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Unexpected Diastereoselectivity in the Formation of 3,5-Disubstituted Indolizidines by Intramolecular Reductive Amination

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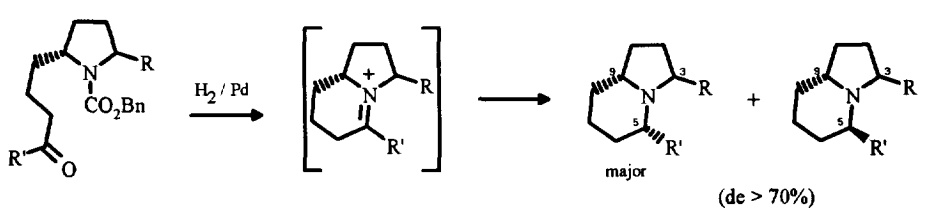
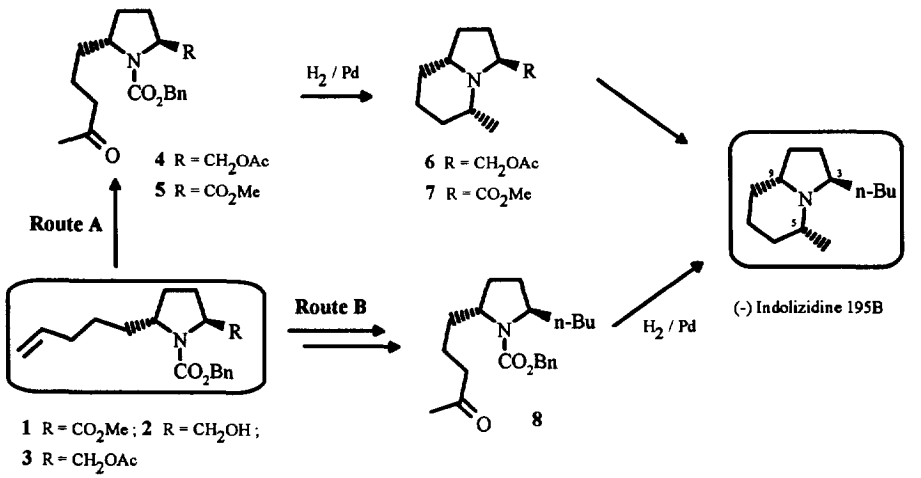
Abstract: The reductive amination of appropriate ketopyrrolidines leading to 3,5-dialkylindolizidines usually gives stereoselectively the indolizidine with a cis relative stereochemistry on the piperidine moiety. We report herein unexpected results concerning the effect of the nature of the C3 substituent on this stereoselectivity.

The indolizidine alkaloids have been detected in animals[1] as well as in vegetables[2]. We have been interested in preparing natural indolizidines extracted from the skin of neotropical frogs[3]. One way to build the indolizidine framework is an intramolecular reductive amination under catalytic hydrogenation conditions. This method has often been used in the synthesis of natural 3,5-disubstituted indolizidines[4] from appropriate ketopyrrolidines (Scheme 1). The main stereomer (de > 70%) has a cis arrangement of C-5 and C-9 hydrogens (indolizidine numbering). Only the center C-9 seems to direct the configuration of C-5 since this cis relationship between C-5 and C-9 hydrogens takes place selectively whatever the C-3 absolute configuration is[4]. This stereoselective cyclisation is presumed to proceed *via* a catalytic reduction of the iminium intermediate formed *in situ* from the free ketoamine (Scheme 1).



Scheme 1

Within the context of our search to use the (S)-proline as a chiral building block in the synthesis of (-) indolizidine 195B[5] we considered two slightly different routes both starting from the common pyrrolidine **1**. In route A, we first decided to construct the indolizidine skeleton by intramolecular reductive amination from substrates **4** (R = CH_2OAc) or **5** (R = CO_2Me) before the C-3 appendage elongation. In route B, the C-3 *n*-butyl substituent elaboration from the carbomethoxy group should be performed before the final reductive amination step (Scheme 2).



Scheme 2

The pyrrolidine **1** was synthesized in a stereoselective manner (de > 90%), in four steps from *L*-proline using the acyliminium methodology[5].

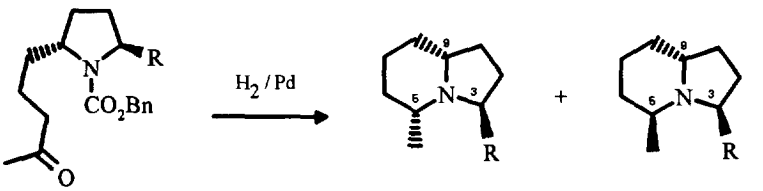
Route A was first examined starting from the trans ketopyrrolidine **4** (R = CH_2OAc). Chemoselective reduction[6] of the ester moiety of **1** and subsequent acylation of the resulting alcohol **2** gave acetate **3**. This latter was submitted to the Wacker oxidation process providing the desired pyrrolidine **4**[6]. Exposure of this compound to an atmosphere of hydrogen in the presence of palladium on charcoal (5%) as catalysts in methanol, caused the amine deprotection, annulation and finally the reduction of the resulting iminium, leading to a mixture of **6a**[7] along with its C5 epimer **6b** in quantitative yield (Scheme 3). The diastereomeric ratio of **6a** and **6b** (64:36) was determined by gas chromatography. This diastereoselectivity (de = 28%) was low compared to the known results with alkyl substituent at the C-3 position (de

> 70%)[4]. Attempts to improve this stereoselectivity by using various solvents and palladium catalysts were unsuccessful.

This drop in selectivity seemed to be due to the presence of the methyleneacetate group. Before we undertook the synthesis of (-) indolizidine 195B according to route B, we decided to carry out the reductive amination on the substrate **5** bearing a carbomethoxy group on C3 carbon in order to check the effect of such a substituent.

Oxidation of the key intermediate **1**[8] under the Wacker type procedure [$PdCl_2(PhCN)_2/CuCl/O_2$] furnished the ketopyrrolidine **5** in 88% isolated yield[8]. The reductive amination of **5** under catalytic hydrogenation conditions was carried out in ethyl acetate as solvent. The crude analysis (GC / MS) showed the presence of four diastereomers of **7** among which the predominent represented more than 90%.

The presence of four isomers was not surprising since the starting material **5** was contamined with its cis isomer[8]. More surprising was the relative stereochemistry of the major indolizidine isolated from the mixture of **7**. Indeed the NOE experiments of this stereomer[9] indicated a cis relative arrangement of C-5 and C-3 hydrogens. No signal enhancement was observed neither between C-9 and C-3, nor between C-9 and C-5 hydrogens. These NOE results were in favor of the epimer **7b** for the major indolizidine obtained (Scheme 3). Moreover a second isolated diastereomer[10] was shown to have a cis arrangement between the C-3, C-5 and C-9 hydrogens on the basis of NOE experiments. The formation of this stereomer could result from the reductive amination of the cis isomer of **5**[8].

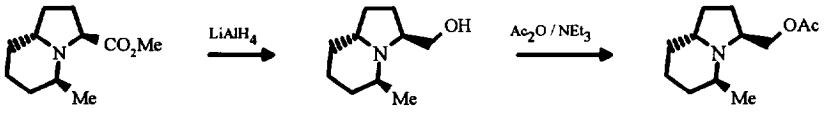


4	$R = CH_2OAc$	**6a** (64%)	**6b** (36%)
5	$R = CO_2Me$	**7a** (see text)	**7b** (> 90%)
8	R = n-Bu	**(-) 195B** (86%)	**5-epi (-)195B** (14%)

Scheme 3

To check this unexpected stereochemistry of the major stereomer **7b**, we decided to transform its ester moiety into a methyleneacetate group and to compare

the obtained product with **6a** and **6b**. The major ester isolated from the mixture of 7 was quantitatively reduced[11] into its primary alcohol **9** which was then protected as an acetate[12] in 93% isolated yield. The acetate thus obtained was found to be identical to **6b** in all respects (Scheme 4).



7b **9** **6b**

Scheme 4

This result confirmed the absolute stereochemistry of the major stereomer **7b** and hence the surprising stereoselectivity in the reductive amination of **5**. At this stage we have no serious evidences to explain this unexpected stereoselectivity.

As we see, route A gave low or reverse stereoselectivity depending on the nature of the C-3 substituent. Finally the synthesis of (-) indolizidine 195B was achieved[5] according to route B via the trans ketopyrrolidine **8** with 72% diastereoselectivity (Scheme 3).

References and notes.

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2. Michael, J. P. *Natural Products Reports* **1990**, 485.
3. Fleurant, A. ; Célérier, J. P. ; Lhommet, G. *Tetrahedron : Asymmetry* **1993**, *4*, 1429.
4. Machinaga, N. ; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178. Momose, T. ; Toyooka, N. ; Seki, S. ; Hirai, Y. *Chem. Pharm. Bull.* **1990**, *38*, 2072.
5. Célimène, C. ; Dhimane, H. ; LeBail, M. ; Lhommet, G. *Tetrahedron Lett.* **1994**, *35*, 6105.Trans and cis isomers of **1** were not separable by chromatography.
6. Reduction of **1** was carried out by using $NaBH_4/CaCl_2$ system in THF/EtOH (1/1). At this stage the pure trans alcohol **2** was isolated in 67% yield. Acetate **3** was prepared from **2** using acetyl chloride in pyridine (92% yield).
7. Epimers **6** were isolated by column chromatography (SiO_2, Et_2O/Pentane, 3/1).
8. The key intermediate **1** could not be separated from its cis isomer (4%) and therefore **5** was used as a trans/cis (96/4) mixture.
9. Product **7b** was purified by column chromatography (SiO_2, Et_2O/Pentane, 3/1)
10. The two others stereomers were present in too low concentration to be isolated.
11. The ester moiety reduction was performed at -78°C using $LiAlH_4$ in THF.
12. This acetate was obtained by refluxing **9** in THF in the presence of Ac_2O (1.1 equiv.) and Et_3N (4 equiv.). Otherwise Ac_2O/Pyridine or Ac_2O/DCC/DMAP left **9** unchanged. The use of AcCl instead of Ac_2O gave a complex mixture.

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