Stereospecific Route to *trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines

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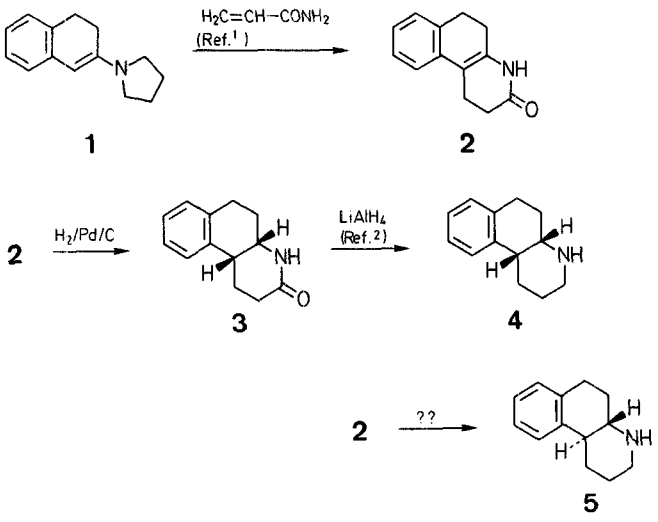
Access to the title compounds from unsaturated lactams **9** involves as the key step reduction of the carbon-carbon double bond with triethylsilane/trifluoroacetic acid reagent to give the *trans*-fused lactam product **10**.

The azaannelation reaction of Ninomiya et al.[1] provides access to lactam derivatives **2** of partially reduced benzo[*f*]quinoline systems, from 2-tetralone enamines **1** (Scheme A).

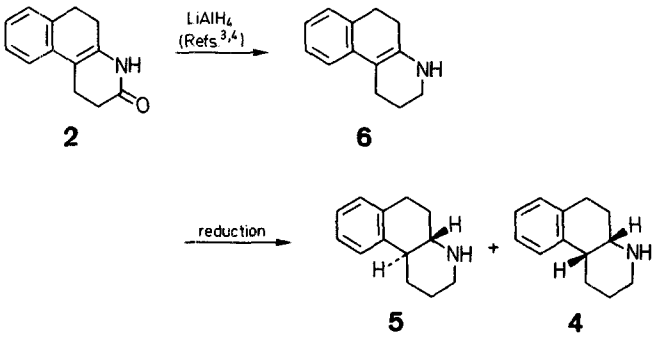


Scheme A

Catalytic hydrogenation of lactam systems typified by **2** leads to formation of the *cis*-ring fused system **3**, which is convertible into the *cis*-amino system **4**[2]. However, a deterrent to more widespread application of the Ninomiya annelation in synthetic chemistry has been the inability of past workers to effect high yield, unequivocal conversion of **2** into the *trans*-octahydro state **5**, by a stereospecific or stereoselective route.

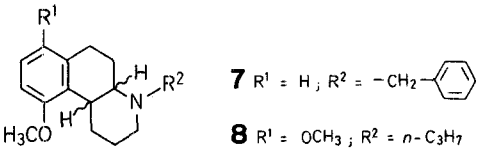
Literature strategies[3,4] have been directed at reduction of the carbonyl group of **2** or of benzene ring-substituted derivatives to give **6** (Scheme B), and then reduction of the enamine double bond of **6** by a variety of methods.

Use of lithium in liquid ammonia, catalytic hydrogenation, or diborane gave mixtures of *cis*- and *trans*-ring fused isomers in which the *cis*: *trans* ratio varied from 1:1 to 3:1. In the case of the 10-methoxy derivative **7**, the best that could



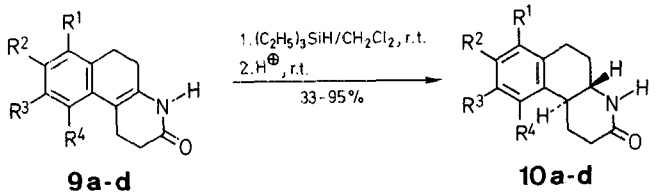
Scheme B

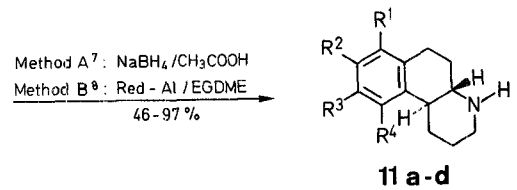
be attained was an 84:16 *cis*: *trans* mixture[4], and in the case of the 7,10-dimethoxy derivative, only an 80:20 *cis*: *trans* ratio was attained[5].



Thus, contrary to earlier literature (as summarized in Ref. 3), neither chemical nor catalytic reduction of the enamines such as **6** gives rise to a single, predictable product, but rather, variable mixtures of *cis*- and *trans*-isomers are formed. Previous literature[2,3,4] has led to the conclusion that the best result to be expected in reduction of these enamines is formation of approximately equal amounts of *cis*- and *trans*-isomers, which necessitates tedious separation and rigorous structure verification.

Kursanov et al.[6], in a review of "ionic hydrogenation" using triethylsilane/trifluoroacetic acid, cited examples where reduction of fused carbocyclic ring systems bearing a carbon-carbon double bond common to two of the rings gave rise to exclusive or greatly predominating *trans*-geometry of ring fusion. In the present study, application of the reagent





EGDME = ethylene glycol dimethyl ether

9,10,11	R1	R2	R3	R4
a	OCH_3	H	H	H
b	OCH_3	OCH_3	H	H
c	H	$-OCH_2-C_6H_5$	OCH_3	H
d	OCH_3	H	H	OCH_3

Scheme C

Table. Reduction Products from Hexahydroquinolines

Product	Reaction Time (10) or Method of C=O Reduction (11)	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] or Lit. m.p. [°C]	I.R. ($CHCl_3$) ν[cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ[ppm]
10a	9 h	95	279–280° (dec) ($CHCl_3$/ether)	$C_{14}H_{17}NO_2$ (231.3)	3400 (NH); 1645 (C=O)	1.66–3.80 (m, 10 H_{aliph}); 3.82 (s, 3H, OCH_3); 6.46 (s, 1H, NH); 6.74 (d, 1 H_{arom}); 6.93 (d, 1 H_{arom}); 7.19 (t, 1 H_{arom})
10b	6.5 h	80	232–233° (ether)	$C_{15}H_{19}NO_3$ (261.3)	1650 (C=O)	1.22–3.40 (m, 10 H_{aliph}); 3.85, 3.95 (2s, 3H each, OCH_3); 6.85, 6.95 (2s, 1 H_{arom} each); 7.45 (s, 1H, NH)
10c	20 h	33	213–215° (acetone)	$C_{12}H_{23}NO_3$ (229.3)	1650 (C=O)	1.20–3.55 (m, 10 H_{aliph}); 3.80 (s, 3H, OCH_3); 5.12 (s, 2H, OCH_2); 6.50, 6.75 (2s, 1 H_{arom} each); 7.12–7.55 (br. s, 6H, NH + 5 H_{arom})
10d	5 h	80	208–210° (ether)	$C_{15}H_{19}NO_3$ (261.3)	3400 (NH); 1660 (C=O)	1.50–3.50 (m, 10 H_{aliph}); 3.80 (s, 6H, OCH_3); 6.70 (s, 2 H_{arom}); 7.20 (br. s, 1H, NH)
11a	B	97	299–300°[b] (C_2H_5OH)	300–301°[c,b]	–	–
11b	A	97	265–266°[b] (acetone)	268–270°[c,b]	–	–
11c	A	46	264–265°[b] (C_2H_5OH/ether)	$C_{21}H_{26}ClNO_2$ (359.9)	3300–3650 (NH); 2840, 2900 (strong, Bohlmann bands)[c,d]	1.00–3.41 (m, 13H, 12 H_{aliph} + NH); 3.85 (s, 3H, OCH_3); 5.15 (s, 2H, OCH_2); 6.60, 6.75 (s, 2 H_{arom}); 7.40 (s, 5 H_{arom})
11d[e]	B	90	279–280° (dec)[b]	256–259°[c,b]	–	–

[a] Satisfactory microanalyses obtained: C, H, N ±0.4%.
[b] m.p. of hydrochloride.
[c] Neat, free base.
[d] These bands are diagnostic of *trans*-fused ring systems[3].
[e] This compound was converted into its *N*-*n*-propyl homolog, which was compared with authentic samples of *cis*- and *trans*-4-*n*-propyl-7,10-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline · HCl[5], and was found to be identical with the *trans*-isomer.

system (triethylsilane/trifluoroacetic acid) to a series of tetrahydroquinolones **9a–d** provided *trans*-fused lactams **10a–d** exclusively (Scheme **C**). This is the first report of application of the triethylsilane/trifluoroacetic acid reagent to reduction of the carbon-carbon double bond in unsaturated lactams. Treatment of the reduced lactams **10** with "Red-Al" or with sodium borohydride/acetic acid provided the *trans*-octahydrobenzo[*f*]quinoline systems **11** in yields that were generally excellent. The *trans*-fused amine systems **11a–d** are known compounds whose geometry of ring fusion has been established[2–5], thus verifying the geometry of ring fusion obtained in the olefin reduction step. Spectral (I.R., N.M.R.) data on all final compounds and intermediates were consistent with the proposed structures.

These results suggest possible greater utility for the triethylsilane/trifluoroacetic acid combination elsewhere in heterocyclic chemistry.

Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus, and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. ^{1}H-N.M.R. spectra were recorded on a Varian Associates EM360 spectrometer with tetramethylsilane as the internal standard. I.R. spectra were recorded on Perkin-Elmer 267 and Beckman 4240 spectrometers.

Triethylsilane/Trifluoroacetic Acid Reduction of Hexahydrobenzo[*f*]quinolones 9a–d; General Procedure:

Triethylsilane (1.33 g, 0.0115 mol) is added to a solution of the hexahydrobenzo[*f*]quinolone **9**[2–5] (0.0039 mol) in dichloromethane (10 ml). The resulting mixture is stirred for 10 min at room temperature, then trifluoroacetic acid (5 ml) is added with cooling in an ice bath. The resulting mixture is stirred at room temperature. Volatiles are evaporated under reduced pressure to leave a solid or oily residue which was taken up in dichloromethane and washed with saturated sodium hydrogen carbonate solution. The organic layer is dried with sodium sulfate, filtered, and evaporated under reduced pressure. Thin layer chromatographic analysis of the residue indicates that the material is homogeneous. This residue is recrystallized (Table).

***trans*-1,2,3,4,4a,5,6,10b-Octahydrobenzo[*f*]quinolines 11a–d:**

Method A: The method[7] using sodium borohydride and glacial acetic acid in dioxane is employed.

Method B: A method involving use of "Red-Al" in ethylene glycol dimethyl ether[8] is employed (Table).

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