

## 27. Synthesis of (5*R*,8*S*,10*R*)-6-(Allyloxy)- and (5*R*,8*S*,10*R*)-6-(Propyloxy)ergolines from the 6-Methyl Precursors

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Novel (5*R*,8*S*,10*R*)-6-(allyloxy)- and (5*R*,8*S*,10*R*)-6-(propyloxy)ergolines have been synthesized by use of a *Meisenheimer* [2,3]-sigmatropic rearrangement of a (5*R*,8*S*,10*R*)-6-allyl-ergoline *N*<sup>6</sup>-oxide as key step.

**1. Introduction.** – Much work has been devoted to the chemical modification of biologically active ergot alkaloids [1]. In recent years, a number of ergot compounds have been described as dopamine agonists and some of them, such as bromocriptine, pergolide, and lisuride have found use in the treatment of hyperprolactinemia, acromegaly, and *Parkinsonism*. We have chosen the potent dopaminomimetic ergot derivatives **1** (CQ 32-084) and **2** (DH-lisuride) for further chemical modification.

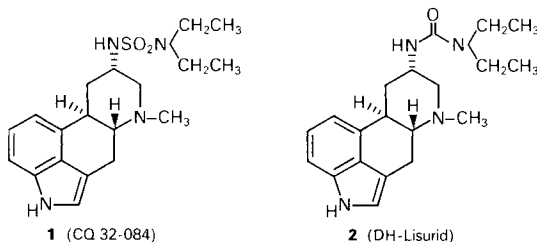
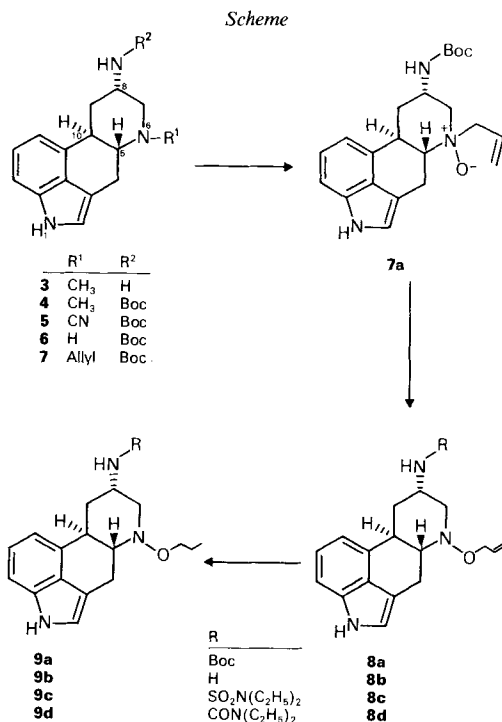


Table. Reaction Conditions and Chemical Yields

Conversion	Conditions	Yield
3→4	(Boc) <sub>2</sub> O, Et <sub>3</sub> N, CH <sub>3</sub> CN, 2 h, r.t.	97%
4→5	BrCN, CHCl <sub>3</sub> , 65 h, r.t.	85%
5→6	<i>Raney</i> -Ni, H <sub>2</sub> , DMF, 96 h, r.t.	65%
6→7	Allyl bromide, K <sub>2</sub> CO <sub>3</sub> , DMF, 96 h, r.t.	64%
7→7a→8a	a) <i>m</i> -Chloroperbenzoic acid, CH <sub>2</sub> Cl <sub>2</sub> , 1 h, –10 °C; b) CH <sub>3</sub> CN, 45 min, reflux	53%
8a→9a	H <sub>2</sub> , 10% Pd/C, 16 h, r.t.	77%
8a→8b		59%
9a→9b	CF <sub>3</sub> COOH, 30 min, r.t.	53%
8b→8c		29%
9b→9c	Et <sub>2</sub> NSO <sub>2</sub> Cl, CHCl <sub>3</sub> , 16 h, 50 °C	25%
8b→8d		31%
9b→9d	Et <sub>2</sub> NCOCI, CHCl <sub>3</sub> , 16 h, 50 °C	33%



We report here the successful application of a *Meisenheimer* [2,3]-sigmatropic rearrangement [2] on a (5*R*,8*S*,10*R*)-6-allyl-ergoline *N*<sup>6</sup>-oxide, which has ultimately led to analogues of **1** and **2** where *N*<sup>6</sup> has become part of a substituted hydroxylamine function. The *Scheme* illustrates our synthesis, whereas reaction conditions and chemical yields are summarized in the *Table*.

**2. Synthesis.** – To generate the substrate for the *Meisenheimer* rearrangement, 8 $\alpha$ -aminoergoline **3** [3] was first protected with (Boc)<sub>2</sub>O to give **4**, which was converted to ergoline **6** *via* **5** by an earlier developed modification of the *von Braun* degradation [4]. Alkylation to 6-allyl-ergoline **7** (crystallized as hydrochloride) completed the first part of our synthesis. Oxidation of the free base **7** with *m*-chloroperbenzoic acid gave a polar product, presumably the *N*<sup>6</sup>-oxide **7a**, which was not isolated but rearranged to 6-(allyloxy)ergoline **8a**. Catalytic hydrogenation of **8a** was surprisingly specific: the terminal double bond was hydrogenated without major cleavage of the N–O bond to yield 6-propyloxyergoline **9a**. The protecting group on the 8 $\alpha$ -amino function was cleaved from both compounds **8a** and **9a** to give **8b** and **9b**, respectively, which were in turn converted to the derivatives **8c** and **9c** as well as **8d** and **9d** bearing the C(8) substituents of **1** and **2**, respectively.

The analytical data of all novel compounds are summarized in the *Table*, *Section 4*.

**3. Pharmacological Evaluation.** – Compounds **8c**, **8d**, **9c**, and **9d** were evaluated for their pharmacological activity. None of them inhibited ovum implantation in rats [5] at doses of 3 mg/kg s.c. (*cf.* **1** (CQ 32-084): *ID*<sub>50</sub> = 0.028 mg/kg s.c. [6]). We conclude that the

modification of  $N^6$  into a hydroxylamine function has completely abolished the dopamine-agonistic activity of **1** (CQ 32-084) and **2** (DH-lisuride) for two reasons: The N-atom of the novel hydroxylamine function in **8c**, **8d**, **9c**, and **9d** is no longer basic. The hydroxylamine derivative **9c** has a  $pK_a < 3$  while the  $pK_a$  of **1** is *ca.* 6. The second reason for the loss of the dopamine-agonist activity might be the novel sidechain at  $N^6$  with 4 atoms, while the introduction of a propyl substituent into position 6 of the ergoline skeleton brings an impressive potentiation of the dopaminometric action as demonstrated first with pergolide [7].

We thank *P. Graff* and *C. Holder* for their capable technical assistance in the synthetic work, *T. Zardin* for interpretation of NMR spectras and *H. R. Wagner* for pharmacological testing. Thanks are also due to *Dr. H. Braunschweiger* and *F. Seemann* for the supply of ample quantities of intermediates.

**4. Analytical Data**<sup>1)</sup>. – (5*R*,8*S*,10*R*)-8-(*tert*-Butoxycarbonylamino)-6-methylergoline (**4**). M.p. 197–199°.  $[\alpha]_D^{20} = +10^\circ$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ , 5%): 3480*m*, 3440*w*, 1700*s*, 1610*w*, 1495*s*. <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ): 1.46 (*s*), 1.61 (*td*,  $J = 12, 3$ , together 10 H, *t*-Bu,  $H_{ax}$ -C(9)); 2.17 (*td*,  $J = 12, 4$ , H-C(5)); 2.39 (*s*), 2.45 (part of *d*, together 4 H); 2.68 (*t*,  $J = 12$ ), 2.75 (*d*,  $J = 12$ , together 2 H,  $H_{ax}$ -C(4),  $H_{eq}$ -C(9)); 2.87 (*d*,  $J = 12$ ,  $H_{eq}$ -C(7)); 3.07 (*ca. t*,  $J = 12$ , H-C(10)); 3.38 (*dd*,  $J = 12, 4$ ,  $H_{eq}$ -C(4)); 4.07 (br., H-C(8)); 5.58 (*d*,  $J = 8$ , NH); 6.86 (part of *d*), 6.89 (*s*, together 2 H, H-C(12), H-C(2)); 7.15 (*t*,  $J = 8$ ), 7.18 (*d*,  $J = 8$ , together 2 H, H-C(13), H-C(14)); 7.95 (br., NH). MS (EI): 341 (52,  $M^+$ ), 285 (88), 268 (31), 267 (29), 224 (78), 223 (100). Anal. calc. for  $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}_2$  (341.45): C 70.4, H 8.0, N 12.3, O 9.4; found: C 70.6, H 8.3, N 12.1, O 9.1.

(5*R*,8*S*,10*R*)-8-(*tert*-Butoxycarbonylamino)-6-carbonitril (**5**). M.p. 236–238°.  $[\alpha]_D^{20} = +54^\circ$  ( $c = 0.52$ ,  $\text{CHCl}_3/\text{EtOH}$  1:1). IR ( $\text{CHCl}_3$ , 5%): 3480*m*, 3450*w*, 2215*s*, 1710*s*, 1605*w*, 1500*s*. <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ): 1.51 (*s*, *t*-Bu); 1.63 (*td*,  $J = 12, 3$ ,  $H_{ax}$ -C(9)); 2.1–2.26 (*m*, 2 H); 2.34 (*t*,  $J = 12$ ,  $H_{ax}$ -C(4)); 3.01 (*td*,  $J = 12, 4$ , H-C(10)); 3.26 (*d*,  $J = 12$ ,  $H_{ax}$ -C(7)); 3.35 (*dd*,  $J = 12, 4$ ,  $H_{eq}$ -C(4)); 3.60 (*d*,  $J = 12$ ,  $H_{eq}$ -C(7)); 4.1 (br., H-C(8)); 5.21 (*d*,  $J = 6$ , NH); 6.79 (*d*,  $J = 8$ , H-C(12)); 6.95 (*s*, H-C(2)); 7.19 (*t*,  $J = 8$ , H-C(13)); 7.28 (*d*,  $J = 8$ , H-C(14)); 8.16 (br., NH). MS (FD): 352 (100,  $M^+$ ). Anal. calc. for  $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_2$  (352.43): C 68.2, H 6.9, N 15.9, O 9.1; found: C 68.0, H 7.2, N 15.7, O 9.3.

(5*R*,8*S*,10*R*)-8-(*tert*-Butoxycarbonylamino)ergoline (**6**). Brownish foam.  $[\alpha]_D^{20} = +27^\circ$  ( $c = 0.23$ ,  $\text{CHCl}_3$ ). IR ( $\text{CHCl}_3$ , 5%): 2980*m*, 2945*m*, 2350*w*, 1700*s*, 2605*w*, 1495*s*. <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ): 1.45 (*s*), 1.64 (*td*,  $J = 12, 3$ , superimposed by br. signal, together 11 H, *t*-Bu,  $H_{ax}$ -C(9), NH(6)); 2.7–3.0 (*m*, 6 H); 3.09 (*d*,  $J = 12, 1$  H); 4.02 (br., H-C(8)); 5.56 (br., NH); 6.83 (part of *d*), 6.84 (*s*, together 2 H, H-C(12), H-C(2)); 7.12 (*t*,  $J = 8$ ), 7.16 (*d*,  $J = 8$ , together 2 H, H-C(13), H-C(14)); 7.90 (br., NH). MS (EI): 327 (5,  $M^+$ ), 271 (36), 209 (61). Anal. calc. for  $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_2$  (327.42): C 69.7, H 7.7, N 12.8, O 9.8; found: C 69.4, H 8.0, N 12.6, O 9.8.

(5*R*,8*S*,10*R*)-6-Allyl-8-(*tert*-butoxycarbonylamino)ergoline Hydrochloride (**7**·HCl). M.p. 250° (dec.).  $[\alpha]_D^{20} = -62^\circ$  ( $c = 0.43$ ,  $\text{EtOH}/\text{H}_2\text{O}$  1:1). IR (free base,  $\text{CHCl}_3$ , 5%): 3480*m*, 3450*m*, 2860*w*, 2810*w*, 1700*s*, 1610*w*, 1495*s*. <sup>1</sup>H-NMR (free base,  $\text{CDCl}_3$ ): 1.47 (*s*), 1.60 (*ca. t*,  $J = 12$ , together 10 H, *t*-Bu,  $H_{ax}$ -C(9)); 2.46–2.58 (*m*, 2 H); 2.65–2.8 (*m*, 2 H); 2.93 (*d*,  $J = 12, 1$  H); 3.09 (*ca. t*,  $J = 12$ , H-C(10)); 3.32 (*dd*,  $J = 12, 5$ ,  $H_{eq}$ -C(4)); 3.37–4.03 (*m*,  $\text{CH}_2$ ); 4.05 (br., H-C(8)); 5.18 (*d*,  $J = 10, 1$  H); 5.21 (*d*,  $J = 18, 1$  H); 5.55 (*d*,  $J = 6$ , NH); 5.85–6.0 (*m*,  $\text{CH}=\text{}$ ); 6.86 (part of *d*), 6.88 (*s*, together 2 H, H-C(12), H-C(2)); 7.14 (*t*,  $J = 8$ ), 7.18 (*d*,  $J = 8$ , together 2 H, H-C(13), H-C(14)); 7.92 (br., NH). MS (EI): 367 (42,  $M^+$ ), 311 (55), 249 (86). Anal. calc. for  $\text{C}_{22}\text{H}_{30}\text{ClO}_2$  (403.95): C 65.4, H 7.5, N 10.4, O 7.9, Cl 8.8; found: C 65.4, H 7.4, N 10.2, O 8.0, Cl 8.6.

(5*R*,8*S*,10*R*)-6-Allyloxy-8-(*tert*-butoxycarbonylamino)ergoline (**8a**). M.p. 78–84°.  $[\alpha]_D^{20} = +85.5^\circ$  ( $c = 0.8$ ,  $\text{Py}$ ). IR ( $\text{CH}_2\text{Cl}_2$ , 5%): 3475*m*, 3440*w*, 1700*s*, 1605*w*, 1490*s*. <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ): 1.48 (*s*, 10 H, *t*-Bu,  $H_{ax}$ -C(9) (not visible)); 2.64 (*d*(*t*),  $J = 12$ ,  $H_{eq}$ -C(9)); 2.7–2.84 (*m*, 3 H); 3.1–3.2 (*m*, 1 H); 3.43 (br. *d*,  $J = 12$ ,  $H_{eq}$ -C(7)); 3.60 (*d*,  $J = 14$ ,  $H_{eq}$ -C(4)); 4.18–4.25 (*m*, H-C(8)); 4.30 (*d*,  $J = 6$ ,  $\text{CH}_2$ ); 5.25 (*d*,  $J = 10, 1$  H); 5.3–6.0 (*m*, NH) superimposed by 5.34 (*d*,  $J = 18$ , together 2 H); 5.94–6.07 (*m*, 1 H); 6.86 (*ca. d*,  $J = 8$ , H-C(12)); 6.89 (*s*, H-C(2)); 7.14 (*t*,  $J = 8$ , H-C(13)); 7.18 (*d*,  $J = 8$ , H-C(14)); 7.88 (br., NH). MS (EI): 384 (8), 383 (33,  $M^+$ ), 327 (25), 326 (100),

<sup>1)</sup> M.p.: Büchi-SMP-20 apparatus; not corrected. <sup>1</sup>H-NMR: Bruker Spektroskop WH 360 (360 MHz) with TMS ( $\delta = 0.00$  ppm) as internal standard,  $J$  [Hz] = coupling constant. MS: AEI MS 30 or Varian MAT 212 spectrometer (EI = electron ionisation, FD = field desorption);  $m/z$  (% relative abundance). IR ( $\tilde{\nu}$  [ $\text{cm}^{-1}$ ]): Perkin Elmer 21.  $[\alpha]_D^{20}$ : Perkin Elmer 241 MC.

325 (32), 311 (8), 310 (37), 287 (16), 286 (69). Anal. calc. for  $C_{22}H_{29}N_3O_3$  (383.50): C 68.9, H 7.6, N 11.0, O 12.5; found: C 68.7, H 7.6, N 10.7, O 12.6.

(5*R*,8*S*,10*R*)-6-*Allyloxy*-8-*aminoergoline* (**8b**). M.p. 193–195°.  $[\alpha]_D^{20} = +63.3^\circ$  ( $c = 1.09$ , Py). IR ( $CH_2Cl_2$ , 5%): 3470s, 1605w, 1460w, 1450w, 1440m.  $^1H$ -NMR ( $CDCl_3$ ): 1.70 (*ca. t*,  $J = 12$ ,  $H_{ax}-C(9)$ ); 1.88 (*br. s*,  $NH_2$ ); 2.46 (*ca. d*,  $J = 12$ ,  $H_{eq}-C(9)$ ); 2.66–2.86 (*m*, 3 H); 3.25–3.35 (*m*,  $H-C(10)$ ); 3.48 (*ca. d*,  $J = 10$ ,  $H_{eq}-C(7)$ ,  $H-C(8)$ ) (not visible); 3.60 (*d*,  $J = 14$ ,  $H_{eq}-C(4)$ ); 4.31 (*d*,  $J = 8$ , 2 H); 5.22 (*d*,  $J = 10$ , 1 H); 5.32 (*d*,  $J = 18$ , 1 H); 5.96–6.08 (*m*, 1 H); 6.85 (*d*,  $J = 8$ ,  $H-C(12)$ ); 6.89 (*s*,  $H-C(2)$ ); 7.14 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.18 (*d*,  $J = 8$ , together 2 H,  $H-C(14)$ ); 7.90 (*br. s*, NH). MS (FD): 284 (22), 283 (100,  $M^+$ ). Anal. calc. for  $C_{17}H_{21}N_3O$  (283.38): C 72.1, H 7.5, N 14.8, O 5.6; found: C 71.7, H 7.7, N 14.2, O 6.0.

*N*-*f*-(5*R*,8*S*,10*R*)-6-(*Allyloxy*)ergoline-8-yl]-*N'*,*N'*-diethylsulfamide (**8c**). M.p. 144–145°.  $[\alpha]_D^{20} = +52.7^\circ$  ( $c = 1.1$ , Py). IR ( $CH_2Cl_2$ , 5%): 3470s, 3380w, 1605w, 1460w, 1450w, 1440m, 1410m, 1330s (*br.*), 1140s.  $^1H$ -NMR ( $CDCl_3$ ): 1.22 (*t*,  $J = 8$ , 6 H); 1.57 (*ca. t*,  $J = 12$ ,  $H_{ax}-C(9)$ ); 2.63–2.82 (*m*, 4 H); 3.12–3.24 (*m*,  $H-C(10)$ ); 3.32 (*q*,  $J = 8$ , 4 H); 3.47–3.64 (*m*, 2 H); 3.84–3.92 (*m*,  $H-C(8)$ ); 4.29 (*d*,  $J = 8$ , 2 H); 5.04 (*ca. d*,  $J = 8$ , NH); 5.26 (*d*,  $J = 10$ , 1 H); 5.34 (*d*,  $J = 18$ , 1 H); 5.94–6.06 (*m*, 1 H); 6.82 (*ca. d*,  $J = 8$ ,  $H-C(12)$ ); 6.90 (*s*,  $H-C(2)$ ); 7.15 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.20 (*d*,  $J = 8$ , together 2 H,  $H-C(14)$ ); 7.90 (*br. s*, NH). MS (EI): 418 (11,  $M^+$ ), 377 (16), 363 (9), 362 (30), 361 (100), 360 (22). Anal. calc. for  $C_{21}H_{30}N_4O_3S$  (418.56): C 60.3, H 7.2, N 13.4, O 11.5, S 7.7; found: C 60.0, H 7.2, N 13.3, O 11.5, S 7.8.

*N*-*f*-(5*R*,8*S*,10*R*)-6-(*Allyloxy*)ergoline-8-yl]-*N'*,*N'*-diethylcarbamamide (**8d**). M.p. 183–184°.  $[\alpha]_D^{20} = +139.2^\circ$  ( $c = 1.02$ , Py). IR ( $CH_2Cl_2$ , 5%): 3470m, 3250w, 1635s, 1505s, 1460m, 1450m, 1440m.  $^1H$ -NMR (DMSO, 150°): 1.09 (*t*,  $J = 8$ , 6 H); 1.52 (*ca. t*,  $J = 12$ ,  $H_{ax}-C(9)$ ); 2.52–2.90 (*m*, 4 H and  $H_2O$ ); 3.12–3.25 (*m*,  $H-C(10)$ ) superimposed by 3.22 (*q*,  $J = 8$ , together 5 H); 3.36–3.50 (*m*, 2 H); 4.20 (*br. s*,  $H-C(8)$ ); 4.28 (*d*,  $J = 8$ , 2 H); 5.18 (*d*,  $J = 10$ , 1 H); 5.30 (*d*,  $J = 18$ , 1 H); 5.50 (*br. s*, 1 H); 5.95–6.10 (*m*, 1 H); 6.71 (*d*,  $J = 8$ ,  $H-C(12)$ ); 6.92 (*s*,  $H-C(2)$ ); 7.00 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.11 (*d*,  $J = 8$ ,  $H-C(14)$ ); 10.18 (*br. s*, NH). MS (EI): 383 (31), 382 (88,  $M^+$ ), 342 (10), 326 (31), 325 (100), 324 (19). Anal. calc. for  $C_{22}H_{30}N_4O_2$  (382.51): C 69.1, H 7.9, N 14.6, O 8.4; found: C 69.0, H 8.1, N 14.4, O 8.6.

(5*R*,8*S*,10*R*)-8-(*tert*-*Butoxycarbonylamino*)-6-(*propyloxy*)ergoline (**9a**). M.p. 87–92°.  $[\alpha]_D^{20} = +80.2^\circ$  ( $c = 1.14$ , Py). IR ( $CH_2Cl_2$ , 5%): 3470m, 3440w, 1700s, 1605w, 1490s.  $^1H$ -NMR ( $CDCl_3$ ): 0.98 (*t*,  $J = 8$ , 3 H); 1.48 (*s*, 10 H, *t*-Bu,  $H_{ax}-C(9)$ ) (not visible); 1.57–1.68 (*m*,  $CH_2$ ); 2.6–2.85 (*m*, 4 H); 3.08–3.20 (*m*, 1 H); 3.39 (*d*,  $J = 12$ ,  $H_{eq}-C(7)$ ); 3.61 (*d*,  $J = 12$ ,  $H_{eq}-C(4)$ ); 3.75 (*t*,  $J = 8$ ,  $CH_2$ ); 4.16–4.25 (*m*,  $H-C(8)$ ); 5.35–5.45 (*br.*, NH); 6.85 (part of *d*,  $H-C(12)$ ) superimposed by 6.89 (*s*, together 2 H,  $H-C(2)$ ); 7.14 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.18 (*d*,  $J = 8$ , together 2 H,  $H-C(14)$ ); 7.88 (*s*, NH). MS (EI): 386 (6), 385 (27,  $M^+$ ), 329 (30), 328 (100), 327 (10), 326 (63), 325 (36), 313 (8), 312 (50), 311 (48). Anal. calc. for  $C_{22}H_{31}N_3O_3$  (385.51): C 68.5, H 8.1, N 10.9, O 12.5; found: C 68.4, H 8.3, N 10.6, O 12.8.

(5*R*,8*S*,10*R*)-8-*Amino*-6-(*propyloxy*)ergoline (**9b**). M.p. 183–184°.  $[\alpha]_D^{20} = +61.20^\circ$  ( $c = 1.29$ , Py). IR (nujol): 1600w, 1570w.  $^1H$ -NMR (DMSO): 0.93 (*t*,  $J = 8$ , 3 H); 1.49 (*t*(*d*),  $J = 12$ ,  $H_{ax}-C(9)$ ); 1.58 (*t*,  $J = 8$ , 2 H); 2.36 (*d*,  $J = 12$ ,  $H_{ax}-C(7)$ ); 2.46–2.54 (*ca. t*,  $H-C(5)$ ); 2.62 (*d*,  $J = 10$ ,  $H_{eq}-C(9)$ ); 2.74 (*t*,  $J = 12$ ,  $H_{ax}-C(4)$ ); 3.20 (*ca. t*,  $J = 10$ ,  $H-C(10)$ ); 3.25–3.35 (*d*,  $J = 12$ , superimposed by *m*,  $H_{eq}-C(7)$ ,  $H-C(8)$ ); 3.50 (*dd*,  $J = 12$ ,  $H_{eq}-C(4)$ ); 3.68 (*t*,  $J = 8$ , 2 H); 3.8–6.6 (*br.*,  $NH_2$ ); 6.71 (*d*,  $J = 8$ ,  $H-C(12)$ ); 6.95 (*s*,  $H-C(2)$ ); 7.01 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.12 (*d*,  $J = 8$ ,  $H-C(14)$ ); 10.62 (*s*, NH). MS (FD): 286 (11), 285 (100,  $M^+$ ). Anal. calc. for  $C_{17}H_{23}N_3O$  (285.39): C 71.5, H 8.1, N 14.7, O 5.6; found: C 71.0, H 8.1, N 14.3, O 6.0.

*N,N*-Diethyl-*N'*-*f*-(5*R*,8*S*,10*R*)-6-(*propyloxy*)ergoline-8-yl]-sulfamide (**9c**). M.p. 142°.  $[\alpha]_D^{20} = +63.3^\circ$  ( $c = 1.09$ , Py). IR ( $CH_2Cl_2$ , 5%): 3450m, 3380w, 1605w, 1460w, 1450w, 1440m, 1410m, 1380w, 1320m, 1140s.  $^1H$ -NMR ( $CDCl_3$ ): 0.97 (*t*,  $J = 8$ , 3 H); 1.23 (*t*,  $J = 8$ , 6 H); 1.53 (part *ca. t*,  $H_{ax}-C(9)$ ) superimposed by 1.65 (*q*,  $J = 8$ , together 3 H); 2.62–2.80 (*m*, 4 H); 3.12–3.24 (*m*,  $H-C(10)$ ); 3.33 (*q*,  $J = 8$ , 4 H); 3.51 (*ca. d*,  $J = 12$ ,  $H_{eq}-C(7)$ ); 3.60 (*d*,  $J = 12$ ,  $H_{eq}-C(4)$ ); 3.73 (*t*,  $J = 6$ , 2 H); 3.83–3.90 (*m*,  $H-C(8)$ ); 5.06 (*ca. d*,  $J = 9$ , NH); 6.83 (*d*,  $J = 8$ ,  $H-C(12)$ ); 6.90 (*s*,  $H-C(2)$ ); 7.15 (*t*,  $J = 8$ ,  $H-C(13)$ ); 7.19 (*d*,  $J = 8$ ,  $H-C(14)$ ); 7.89 (*s*, NH). MS (EI): 421 (29), 420 (100,  $M^+$ ), 363 (10), 362 (27), 361 (100), 360 (12). Anal. calc. for  $C_{21}H_{32}N_4O_3S$  (420.58): C 60.0, H 7.7, N 13.3, O 11.4, S 7.6; found: C 59.8, H 7.6, N 13.2, O 11.6, S 7.9.

*N,N*-Diethyl-*N'*-*f*-(5*R*,8*S*,10*R*)-6-(*propyloxy*)ergoline-8-yl]-carbamamide (**9d**). M.p. 182°.  $[\alpha]_D^{20} = +118.9^\circ$  ( $c = 1.16$ , Py). IR ( $CH_2Cl_2$ , 5%): 3470m, 3250w, 1635s, 1500s, 1460m, 1445m, 1435m.  $^1H$ -NMR (DMSO, 150°): 0.92 (*ca. t*,  $J = 8$ , 3 H); 1.09 (*ca. t*,  $J = 8$ , 6 H); 1.54 (*br. t*,  $J = 12$ ,  $H_{ax}-C(9)$ ) partially superimposed by 1.60 (*ca. q*,  $J = 8$ , together 3 H); 2.52–2.85 (*m*, 4 H and  $H_2O$ ); 3.10–3.25 (*m*,  $H-C(10)$ ) superimposed by 3.24 (*ca. q*,  $J = 8$ , together 5 H); 3.35–3.50 (*m*, 2 H); 3.70 (*br. s*, 2 H); 4.19 (*br. s*,  $H-C(8)$ ); 5.50 (*br. s*, 1 H); 6.71 (*ca. d*, *br.*,  $H-C(12)$ ); 6.92 (*s*,  $H-C(2)$ ); 7.00 (*ca. t*, *br.*,  $H-C(13)$ ); 7.61 (*br. d*,  $H-C(14)$ ); 10.18 (*br. s*, NH). MS (EI): 385 (29), 384 (100,  $M^+$ ), 326 (15), 325 (54), 324 (14). Anal. calc. for  $C_{22}H_{32}N_4O_2$  (384.53): C 68.7, H 8.4, N 14.6, O 8.3; found: C 68.8, H 8.5, N 14.4, O 8.4.

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