with the aim of understanding the reaction outcome more fully, and possibly to identify the structural features required for such reaction.

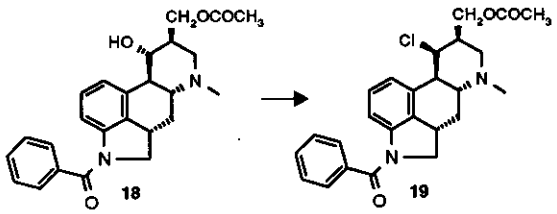
Under the same conditions employed, two completely different reaction outcomes were observed.When compound (**16**), which was easily obtained by demethylation of **6** with cyanogen bromide (Von Braun's reaction), was submitted to the action of $CCl_4/(Ph)_3P$ in acetonitrile to furnish quantitatively (**17**).[12]

Scheme V



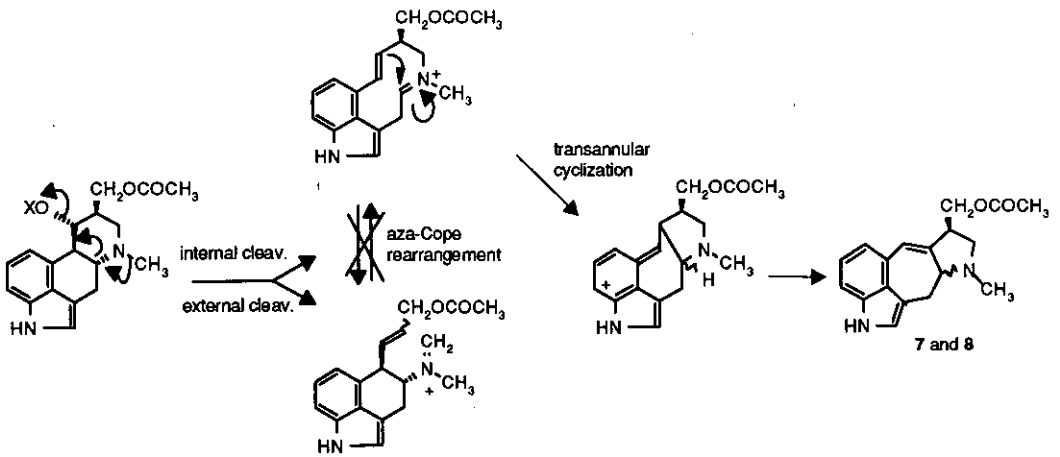
Compound (**18**), prepared by the reduction of compound (**6**) to the corresponding 2,3-dihydro derivative, with sodium borohydride in trifluoroacetic acid at low temperature and subsequent benzoylation of the indoline nitrogen, gave rise to **19** as the only reaction product.[13]

Scheme VI



Analogous result was obtained by Ninomiya in its total synthesis of (±)-lysergol, employing thionyl chloride as dehydrating agent.[14] In both cases, the products arising from a SN2 nucleophilic substitution with Walden invertion at C-9 or through a similar mechanism, were the only compounds formed. These results imply an active role of the 6-nitrogen and the indole ring system in the reaction mechanism leading to the formation of the abeo derivatives (**7**) and (**8**). It can be hypothesized that the two diastereomers **7** and **8** were formed from an azecine intermediate *via* a Grob heterolytic fragmentation (internal cleavage). The azecine intermediate subsequently underwent a transannular cyclization leading to the formation of the transposed compounds (**7**) and (**8**).[15]

Scheme VII



The reaction outcomes depicted in the Schemes VI and VII appears to substantiate this mechanism. Indeed, a basic 6-nitrogen would be required for the formation of the azecine and

a fully aromatic indole would be necessary for the stabilization of the benzylic carbocation deriving from the transannular rearrangement.

A mechanism having some resemblance to those reported has been recently described by Weinreb *et al.* in a paper dealing with the total synthesis of (±)-lysergic acid *via* an alkene/*N*-sulfonylimine cyclization.[16]

The absence of 6,7-secoergolines in the reaction's products would indicate the preference for internal versus external cleavage in the Grob fragmentation in accordance with Marshall's observations related to the fragmentation of 4-substituted decahydroisoquinolines. This fact also point out that the aza-Cope rearrangement does not occur in the reaction pathway.

Otherwise according to Ninomiya, the resulting open intermediate of the external cleavage would yield 6,7-secoergolines.[17]

The results obtained by others and those reported in this paper underline the extreme sensitiveness of the nature of the substrate, of the leaving group, and of the solvents and the reagents employed as far as the reaction's products are concerned.[18] This work unveiled the intrigueing possibility to prepare (5 R, 8 R) and (5 S, 8 R)-5(10→9)abeo-ergolines in diastereoselective manner from a common chiral intermediate. In particular, compounds with the unnatural stereochemistry (5 S, 8 R) can be used for the synthesis of potential biological active substances or for gaining a better understanding of the role of the stereochemistry in determining the biological activity of compounds of this class.[19]

EXPERIMENTAL PART

1H-NMR spectra were recorded on Varian VXR-200 MHz and Varian VXR 400 S MHz spectrometers using TMS as an internal standard. Optical rotation were measured at 589 nm using a JASCO DIP-140 polarimeter. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. Electron-impact mass spectra were recorded in form of m/z (intensity to base=100) on a Finnigan MAT SSQ 7000 mass spectrometer.

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

To a stirred solution of methyl lysergate (**4**) (35.7 g, 125 mmol) containing $NaBH_4$ (24.2 g, 638 mmol) in THF (600 mL) was added dropwise $BF_3{\cdot}Et_2O$ (23 mL, 210 mmol) at -30°C under nitrogen. After stirring overnight at rt, H_2O (25 mL) in THF (150 mL) was carefully added maintaining the temperature at -25 - -15°C by cooling. Then the mixture was gradually warmed up at rt followed by concomitant addition of H_2O_2 120 vol. (100 mL) and a solution of KOH (50

g, 877 mmol) in H_2O (350 mL). Afterwards, the resulting suspension was heated at 45°C for 4 h, then the solvents were removed and the residue taken up in MeOH (250 mL) was refluxed for 5 h. After removal of the solvent, the crude reaction mixture was dissolved in boiling H_2O (500 mL) and set aside at rt. The precipitate was collected, washed with H_2O, then crystallized twice from boiling methanol to give after drying, compound (**5**) (22.5 g, 65%), as white needles, mp 278-281°C. $[\alpha]^{20}_D$ -25.3° (c= 0.124, 1 N HCl). MS m/z: 272 ($C_{16}H_{20}N_2O_2$, 100, $[M]^{+\cdot}$), 255 (84, $[M-OH]^+$), 223 (32, $[M-CH_2OH-H_2O]^+$), 167 (11, ion c), 154 (91, ion d), 144 (32, ion e), 127 (40, ion f). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.92 (m, 2 H, 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, CH(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). *Anal.* Calcd for $C_{16}H_{20}N_2O_2$: C 70.56, H 7.40, N 10.29. Found: C 70.32, H 7.21, N 10.38.

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

Acetyl chloride (19.5 mL, 275 mmol) was added dropwise to a stirred suspension of **5** (41 g, 150 mmol) in pyridine (750 mL) at 0°C and the mixture was stirred at rt for 5 h. Ice water (1500 mL) was added to the solution and the mixture was extracted with AcOEt. The extract was successively washed with water, saturated aqueous $NaHCO_3$, and brine and then dried over anhydrous Na_2SO_4. Concentration of the solvent in vacuo gave product (**6**) which was crystallized from AcOEt affording **6** (39 g, 83%) as white crystals, mp 205-207°C. $[\alpha]^{20}_D$ -67° (c= 0.147, pyridine). MS m/z: 314 ($C_{18}H_{22}N_2O_3$, 100, $[M]^{+\cdot}$), 297 (44, $[M-OH]^+$), 253 (27, $[M-OH-CH_3CO]^+$), 237 (53, $[M-OH-CH_3COO]^+$), 223 (20, $[M-H_2O-CH_3COOCH_2]^+$), 154 (72, ion d), 144 (17, ion e), 127 (27, ion f). ^{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, CH(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). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C 68.77, H 7.05, N 8.91. Found: C 68.96, H 7.23, N 8.83.

(5 R, 8 R)-5(10→9)abeo-6-Methyl-8β-acetyloxymethyl-9,10-didehydroergoline (**7**)

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

(5 R, 8 R)-6-Methyl-8β-acetyloxymethyl-9β-chloroergoline (**9**)

Triphenyl phosphine (5.2 g, 19.8 mmol) and CCl_4 (1.65 mL, 17 mmol) were slowly added to a stirred solution of **6** (5 g, 16 mmol) in acetonitrile (100 mL), then the resulting solution was refluxed for 10 h. After removal of the solvent in vacuo, the residue was taken up in AcOEt and the organic layer was washed with saturated aqueous $NaHCO_3$, with brine, and then dried over Na_2SO_4. Removal of the solvent gave a residue, which was purified by chromatography on silica gel (AcOEt/Hexane 7/3) to give, after crystallization from Et_2O, compound (**9**) (0.27 g, 7%) as colorless crystals, mp 227-229°C. $[\alpha]^{20}_D$ -83° (c= 0.135, pyridine). MS m/z: 332 ($C_{18}H_{21}ClN_2O_2$, 21, $[M]^{+\cdot}$), 297 (29, $[M-Cl]^+$), 296 (44, $[M-HCl]^{+\cdot}$), 237 (100, $[M-HCl-CH_3COO]^+$), 223 (40, $[M-HCl-CH_3COOCH_2]^+$), 192 (23, ion a), 180 (10, ion b), 167 (10, ion c), 154 (19, ion d), 127 (27, ion f). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.12 (s, 3 H, $OCOCH_3$), 2.51 (s, 3 H, NCH_3), 2.6-2.9 (m, 5 H, H-4ax, H-5, CH_2-7, H-8), 3.35 (m, 1 H, H-10ax), 3.42 (dd, J=4.0, 14.0 Hz, 1 H, H-4eq), 4.20 (m, CH_2OCOCH_3), 5.23 (br s, 1 H, H-9), 6.89 (s, 1 H, H-2), 6.9-7.3 (m, 3 H, H-12, H-13, H-14), 7.96 (br s, 1 H, NH-1). *Anal.* Calcd for $C_{18}H_{21}N_2O_2Cl$: C 64.86, H 6.36, N 8.42. Found: C 64.93, H 6.23, N 8.53.

The mixture of compounds (**7**) and (**8**) was separated by flash chromatography (AcOEt/cyclohexane 9/2) to furnish **7** as the more polar product and **8** as the less polar product in a ratio of about 1:5.

Compound (**7**) (0.57 g, 12%) crystallized from AcOEt as white crystals, mp 147-150°C. $[\alpha]^{20}_D$ -223° (c= 0.102, pyridine). MS m/z: 296 ($C_{18}H_{20}N_2O_2$, 18, $[M]^{+\cdot}$), 235 (11, $[M-CH_3COO-2\ H]^+$), 223 (100, $[M-CH_3COOCH_2]$+), 221 (18, $[M-CH_3COO-2\ H]^+$), 192 (13, ion a), 180 (10, ion b), 167 (12, ion c), 154 (18, ion d), 117 (16, ion g), 111 (23, ion h), 110 (24, ion i). ^{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), 3.10 (m, 1 H, H-5), 3.28 (m, 1 H, H-8), 3.35 (m, 2 H, H-4β, H-7α), 4.16 (dd, J=7.8, 11.0 Hz, 1 H, C<u>H</u>(H)$OCOCH_3$), 4.51 (dd, J=4.8, 11.0 Hz, CH(<u>H</u>)$OCOCH_3$), 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, 2 H, H-13, H-14), 8.17 (br s, 1 H, NH-1). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C 72.85, H 6.80, N 9.45. Found: C 73.06, H 6.53, N 9.58.

Compound (**8**) (3.1g, 68%) crystallized from AcOEt as white crystals, mp 129-131°C. $[\alpha]^{20}_D$ +185° (c= 0.098, pyridine). MS m/z: 296 ($C_{18}H_{20}N_2O_2$, 20, $[M]^{+\cdot}$), 235 (12, $[M-CH_3COO-2\ H]^+$), 223 (100, $[M-CH_3COOCH_2]$+), 221 (13, $[M-CH_3COOCH_2-2\ H]$+), 192 (8, ion a), 180 (6, ion b), 167 (ion c), 154 (9, ion d), 117 (9, ion g), 111 (12, ion h), 110 (10, ion i). ^{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, 2 H, 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<u>H</u>(H)$OCOCH_3$), 4.22 (dd, J=6.3, 10.6 Hz, 1 H, CH(<u>H</u>)$OCOCH_3$), 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). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C 68.77, H 7.05, N 8.91. Found: C 68.96, H 7.23, N 8.73.

<u>(5 R, 8 R)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-9,10-didehydroergoline (**10**)</u>

A stirred solution of **7** (1.25 g, 4.2 mmol) in MeOH (30 mL) was treated with 1 M NaOH (5 mL, 5 mmol) at rt for 1 h. The solvent was removed <u>in vacuo</u> and the residue dissolved in $CHCl_3$/MeOH 9.5/1 was washed with water, then brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue crystallized from MeOH furnished **10** (1.1 g, 85%) as white crystals, mp 251-253°C. $[\alpha]^{20}_D$ -274° (c= 0.168; pyridine). MS m/z: 254 ($C_{16}H_{18}N_2O$, 23, $[M]^{+\cdot}$), 223 (100, $[M\text{-}CH_2OH]^+$), 221 (15, $[M\text{-}CH_2OH\text{-}2\ H]^+$), 192 (14, ion a), 180 (13, ion b), 167 (15, ion c), 154 (20, ion d), 117 (8, ion g), 111 (42, ion h), 110 (31, ion i), 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<u>H</u>(H)OH), 3.82 (m, 1 H, CH(<u>H</u>)OH), 4.62 (dd, J=5.0, 5.0 Hz, 1 H, CH_2O<u>H</u>), 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). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C 75.56, H 7.05, N 11.01. Found: C 75.32, H 7.23, N 11.37.

<u>(5 S, 8 R)-5(10→9)abeo-6-Methyl-8β-hydroxymethyl-9,10-didehydroergoline (**11**)</u>

The same treatment of **8** (2.5 g, 84 mmol) as described for the preparation of **10** from **7**, gave **11** (1.8 g, 84%) after crystallization from acetone, mp 215-218°C. $[\alpha]^{20}_D$ +188° (c= 0.178; pyridine). MS m/z: 254 ($C_{16}H_{18}N_2O$, 23, $[M]^{+\cdot}$), 223 (100, $[M\text{-}CH_2OH]^+$), 221 (17, $[M\text{-}CH_2OH\text{-}2\ H]^+$), 192 (15, ion a), 180 (12, ion b), 167 (14, ion c), 154 (14, ion d), 117 (3, ion g), 111 (16, ion h), 110 (11, ion i). ^{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<u>H</u>(H)OH), 3.89 (dd, J=4.4, 9.7 Hz, CH(<u>H</u>)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). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C 75.56, H 7.05, N 11.01. Found: C 75.39, H 7.29, N 11.12.

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

To a stirred solution of **10** (0.65 g, 2.5 mmol) in pyridine (20 mL) was slowly added dropwise $POCl_3$ (0.5 g, 3.2 mmol) at rt. After stirring for 2 h, the solvent was removed in vacuo and the residue taken up in AcOEt was washed with 10% NH_4OH solution, then with brine and dried over anhydrous Na_2SO_4. Removal of the solvent, charcoalization and crystallization from a small volume of acetone, afforded **12** (0.53 g, 77%), mp 183-185°C. $[\alpha]^{20}_D$ -153° (c= 0.076; pyridine). Ms m/z: 272 ($C_{16}H_{17}N_2Cl$, 43, $[M]^{+\cdot}$), 237 (32, $[M\text{-}Cl]^+$), 223 (100, $[M\text{-}CH_2Cl]^+$), 221 (11, $[M\text{-}CH_2Cl\text{-}2\ H]^+$), 192 (8, ion a), 180 (9, ion b), 167 (7, ion c), 154 (14, ion d), 117 (6, ion g), 111 (13, ion h), 110 (15, ion i). ^{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, 2 H, H-4β, H-7α), 3.70 (dd, J=8.6, 10.7 Hz, 1 H, C<u>H</u>(H)Cl), 4.12 (dd, J=3.8, 10.7 Hz, 1 H, C<u>H</u>(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). *Anal.* Calcd for $C_{16}H_{17}N_2Cl$: C 70.45, H 6.28, N 10.27. Found: C 70.38, H 6.06, N 10.34.

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

To a stirred solution containing **11** (0.35 g, 1.3 mmol), $(Ph)_3P$ (0.54 g, 2 mmol), and imidazole (0.19 g, 2.8 mmol) in THF (30 mL) was slowly added dropwise a solution of iodine (0.52 g, 2 mmol) in THF (10 mL) at rt. After stirring for 1 h, the solution was diluted with AcOEt and washed with 1 M $NaHSO_3$, then with 10% NH_4OH solution, and subsequently with brine. After drying over anhydrous Na_2SO_4, the solvent was removed in vacuo and the resulting residue was chromatographed on silica gel eluting with AcOEt/cyclohexane 5/3 to give after crystallization from AcOEt **13** (0.39 g, 78%) as white crystals, mp 246-250°C. $[\alpha]^{20}_D$ +177°(c= 0.089; pyridine). MS m/z: 364 ($C_{16}H_{17}IN_2$, 23, $[M]^{+\cdot}$), 237 (100, $[M\text{-}I]^+$), 223 (42, $[M\text{-}CH_2I]_+$), 221 (12, $[M\text{-}CH_2I\text{-}2\ H]^+$), 192 810, ion a), 180 (10, ion b), 167 (13, ion c), 154 (13, ion d), 128 (52, $[HI]^{+\cdot}$), 127 (52, $[I]^+$), 117 (12, ion g), 111 (8, ion h), 110 (22, ion i). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.54 (s, 3 H, NCH_3), 2.74 (ddd, J=1.2, 6.0, 9.7 Hz, 1 H, H-7α), 3.15 (ddd, J=1.5, 10.4, 13.8 Hz, 1 H, H-4β), 3.22 (m, 1 H, H-8), 3.4-3.5 (m, 3 H, H-5, H-7β, C<u>H</u>(H)I), 3.66 (dd, J=2.7, 13.8 Hz, 1 H, H-4α), 3.80 (dd, J=9.5, 12.2 Hz, 1 H, CH(<u>H</u>)I), 6.73 (dd, J=1.3, 1.4 Hz, 1

H, H-10), 7.2-7.6 (m, 4 H, H-12, H-13, H-14, H-2), 12.07 (br s, 1 H, NH-1). Anal. Calcd for $C_{16}H_{17}N_2I$: C 52.76, H 4.70, N 7.69. Found: C 52.53, H 4.91, N 7.73.

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

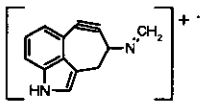
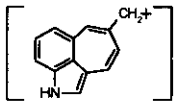
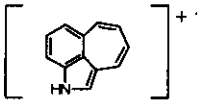
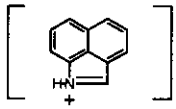
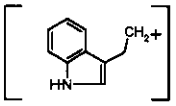
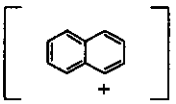
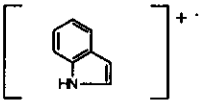
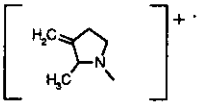
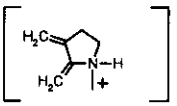
To a solution of **12** (0.5 g, 1.3 mmol) in DMF (5 mL) was added DBN (0.59 g, 5 mmol) at 0°C. After stirring for 2 h at 0-5°C, the solution was diluted with water and extracted with EtOAc. The extract was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was filtered on a small pad of silica gel eluting with acetone/cyclohexane 1/3, to give **14** (0.36 g, 83%) after crystallization from acetone, mp 230-232°C. $[\alpha]^{20}_D$ -87.4°. (c= 0.134; pyridine). MS m/z: 236 ($C_{16}H_{16}N_2$, 93, $[M]^{+\cdot}$), 235 (100, $[M-H]^+$), 221 (20, $[M-CH_3]^+$), 220 (15, $[M-CH_3-H]^+$), 192 (11, ion a), 180 (4, ion b), 167 (4, ion c), 154 (15, ion d), 117 (23, ion g), 111 (17, ion h), 110 (18, ion i). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.41 (s, 3 H, NCH_3), 3.0-3.2 (m, 2 H, CH(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, 1 H, CH(H)=), 7.2-7.5 (m, 4 H, H-12, H-13, H-14, H-2), 12.00 (br s, 1 H, NH-1). *Anal.* Calcd for $C_{16}H_{16}N_2$: C 81.32, H 4.82, N 11.85. Found: C 81.63, H 4.97, N 11.51.

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

The same treatment of **13** (0.35 g, 0.9 mmol) as described for the preparation of **14** from **12**, gave **15** (0.18 g, 79%) after crystallization from acetone, mp 229-231°C. $[\alpha]^{20}_D$ +88.7° (c= 0.162; pyridine). MS m/z: 236 ($C_{16}H_{16}N_2$, 95, $[M]^{+\cdot}$), 235 (100, $[M-H]^+$), 221 (23, $[M-CH_3]^+$), 220 (25, $[M-CH_3-H]^+$), 192 (22, ion a), 180 (7, ion b), 167 (8, ion c), 154 (28, ion d), 117 (4, ion g), 111 (12, ion h), 110 (20, ion i). ^{1}H-NMR (200 MHz, Pyridine-d_5): δ 2.42 (s, 3 H, NCH_3), 3.0-3.2 (m, 2 H, CH(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, 1 H, CH(H)=), 7.2-7.5 (m, 4 H, H-12, H-13, H-14, H-2), 12.00 (br s, 1 H, NH-1). *Anal.* Calcd for $C_{16}H_{16}N_2$: C 81.32, H 4.82, N 11.85. Found: C 81.59, H 4.97, N 11.56.

STRUCTURES OF THE MASS'FRAGMENTS

Chemical structures were tentatively attributed to the more significant fragments, starting from m/z 100 for all compounds.

m/z	Chemical Formula	Proposed Structure
192 (ion a)	$C_{13}H_{10}N_2$	
180 (ion b)	$C_{13}H_{10}N$	
167 (ion c)	$C_{12}H_9N$	
154 (ion d)	$C_{11}H_8N$	
144 (ion e)	$C_{10}H_{10}N$	
127 (ion f)	$C_{10}H_7$	
117 (ion g)	C_8H_7N	
111 (ion h)	$C_7H_{13}N$	
110 (ion i)	$C_7H_{12}N$	

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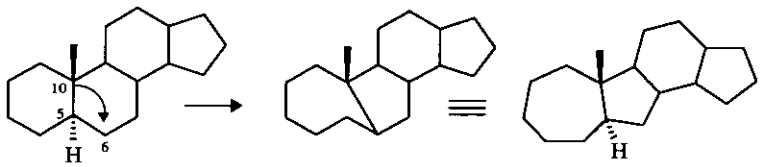
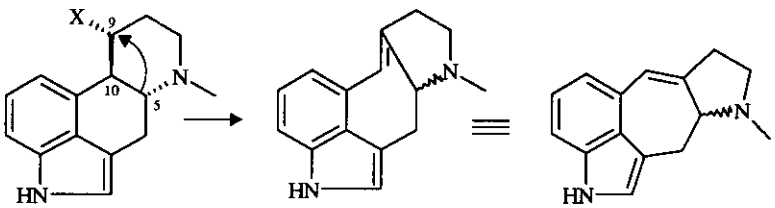
USE OF THE PREFIX ***abeo***

The use of the prefix ***abeo*** as an alternative application of nor- and homo- to the same molecule has found a widely acceptance especially in the steroid chemistry.

The term **abeo** is a Latin verb meaning -to go hence-.



Androstane 10(5→6)*abeo*-6*a*(H)-Androstane



Ergoline 5(10→9)*abeo*-9,10-Didehydro-ergoline

Many examples of such terminology can be found in:

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