

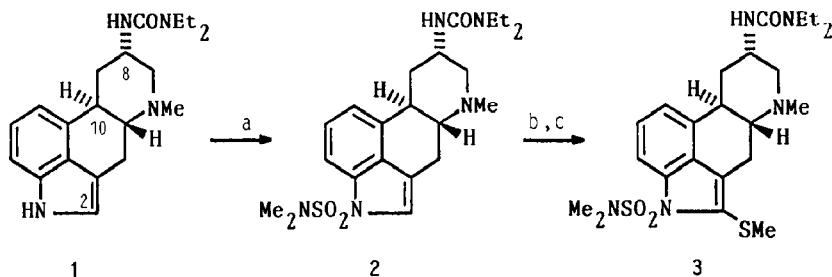
## STRIKING INFLUENCE OF THE REACTION CONDITIONS ON THE STEREOSELECTIVITY IN ELECTROPHILIC SUBSTITUTION OF A 10-LITHIO-ERGOLINYL-UREA

GERHARD SAUER\*, BERND SCHRÖTER, and HERMANN KÜNZER

Research Laboratories, Schering AG Berlin/Bergkamen,  
Müllerstraße 170-178, D-1000 Berlin 65, West Germany

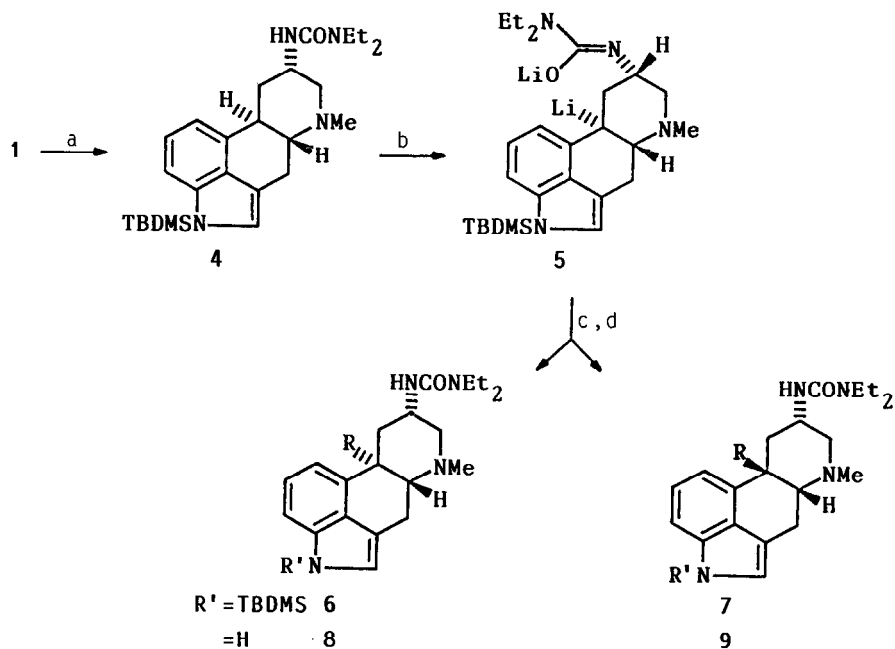
**SUMMARY:** The regioselectivity of the deprotonation of the 8 $\alpha$ -ergolinyl-urea **1** (terguride) depends on the substituent at the indole nitrogen. A *tert.*-butyl-dimethylsilyl (TBDMS) protecting group facilitates the removal of the angular benzylic proton in position 10. The reaction of the 10-lithio compound **5** with electrophiles affords *cis* or *trans* fused products, depending on reagent and reaction conditions.

Often lithiation allows electrophilic reactions in positions which are not easily accessible to direct substitution. This metalation can be performed by bromine-lithium exchange<sup>1</sup> or by deprotonation with a strong lithium base. The latter reaction has been studied in different aromatic systems<sup>2</sup> and also successfully applied to indole derivatives.<sup>3</sup> We communicate our results on the regio- and stereoselectivity of the deprotonation of the 1-substituted 1,1-diethyl-3-((5R,8S,10R)-6-methyl-8-ergolinyl)-urea derivatives **2** and **4** and the stereochemistry of the ensuing reaction with electrophiles. Dimethylamino-ergolinyl-sulfone **2** is deprotonated in position 2 by *tert.*-butyllithium as anticipated by comparison with similar reactions of acceptor substituted indole derivatives.<sup>3</sup> Reactive electrophiles, like S-methyl-methylthiosulfonate,<sup>4</sup> furnish 2-substituted ergoline derivatives.<sup>5</sup>



a: CH<sub>2</sub>Cl<sub>2</sub>, solid KOH, NBu<sub>4</sub>HSO<sub>4</sub>, (CH<sub>3</sub>)<sub>2</sub>NSO<sub>2</sub>Cl, r.t., 16 h (36%); b: THF, *tert.*-butyllithium, -78°C, 30 min; c: THF, CH<sub>3</sub>SO<sub>2</sub>SCH<sub>3</sub>, -78°C, 30 min (67%).

By contrast, the 1-silylated 8 $\alpha$ -ergolinyl-urea **4** is metalated in the angular, benzylic position 10 as determined by the isolation of two products **6** and **7** after addition of an electrophile.<sup>6</sup>



a: THF, LDA, TBDMSCl,  $-20^{\circ}\text{C}$  to r.t. (73%); b: THF, 10 equiv. *tert.*-butyllithium,<sup>7</sup>  $-78^{\circ}\text{C}$ , 30 min; c: 10 equiv. electrophile in THF,  $-78^{\circ}\text{C}$ , 30 min; d: method A: THF with 10% water,  $\text{NBu}_4\text{F}$ , r.t., 1 h; method B: methanol, 14molar KOH, r.t., 16 h.

Metalation of a benzylic position by butyllithium has been reported in the tetrahydro- $\beta$ -carboline and tetrahydro-isoquinoline series, provided suitable donor ligands (e.g. methoxymethyl or formamidine) are available in appropriate positions to stabilize the lithium cation.<sup>8</sup> In our case, the  $8\alpha$ -urea group apparently enhances the kinetic acidity of the  $10\alpha$ -H by concomitant formation of a chelate species **5**.<sup>9</sup> Typically, the  $8\beta$ -epimer of **4** is not metalated under the same conditions.

With electrophiles, **5** may react at the 10-position under retention or inversion of configuration with respect to lithium. In a related case Meyers et al. observed inversion with methyl iodide and retention with  $\text{DMSO-d}_6$ .<sup>10</sup> The same is observed for **5** (table, entries 3 and 6). However, on further investigation, we became aware of surprising changes of stereoselectivity with varying electrophiles and solvent additives. For instance, addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) totally reverses the face selectivity of methylation from  $\beta$  to  $\alpha$  (entry 6 vs. 7) whereas ethyl iodide, under identical conditions, adds to the  $\beta$ -face exclusively (entry 8). The  $10\alpha$ -ethyl derivative may be obtained with triethylxonium fluoroborate (entry 9), the  $10\alpha$ -aldehyde with DMF (entry 11). No changes of the facial selectivity are found for other electrophiles, with or without DMPU additive.

At present, we are not in a position to offer a conclusive interpretation of these puzzling results.

**Table:** Substitution of 1-TBDMS Terguride **4** in Position 10 by Reaction with tert.-Butyllithium and Different Electrophiles

Entry	Reaction Conditions		Products		Yield [%] <sup>a)</sup>		
	Electrophile	DMPU	R	No.	6	7	6/7
1	H <sub>2</sub> O	-	H	a	50	44 <sup>12)</sup>	1.12
2	H <sub>2</sub> O	+	H	a	91	< 1	> 90
3	DMSO <sup>11)</sup>	-	H	a	81	< 1	> 80
4	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub>	-	H	a	14	56	0.25
5	MgBr <sub>2</sub> Et <sub>2</sub> O/H <sub>2</sub> O	-	H	a	23	61	0.37
6	CH <sub>3</sub> I	-	CH <sub>3</sub>	b	6	73	0.08
7	CH <sub>3</sub> I	+	CH <sub>3</sub>	b	82	10	8
8	C <sub>2</sub> H <sub>5</sub> I	+ <sup>b)</sup>	C <sub>2</sub> H <sub>5</sub>	c	-	75	< 0.02
9	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> OBF <sub>4</sub>	+ <sup>b)</sup>	C <sub>2</sub> H <sub>5</sub>	c	96	trace	> 50
10	CH <sub>3</sub> SO <sub>2</sub> SCH <sub>3</sub>	- <sup>b)</sup>	SCH <sub>3</sub>	d	36	36	1
11	DMF	-	CHO	e	84	1.4	60
12	CH <sub>3</sub> N=C=O	+ <sup>b)</sup>	CONHCH <sub>3</sub>	f	17	trace	> 10
13	CH <sub>3</sub> N=C=S	- <sup>b)</sup>	CSNHCH <sub>3</sub>	g	-	78	< 0.02
14	C <sub>6</sub> H <sub>5</sub> N=C=O	+ <sup>b)</sup>	CONHC <sub>6</sub> H <sub>5</sub>	h	trace	35	> 0.05
15	ClCOOCH <sub>3</sub>	- <sup>b)</sup>	COOCH <sub>3</sub>	i	4	15	0.27
16	CO(OCH <sub>3</sub> ) <sub>2</sub>	- <sup>b)</sup>	COOCH <sub>3</sub>	i	46	< 2	> 20

a) Yields of **6a** and **7a** are determined by HPLC. (The putative alkaloid fraction is defined as 100%. HPLC is run on a C-18-RP-column, Waters Millipore Rad-Pak C 18, 10  $\mu$ , length 100 mm and 8 mm i.d. with UV detection at  $\lambda = 275$  nm and a mobile phase of methanol/water/triethylamine (75:24,95:0.05, v/v/v), flow rate 1 ml/min). Yields of all other compounds are determined after chromatography.

b) DMPU does not significantly affect the ratio of **6/7**.

The crystalline end products **8** and **9**<sup>13)</sup> are prepared by cleavage of the silyl group with tetra-n-butyl-ammonium fluoride.<sup>14)</sup>

First-order analysis of <sup>1</sup>HNMR spectra including assignment of stereochemistry at C-10 is most straightforward for the thioether derivatives **8d** and **9d** due to minimal signal overlap and a literature precedent for a pair of related C-10 methyl ethers.<sup>15)</sup>

One diastereomer lacks any trans diaxial coupling between vicinal protons at C-4/C-5, C-7/C-8, and C-8/C-9. This fact is compatible with a chair-like piperidine ring bearing the substituent at C-10 in an equatorial position on the  $\beta$ -face of the molecule and the side chain at C-8 in an axial position on the opposite side, **9d**.

From the data for the second isomer (trans diaxial coupling between protons at C-4/C-5) a trans juncture of rings C and D with a chair-like piperidine ring carrying both substituents at C-8 and C-10 in an axial position on the  $\alpha$ -side of the molecule is deduced.

The assignment of the remaining pairs of C-10 epimers is based on similar observations.

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## REFERENCES AND NOTES

- This work is dedicated to Prof. Dr. R. Wiechert on the occasion of his 60th birthday.
- G. Sauer, J. Heindl, and H. Wachtel, *Tetrahedron Lett.*, preceding communication.
  - H.W. Gschwend and H.R. Rodriguez, *Organic Reactions*, **26**, 1 (1979).
  - R.J. Sundberg and H.F. Russell, *J. Org. Chem.*, **38**, 3324 (1973); M.G. Saulnier and G.W. Gribble, *J. Org. Chem.*, **47**, 757 (1982); G.W. Gribble, M.G. Saulnier, M.P. Sibi, and J.A. Obaza-Nutaitis, *J. Org. Chem.*, **49**, 4518 (1984).
  - D. Scholz, *Synthesis*, **1983**, 944.
  - Weaker electrophiles, like methyl isothiocyanate, do not react in this sequence.
  - No migration of the 1-silyl group<sup>3</sup> to the position 2 is observed at -78°C in 30 min. 1-TBDMS-2-lithio-ergolinyl-urea, formed by bromine-lithium exchange,<sup>1</sup> rearranges to the 2-silyl derivative at about -20°C.
  - n-Butyllithium is useful for the deprotonation as well. However, alkyl iodides react with excess reagent under formation of n-butyl iodide which competes in the alkylation step.
  - M.F. Loewe and A.I. Meyers, *Tetrahedron Lett.*, **1985**, 3291; A.I. Meyers, T. Sohda, and M.F. Loewe, *J. Org. Chem.*, **51**, 3108 (1986). D.A. Dickman and A.I. Meyers, *Tetrahedron Lett.*, **1986**, 1465; P. Beak and A.I. Meyers, *Acc. Chem. Res.*, **19**, 356 (1986); D. Seebach, I.M.P. Huber, and M.A. Syfrig, *Helv. Chimica Acta*, **70**, 1357 (1987).
  - The possibility of competing complexation of lithium in 1-methoxymethyl-8 $\alpha$ -ergolinyl-urea gives rise to mixtures of 2,10 $\alpha$ ,10 $\beta$ , and disubstituted products after reaction with an electrophile.
  - M.F. Loewe, M. Boes, and A.I. Meyers, *Tetrahedron Lett.*, **1985**, 3295; A.I. Meyers and D.A. Dickman, *J. Am. Chem. Soc.*, **109**, 1263 (1987); R.E. Gawley, *J. Am. Chem. Soc.*, **109**, 1265 (1987).
  - With DMSO-d<sub>6</sub> a 10 $\alpha$ -deuterated product is obtained.
  - G. Sauer, G. Haffer, and H. Wachtel, *Synthesis*, **1986**, 1007.
  - 2: m.p. 160-162°C; [ $\alpha$ ]<sub>D</sub>: -12° (CHCl<sub>3</sub> 0.1). 3: m.p. 180-183°C; [ $\alpha$ ]<sub>D</sub>: +9.5° (CHCl<sub>3</sub> 0.5). 4: m.p. 185-187°C (dec.); [ $\alpha$ ]<sub>D</sub>: +7° (CHCl<sub>3</sub> 0.5). 8b (hydrogentartrate): m.p. 156-162°C (dec.); [ $\alpha$ ]<sub>D</sub>: +39° (pyridine 0.5). 9b: m.p. 221-225°C; [ $\alpha$ ]<sub>D</sub>: -53° (CHCl<sub>3</sub> 0.5). 8c: m.p. 103-106°C; [ $\alpha$ ]<sub>D</sub>: +34° (CHCl<sub>3</sub> 0.5); <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.06 (br s, NH), 7.16 (d, J=7.6 Hz, 14-H), 7.11 (m, 13-H), 6.89 (br s, 2-H), 6.82 (d, J=6.8 Hz, 12-H); 5.18 (d, J=7.9 Hz, NHCONET<sub>2</sub>), 4.17-4.15 (br m, 8 $\beta$ -H), 3.41-3.19 (m, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.19 (dd, J=14.8, J=4.6 Hz, 4 $\beta$ -H), 2.91 (d, J=14.3 Hz, 9 $\alpha$ -H), 2.86 (d, J=11.8 Hz, 7 $\alpha$ -H), 2.79 (dd, J=14.8, J=11.5 Hz, 4 $\alpha$ -H), 2.45 (dd, J=11.8, J=3.1 Hz, 2-H), 2.39 (s, NCH<sub>3</sub>), 2.36 (dd, J=11.5, J=4.6 Hz, 5 $\beta$ -H), 2.18-2.06 (m, CH<sub>2</sub>CH<sub>3</sub>), 1.62 (dd, J=14.3, J=4.2 Hz, 9 $\beta$ -H), 1.48-1.36 (m, CH<sub>2</sub>CH<sub>3</sub>), 1.17 (t, J=7.1 Hz, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 0.75 (t, J=7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>). 9c: m.p. 222-226°C (dec.); [ $\alpha$ ]<sub>D</sub>: -40° (CHCl<sub>3</sub> 0.5); <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.03 (br s, NH), 7.15 (d, J=8.0 Hz, 14-H), 7.08 (m, 13-H), 6.96 (d, J=7.0 Hz, 12-H), 6.88 (br s, 2-H), 4.52 (br s, NHCONET<sub>2</sub>), 4.07 (br s, 8 $\beta$ -H), 3.20 (dd, J=16.8, J=3.0 Hz, 4 $\beta$ -H), 3.02 (d, J=16.8 Hz, 4 $\alpha$ -H), 2.24 (s, NCH<sub>3</sub>), 1.70 (dd, J=14.4, J=4.7 Hz, 9 $\beta$ -H), 0.94-0.78 (m, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>3</sub>). 8d: m.p. 203-204°C (dec.); [ $\alpha$ ]<sub>D</sub>: +135° (CHCl<sub>3</sub> 0.5); <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.05 (br s, NH), 7.23 (d, J=8.2 Hz, NHCONET<sub>2</sub>, 14-H), 7.12 (m, 13-H), 6.95 (br s, 2-H), 6.78 (d, J=7.1 Hz, 12-H), 4.38-4.29 (br m, 8 $\beta$ -H), 3.32 (q, J=7.1 Hz, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 3.28 (dd, J=13.5, J=4.7 Hz, 4 $\beta$ -H), 3.12 (dd, J=13.5, J=11.3 Hz, 4 $\alpha$ -H), 3.01 (d, J=11.5 Hz, 7 $\alpha$ -H), 2.88 (d, J=15.0 Hz, 9 $\alpha$ -H), 2.61 (dd, J=11.3, J=4.7 Hz, 5 $\beta$ -H), 2.46 (dd, J=11.5, J=2.9 Hz, 7 $\beta$ -H), 2.42 (s, NCH<sub>3</sub>), 2.02 (dd, J=15.0, J=5.3 Hz, 9 $\beta$ -H), 1.73 (s, SCH<sub>3</sub>), 1.17 (t, J=7.1 Hz, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>). 9d: m.p. 202-206°C (dec.); [ $\alpha$ ]<sub>D</sub>: -150° (CHCl<sub>3</sub> 0.5); <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.15 (br s, NH), 7.20 (d, J=7.9 Hz, 14-H), 7.11 (m, 13-H), 7.03 (d, J=7.0 Hz, 12-H), 6.91 (t, J=1.7 Hz, 2-H), 4.48 (d, J=8.9 Hz, NHCONET<sub>2</sub>), 4.10-4.03 (br m, 8 $\beta$ -H), 3.39 (d, J=16.8 Hz, 4 $\alpha$ -H), 3.26 (dd, J=16.8, J=2.8 Hz, 4 $\beta$ -H), 3.15 (d, J=14.3 Hz, 9 $\alpha$ -H), 2.82-2.70 (m, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, 5 $\beta$ -H, 7 $\alpha$ -H), 2.52 (dd, J=11.7, J=2.5 Hz, 7 $\beta$ -H), 2.27 (s, NCH<sub>3</sub>), 2.15 (dd, J=14.3, J=4.6 Hz, 9 $\beta$ -H), 1.80 (s, SCH<sub>3</sub>), 0.84 (t, J=7.1 Hz, N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>). 8e: m.p. 115-118°C; [ $\alpha$ ]<sub>D</sub>: +139° (CHCl<sub>3</sub> 0.5). 8f: m.p. 233-236°C (dec.); [ $\alpha$ ]<sub>D</sub>: +26° (CHCl<sub>3</sub> 0.5). 9g: m.p. 234-238°C (dec.); [ $\alpha$ ]<sub>D</sub>: +102° (CHCl<sub>3</sub> 0.5). 9h: m.p. 130-134°C; [ $\alpha$ ]<sub>D</sub>: -32° (CHCl<sub>3</sub> 0.1). 8i: m.p. 206-209°C; [ $\alpha$ ]<sub>D</sub>: +89° (CHCl<sub>3</sub> 0.5). 9i: m.p. 185-188°C; [ $\alpha$ ]<sub>D</sub>: -11° (CHCl<sub>3</sub> 0.5).
  - E.J. Corey and B.B. Snider, *J. Am. Chem. Soc.*, **94**, 2549 (1972).
  - L. Zetta and G. Gatti, *Tetrahedron*, **31**, 1403 (1975).

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