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DIASTEREOSELECTIVITY IN ERGOLINE SYNTHESIS: A FACE SELECTIVE EPOXIDATION

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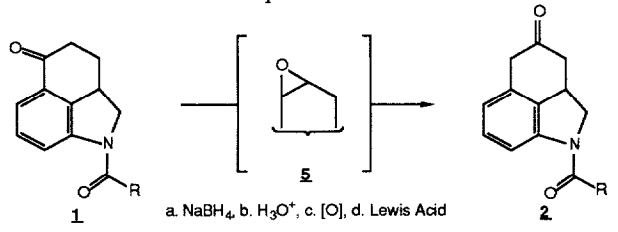
Summary: Epoxidation of 1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (**4a**) proceeded smoothly with meta-chloroperbenzoic acid with high exo diastereoselectivity (de = 96%) and chemical yield (97%). The basis for this selectivity was probed with substituent effects, and was extended to other oxidation media.

The Kornfeld-Woodward ketone **1**[1] has proven itself to be an invaluable intermediate in the synthesis of ergot alkaloids and related compounds.[2] Furthermore, the carbonyl moiety is readily transposed via a reduction-epoxidation-pinacol rearrangement sequence in a very expedient and efficient manner[3] (scheme below). The transposed ketone **2** has also been utilized as a pivotal intermediate in synthesis. Although the intermediate epoxide **5** has been cited in previous reports[3,4], the stereochemical information regarding this epoxide was not discussed, perhaps since it was lost in the Lewis acid mediated carbonyl transposition. It is the subject of this report to supply data which clarify the stereochemical features of this epoxidation.



The requisite olefins **4a-e** were prepared as follows. The olefin **4a** was prepared via $NaBH_4$ reduction of the ketone **1**, to provide a mixture of alcohols **3a** (6:1 β:α-OH), which was subsequently dehydrated by the published procedure[3]. Removal of the benzoyl moiety of **4a** by the action of n-BuLi in THF (-78°C) and reaction with p-toluenesulfonyl chloride then gave the N-Ts olefin **4e**. The mixture of alcohols **3a** was also brominated (Br_2 / HOAc / NaOAc) to provide the bromo alcohols **3c**, which was dehydrated as before to yield **4c**. The Rosemund-von Braun CuCN displacement[5] of **4c** in NMP at 200°C proceeded cleanly to **4d**. Finally, the methoxy olefin **4b** was prepared by the published procedure from 5-methoxyindole.[4]

Epoxidation of the olefin **4a** with m-CPBA in $CHCl_3$ provided the α-epoxide in preference to the corresponding β-epoxide (procedure A, 98:2, respectively, HPLC). In accordance with the epoxidation results, NBS in wet DMSO attacked the α-face of **4a** selectively to provide a bromohydrin, which when treated with base cyclized to the complementary β-epoxide (procedure B). The diastereoselectivity in this sequence was consistent with the epoxidation results, and yielded a ratio of 2:98, α:β-epoxides. Separation of the epoxides by HPLC or TLC was accomplished without difficulty. Both of these oxidation procedures were applied to several substrates commonly

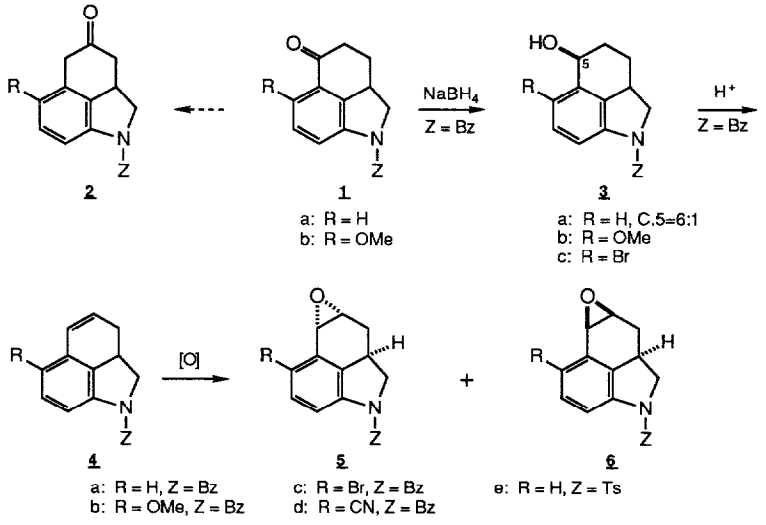


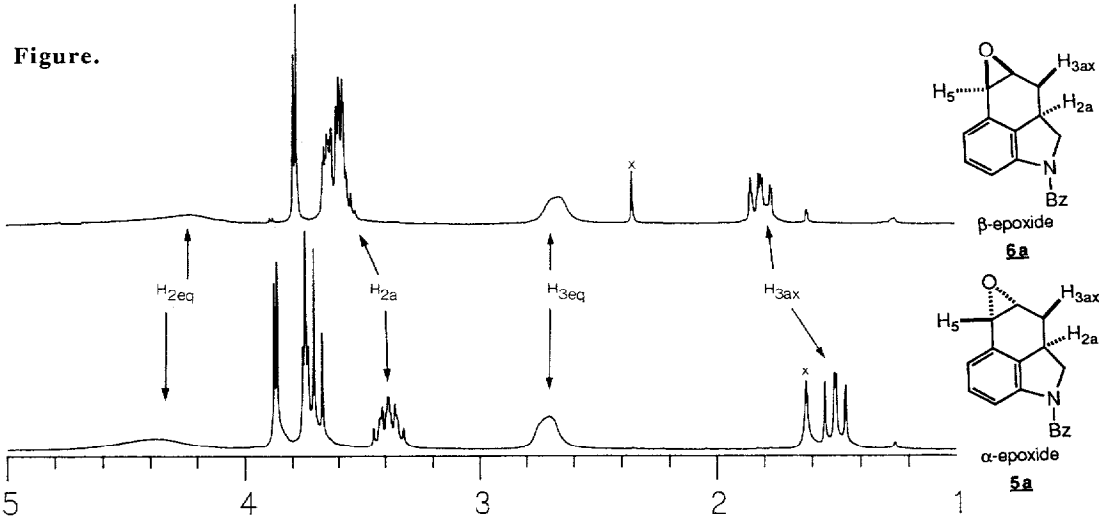
Table: Oxidation of the Tricyclic Olefin 4

entry		[O]*	R	Z	time (temp)	yield†	α : β ratio (5 : 6)	m.p.
1	a	A	H	Bz	6 h (-3°C)	97%	98 : 2	109-110°C
2	b	A	OMe	Bz	2 h (0°C)	89%	99 : 1	182-184°C
3	c	A	Br	Bz	36 h (0°C)	99%	97 : 3	136.5-138°C
4	d	A	CN	Bz	50 h (0°C)	95%	93 : 7	172-173°C
5	e	A	H	Ts	23 h (-9°C)	83%	97 : 3	148-150°C
6	a	B	H	Bz	1 h (23°C)	65%	1 : 99	147-149°C
7	b	B	OMe	Bz	0.25 h (23°C)	64%	1 : 99	oil
8	c	B	Br	Bz	0.75 h (23°C)	71%	2 : 98	196-198°C
9	e	B	H	Ts	0.75 h (23°C)	62%	1 : 99	147-150°C
10	a	A	H	Bz	6 h (62°C)	87%	90 : 10	oil

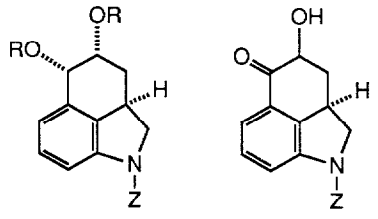
*Oxidation procedure A: epoxidation directly with m-CPBA in $CHCl_3$; procedure B: NBS in wet DMSO afforded the bromohydrin at ambient temperature (times shown), followed by epoxide formation with powdered NaOH in $PhCH_3$ for 30 minutes at room temperature. †Chromatographed yield (SiO_2, EtOAc/Hexanes), except entry 6 which was crystallized. The α : β ratio was determined from the crude reaction mixture by HPLC RP ODS in 50% aqueous CH_3CN, except entries 2 & 7 which were determined by NMR (300 MHz). All yields refer to isolated and purified compounds with correct physical data.

utilized in ergot synthesis, and the results are given in the Table. As might be expected, *a priori*, the two epoxides are easily distinguishable by ^{1}H-NMR due to the influence of the epoxide oxygen on H_{2a}, H_{3ax}, as well as H_5 (see Figure). The β-epoxide H_{2a} and H_{3ax} are shifted to lower field in the ^{1}H-NMR (300 MHz, $CDCl_3$) relative to the α-epoxide ($\Delta\delta$=0.3 ppm). The fact that the β-epoxide displayed a deshielding effect on H_{3ax} whereas the diastereomeric α-epoxide had a shielding effect on H_{2a} is consistent with the previous observations.[6] A representative comparison of the NMR spectra is given in the Figure. The methoxy epoxides, entries 2 & 7, were extremely sensitive to hydrolysis, but NMR measurements were possible in $CDCl_3$. The epoxides **5a** and **6a** were independently converted to the "transformed" ketone **2a** with ZnI_2.

Figure.

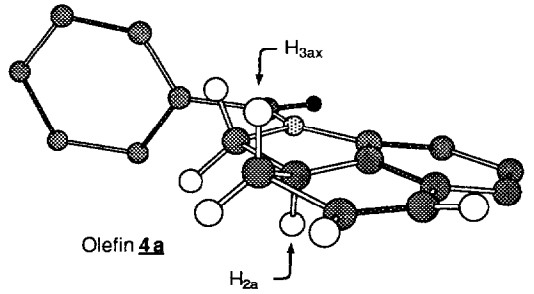


Osmylation[7] of the olefin **4a** with either catalytic or stoichiometric OsO_4 in acetone/water at ambient temperature afforded two oxidized products in excellent yield (92%) with a ratio of 7 : 1. The major product **7** was converted to the acetonide **8** (to improve its solubility) and characterized as the diol from α-face attack. The ^{1}H-NMR data was in complete agreement with the epoxide chemical shifts. The minor component proved to be an over-oxidation product **9**, commonly encountered in the osmylation of styrene-type substrates.[8]



7: R = H, Z = Bz
8: R = $(CH_3)_2C$, Z = Bz

9: Z = Bz



Olefin **4a**

The stereochemical bias in these epoxide-forming reactions clearly indicates that there is a preference for electrophilic attack on the α-face. Epoxidation at reflux in $CHCl_3$ resulted in slightly less diastereoselectivity, de = 80. Inspection of Dreiding models shows a very subtle difference between the two faces: the α-face possesses a remote axial H_{2a}, whereas the β-face possesses an axial H_{3ax} in a much closer proximity to the olefin π-system.

MM2 calculations have shown a 12° distortion of the olefin π-system from coplanarity with the aromatic π-system. The substituent (R) para to the indoline nitrogen and conjugated to the olefin had an effect only on the reaction kinetics. Furthermore, the axial C_3-H bond in olefin **4a** is perpendicular to the π-system and is anti-periplanar to the electrophile trajectory. This arrangement of atoms has been discussed by Houk[9] as the "perpendicular model." In this conformation, attack occurs on the face opposite to the axial hydrogen due to an electronic difference caused by σ*-π hyperconjugation. There have been more recent examples of this electronic aspect.[10] A similar effect has been previously reported with such conformationally rigid systems,[11] but this was attributed to steric constraints. The observed level of diastereoselectivity in all of these examples is remarkable and cannot be explained on steric grounds alone. The exploitation of this phenomenon in the ergoline ring system is currently being investigated and will be reported at a later time.

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6. L.A. Paquette, W.E. Fristad, C.A. Schuman, M.A. Beno, G.C. Cristoph *J. Am. Chem. Soc.* **1979**, *101*, 4645.
7. The olefin **4a** (9.0 g) was dissolved in acetone : water (400 mL, 10:1), and treated sequentially with N-methyl morpholine N-oxide (7.2 g) and OsO_4 (6 mmole) at room temperature. After 2.5 hr, the reagent was destroyed with $NaHSO_3$ (aq) and extracted with $CHCl_3$. Crystallization from EtOAc afforded 7.1 g (70.2%) pure **7**, mp 181-183°C; IR: ($CHCl_3$) 3620, 3420, 1637 cm^{-1}; NMR: (^1H NMR, $CDCl_3$, 300MHz) 7.07-7.63 (m, 8H), 4.77 (br s, 1H), 4.34 (br s, 1H), 4.29 (br s, 1H), 3.72 (m, 1H), 3.67 (m, 1H), 2.84 (br s, 2H, exchanges with D_2O), 2.45 (m, 1H), 1.69 (m, 1H); M.S.: 295 (41), 105 (100), 77 (94); U.V.: λ nm (ε): 293 (8350), 265 (10500) in EtOH; Analysis: C,H,N theory-73.20, 5.80, 4.74; found-72.97, 5.84, 4.61. The diol was converted to the acetonide **8**, in the usual manner (acetone, 2,2-dimethoxypropane, cat. TsOH), mp 164-166°C (Hex:EtOAc 1:1); IR ($CHCl_3$) 3019, 1640 (amide), 1614, 1472, 1460, 1394, 1383, 1222, 1215 cm^{-1}; ^{1}NMR ($CDCl_3$, 300 MHz) 7.02-7.60 (m, 8H), 5.20 (d, 1H, J =6.5 Hz), 4.73 (dt, 1H, J = 2.6, 6.5 Hz), 4.40 (br s, 1H), 3.70 (t, 1H, J = 10.5 Hz), 3.55 (m, 1H), 2.50 (m, 1H), 1.51 (m, 1H), 1.46 (s, 3H), 1.39 (s, 3H); M.S.: 335 (43), 320 (2), 278 (19), 260 (8), 105 (100), 77 (43).335 (43), 320 (2), 278 (19), 260 (8), 105 (100), 77 (43); U.V.: λ nm (ε): 293 (8640), 264 (11100) in EtOH; Analysis: C,H,N theory-75.20, 6.31, 4.18; found-75.03, 6.26, 4.06.
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10. For example, see: M.-H. Lin, W.J. le Noble *J. Org. Chem.* **1989**, *54*, 997 and references cited therein.
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