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(-)-INDOLIZIDINE 167B VIA 4-PYRROLYLBUTANALS: TWO SYNTHETIC METHODOLOGIES AT COMPARISON

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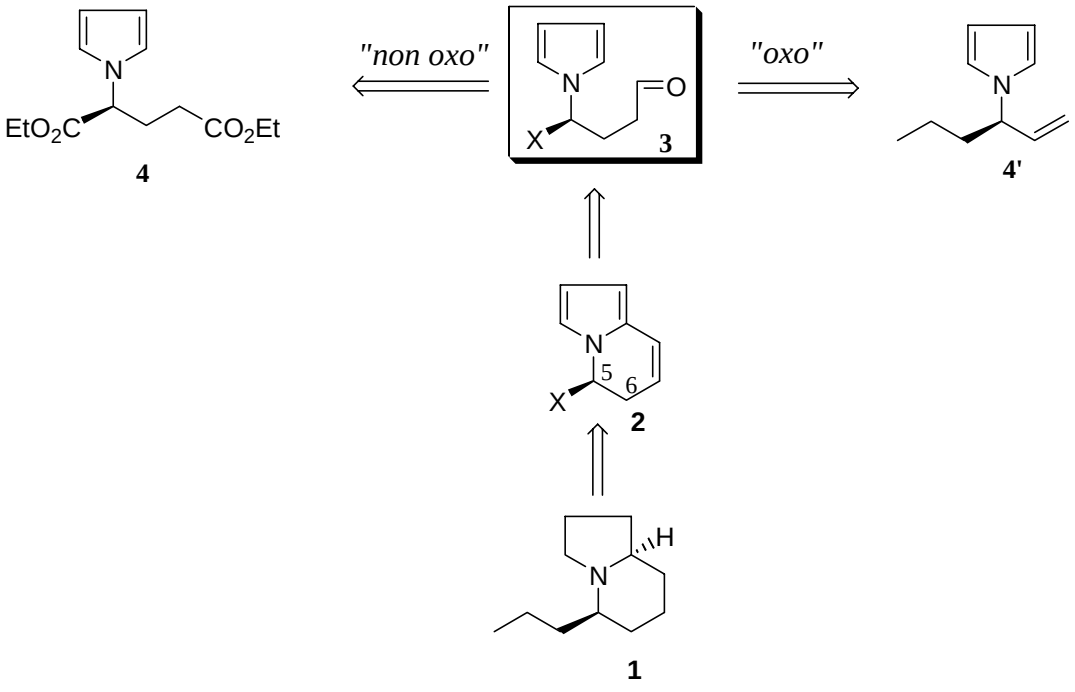
Dedicated to the Memory of Dr. John Daly

Abstract – This review relates the results that we obtained in the field of the total synthesis of (-)-indolizidine 167B, based on the intramolecular cyclodehydration of a 4-pyrrolylbutanal to a 5,6-dihydroindolizine core, according to "oxo" or "non oxo" methodology. In the former pathway the butanal was (*R*)-4-(pyrrol-1-yl)heptanal and originated from (*R*)-3-(pyrrol-1-yl)but-1-ene *via* rhodium-catalyzed hydroformylation. In the latter one the proper (*R*)-4-carboxyethyl-4-(pyrrol-1-yl)butanal intermediate was obtained from diethyl-2-(pyrrol-1-yl)pentanedioate *via* chemo- and regioselective reduction of the sole distal ester group. In both cases a diastereoselective hydrogenation of the final 5-*n*-propyl-5,6-dihydroindolizine gave the target compound.

CONTENTS

1. INTRODUCTION

Indolizidine are commonly occurring structural skeleta in natural alkaloids with a wide range of biological activities. Among these, indolizidine 167B (**1**), which was detected by Daly and his group from neotropical frog genera Dentrobates,[1,2] is a noncompetitive blocker of neuromuscular transmission. Although the structure has been questioned,[3] this alkaloid remains a target for many research groups, both in its racemic and optically active form.[4] Most of the synthetic strategies proposed for the total synthesis of indolizidine 167B begin with the pyrrolidine ring and then construction of the piperidine ring, the most frequent disconnection being at the N4-C5 bond, although cyclisation *via* the C8-C9 bond is also known. We envisaged that the target compound **1** could be directly obtained from 5,6-dihydroindolizine **2** (Scheme 1), where the alkyl group present in position 5 of the ring skeleton is the same or a direct precursor of that in the target molecule. Compound **2** could be obtained through an intramolecular cyclodehydration of 4-(pyrrol-1-yl)butanal **3**. The pyrrolylbutanals are a unknown class of compounds in literature. As far as homologue compounds is concerned, there is a sole case of pyrrolylethanal synthesis[5] *via* oxidation of the corresponding alcohol and few examples of pyrrolylpropanals preparation.[5,6-8] Depending on the pathway to the butanal intermediate adopted by us, if rhodium-catalyzed hydroformylation based or not, the synthetic approach is named “oxo” or “non oxo” into the following review (Scheme 1).



Scheme 1

The hydroformylation or "*oxo*" process is a catalytic reaction, which elongates the olefinic chain by one carbon atom, simultaneously introducing an aldehydic functionality. This atom economic process is widely used for industrial purposes and is more and more employed in fine chemistry.[9,10] The rhodium catalyzed hydroformylation of olefins has been studied by us for many years.[11-15] Recently the oxo process applied to heteroaromatic olefins such as styrene, vinylpyrroles, allylpyrroles and indoles became also a versatile synthetic instrument. In particular the domino hydroformylation/cyclodehydration of the formed pyrrolylbutanals reactions sequence found under optically active *N*-allylpyrroles oxo conditions allowed us to prepare many dihydroindolizines in high optical purity.[16] In order to evaluate if the pyrrolylbutanals can be suitable synthetic intermediates to indolizine derivatives, we began also a study of their preparation and transformation into indolizine nucleus *via* sequences of traditional organic reactions ("*non oxo*" process). In particular this attempt has been made by using a pyrrolyl derivative already bearing a four carbon atom alkyl chain *via* functional group transformation. In this review the two approaches are applied to the indolizidine 167B synthesis but they appear of high potentiality for indolizines synthesis in general.

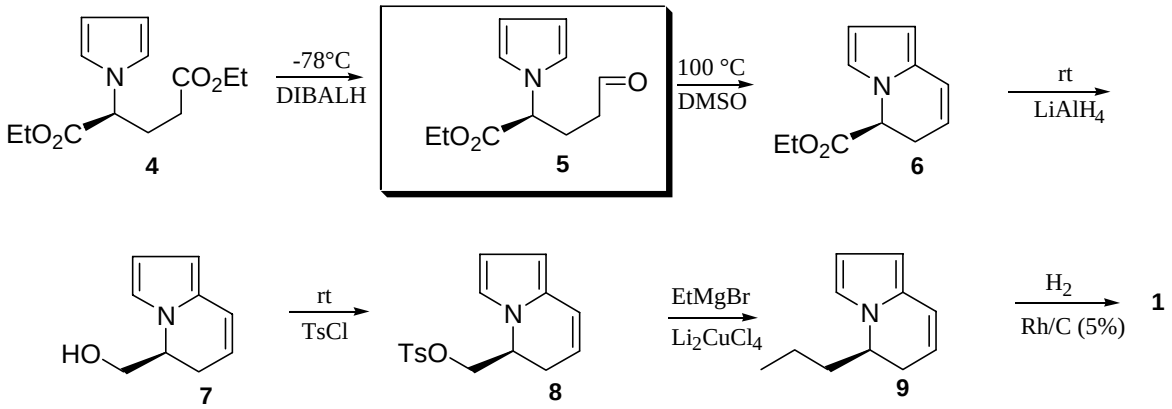
2. "*NON OXO*" SYNTHETIC METHODOLOGY

The synthetic pathway we adopted is described in Scheme 2. 4-Carboxyethyl-4-(pyrrol-1-yl)butanal (**5**) was the pivotal intermediate. This compound has been synthesized from glutamic acid, *via* pyrrolation to diethyl-2-(pyrrol-1-yl)pentanedioate (**4**) and successive reduction using DIBALH in hexane at -78°C.[17] Although a preliminary attempt on 4-(pyrrol-1-yl)butanoate should gave a complete reduction of the ester group,[18] the same reaction applied to diester group has been very surprising, the chemo- and regioselective reduction of the sole distal ester group occurring.

By treatment with DMSO at high temperature (100 °C) **5** undergoes intramolecular cyclization to dihydroindolizine **6**. The ester group of **6** was transformed into the hydroxymethyl group of **7** with $LiAlH_4$ in THF giving (+)-(*S*)-hydroxymethyl-5,6-dihydroindolizine in almost quantitative yield and enantiomerically pure form (98% ee). After the reduction step, the tosylation occurs also very easily: the reactants are mixed together and stirred at rt, providing (+)-(*S*)-5-(*p*-toluenesulfonyloxymethyl)-5,6-dihydroindolizine (**8**) in good yield (69%).[19]

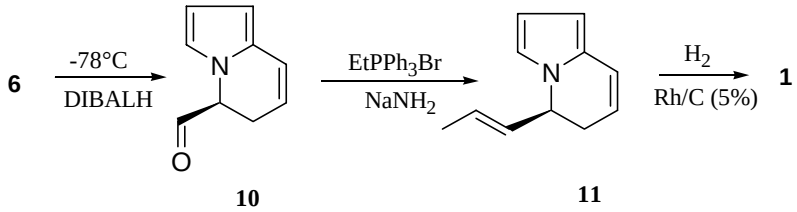
Tamura and Kochi Cu(II) system[20] seemed to be the proper reagent for the introduction of an ethyl group in place of the tosyl one in forming the n-propyl substituent at C5. Preliminary tests showed that by using catalytic quantities (5%) of Li_2CuCl_4 (added as a THF solution) with high excess of EtMgBr (-)-(*R*)-*n*-propyl-5,6-dihydroindolizine (**9**) was formed but only partial conversion (20%) of the starting material was observed. Increasing the quantity of the reagent (50%), the conversion of the starting material rises to 70%, but also side products start to appear. In both cases

(-)-(*R*)-*n*-propyl-5,6-dihydroindolizine with ee 98% was obtained:[21] a final diastereoselective hydrogenation with 5% Rh on carbon gave (-)-indolizidine 167B in 65% yield.



Scheme 2

The above pathway is the best approach to **1**. A synthetic alternative *via* **6** is depicted in Scheme 3.

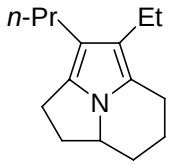


Scheme 3

The reduction of (-)-**6** to aldehyde (-)-**10** was carried out at -78 °C. From our previous work on an analogous transformation in the synthesis of optically active 1-allylpyrroles from the corresponding α-amino acids,[22] we knew that the ester reduction might cause racemisation but only in a low extent if the addition of the quenching tartrate solution occurs at -78 °C. In this case we obtained (-)-(*S*)-5-formyl-5,6-dihydroindolizine (**10**) with an optical purity of 80%. The olefination of (-)-**10** into (+)-**11** was carried out with the Schlosser-Schaub instant ylide reagent at -30 °C to avoid racemisation. This has proven to be the lowest temperature at which we can observe any reaction between the reagents, but the reaction mixture must be warmed to room temperature to obtain a complete conversion of the starting material. The target compound **1** obtained from **11** *via* hydrogenation with Rh/C catalytic system resulted with an optical purity of 42%: the slow olefination step was critical allowing the aldehyde enolisation. The drawback of the C5 configurational lability in (-)-**10** during the olefination step to (+)-**11**, don't occur when **10** is reduced to (+)-(*S*)-5-hydroxymethyl-5,6-dihydroindolizine **7** (optical purity (80%)) with $NaBH_4$ in MeOH (Scheme 2).

The "non oxo" approach depicted above is a good way to indolizidine 167B. Indeed other 5-alkylsubstituted indolizidines can be likely obtained *via* the same synthetic sequence, in which the

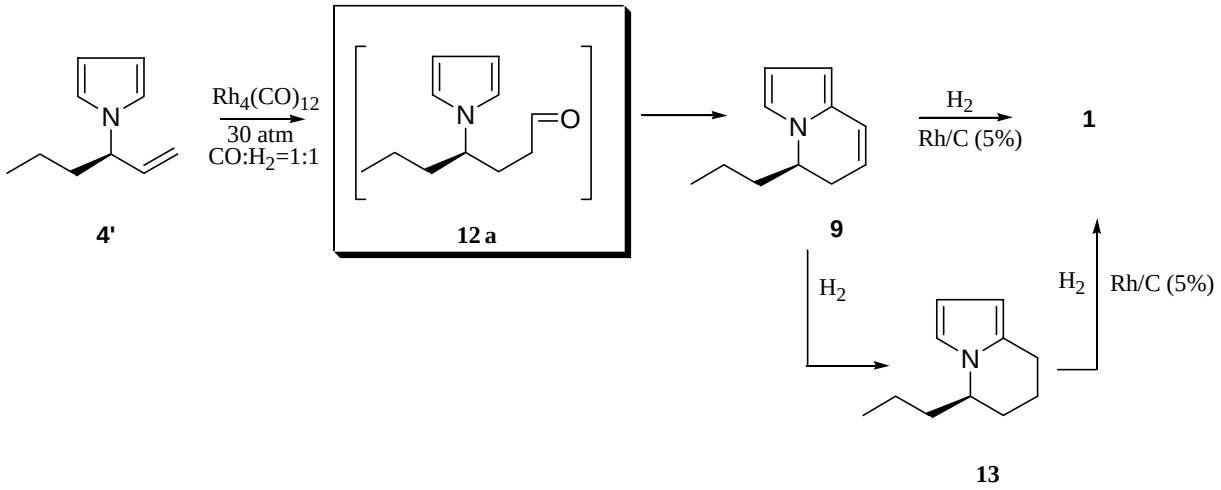
availability of the Wittig reagent to introduce the proper alkenyl group at C5 on 5-formyl-5,6-dihydroindolizine **5** is the sole crucial key. A recent successful application of "*non oxo*" methodology to the preparation of natural alkaloids was the formal synthesis of myrmicarin 217 (Scheme 4) *via* intermediate **6**. [17]



Scheme 4

3. "OXO" SYNTHETIC METHODOLOGY

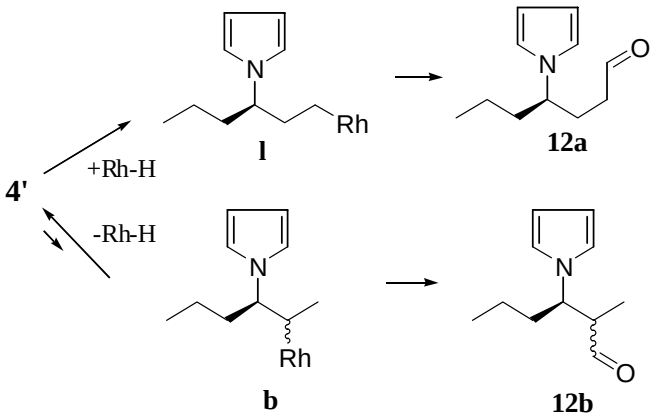
In the synthesis of indolizidine 167B described here (Scheme 5), the construction of the bicyclic core still occurs *via* a pyrrolylbutanal; unlike the previous case, the aldehyde is 3-(pyrrol-1-yl)heptanal (**12a**) and comes from rhodium-catalyzed hydroformylation of optically active (*R*)-3-(pyrrol-1-yl)hex-1-ene (**4'**) (Scheme 5).[23]



Scheme 5

The optically active starting material **4'** (92% ee) was prepared from the corresponding amino acid D-norvaline as previously reported.[22] Then **4'** was introduced in a 25 ml stainless steel autoclave, in the presence of $Rh_4(CO)_{12}$, at 125 °C and 30 atm total pressure (CO/H_2= 1:1), in toluene as a solvent. After 25 min, the olefin was completely consumed and 5-*n*-propyl-5,6-dihydroindolizine (**9**) was the predominant product (Scheme 5). As far as the typical oxo products are concerned, i.e. the aldehyde isomers, the linear **12a** was present only in traces amounts in the reaction mixture while the branched one

12b (Scheme 6) was in 13% with respect to the indolizine structure (Scheme 5). While at room temperature and high pressure **12a**/**12b** ratio is largely favorable to the branched aldehyde (29/71),[24] under the above conditions (high temperature and low pressure) a highly regioselective hydroformylation into the linear aldehyde takes place; this is a consequence of the isomerization of the branched alkyl-rhodium intermediate **b**, precursor of **12b**, into the linear one **l**, precursor of **12a**, *via* a β-elimination process with formation of olefin **4'** (Scheme 6).[25]



Scheme 6

This transformation is completely stereospecific and it does not involve the chiral center. An evaluation of the enantiomeric excess of both unconverted **4'** and produced **12a** was carried out in order to test the configurational stability of these structures under hydroformylation conditions. Interestingly **4'** showed, at all conversions, practically the same ee, that is the starting ee value (92%). A similar behavior occurred for dihydroindolizine **9**, its ee value remaining the same as that of the corresponding olefin **4'** (ee 92%) at all reaction times. The isomerization of **b** into **l** and the absence of racemization of starting substrate are the peculiar features of this process.

When, at complete conversion of **4'**, the gas mixture was removed from the crude hydroformylation product and H_2 was added and the reaction vessel heated for long time, **9** disappeared and the corresponding 5,6,7,8-tetrahydroindolizine **13** was obtained (Scheme 5): additional reduction of the pyrrole nucleus was never observed even by forcing the conditions (high pressure and high temperture). This goal was successfully reached by hydrogenation of **13** (or **9**) with 5% Rh on carbon. It is to remark that the global synthesis is completely stereospecific, the final product having the same optical purity as the starting olefin (92% ee).

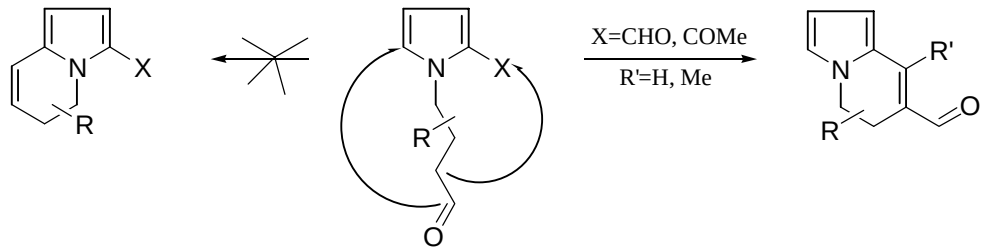
The "*oxo*" methodology described above is a good way to indolizidine 167B. It deals with a multi-step domino process which starts with the interconversion of the isomeric rhodium-alkyl intermediates and carries on with the intramolecular cyclodehydration of the formed linear aldehyde followed by hydrogenation: a more complex structure from a simple one was obtained in a one-pot, convenient and environmentally safe operation. All steps occur with almost complete configurational stability and the

final indolizine has the same optical purity as the starting material. Depending on the employed allylpyrrole, i. e. on the alkyl group in the starting α-amino acid, the method can be used for the synthesis of indolizine derivatives in general.

4. MECHANISTIC CONSIDERATION

i) ON THE PYRROLYLBUTANAL INTERMEDIATE

With respect to "*non oxo*" approach, in the "*oxo*" one the butanal intermediate is a transient species which, as it forms, evolves into a dihydroindolizine one. We do not know if the cyclization is rhodium-promoted or not because the aldehyde cannot be isolated under hydroformylation conditions. The high reactivity of the butanal is likely due to the high nucleophilic character of 2 pyrrole carbon atom with respect to the vicinal carbonyl carbon one. On the other hand a some rhodium species could accelerate the process making the carbonyl carbon atom more electrophilic *via* oxygen coordination. Evidence for an almost spontaneous cyclization have been found also in the "*non oxo*" approach.[26] The treatment of the pyrrolylbutanal **5** with DMSO at high temperature is the fastest way to bicyclic **6**. However the formation of **6** was also observed after many hours by solving **5** in cool DMSO/H_2O in the presence of glycine (15%). The coordinating character of DMSO together with the mild acid conditions adopted are likely responsible for the approaching of the formyl group to the pyrrole α position. Indeed **5** cyclizes to **6** also on standing at 0 °C in the absence of solvent, the glass acidity being enough to induce the already well favoured cyclization. Although, under oxo conditions, the cyclization in α positions is much faster than hydroformylation, it can be very slow when an electron-withdrawing group is present on β position of pyrrole [15] and does not occur with 2-acyl substituted allylpyrroles:[14] in this case an intramolecular aldol condensation takes place giving also an indolizine *via* formation of C7-C8 bond instead of C8-C9 one (Scheme 7).

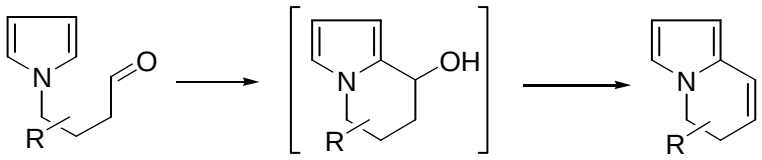


Scheme 7

When the pyrrole nucleus is substituted with the indole, the intramolecular cyclization on the α position only occurs if an electron-donating group such as a methyl group is present on the β position able to compensate the weak nucleophilic character of position α.[27]

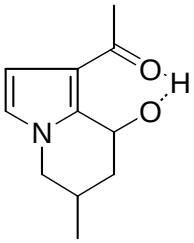
ii) ON THE BICYCLIC ALCOHOL INTERMEDIATE

The cyclization process likely involves the initial formation of a bicyclic alcohol *via* C8-C9 bond construction: a following elimination of water gives the highly conjugated dihydroindolizine (Scheme 8).



Scheme 8

The alcohol has never been observed under oxo condition except for in the case of hydroformylation of 1-acetyl-6-methyl-8-hydroxy-5,6,7,8-tetrahydroindolizine[15]: a tricyclic structure (Scheme 9) bearing an intramolecular hydrogen bond between the hydroxyl group and the acetyl group at the 3-position of the pyrrole nucleus occurs, accounting for the unusual resistance of the hydroxyl group to dehydration. However the treatment of the alcohol with HClg immediately gives the corresponding 2-acetyl-6-methyl-5,6-dihydroindolizine[15] *via* water elimination.



Scheme 9

Evidence for the formation of a bicyclic alcohol as intermediate, has been found also under "*non oxo*" approach when 4-(pyrrol-1-yl)butanoate was reduced with DIBALH.[18]

5. CONCLUSIONS

In conclusion two stereoselective synthesis of indolizidine 167B have been reported *via* an intramolecular cyclodehydration of a 4-pyrrolylbutanal. As far as the synthetic yields and the optical purity of the target compounds, the two procedures are very similar, the use of one or other depending on the affinity with the experimental conditions required. The synthesis of indolizidine 167B is a frequent topic for many research group *via* the most different philosophoes. The preparation reported here *via* pyrrolylbutanal, easily available from glutamic acid, *via* stoichiometric organic reactions, or from α-amino acids, *via* catalytic hydroformylation, is an original method of our research group.

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Her research interests are primarily in the development of new synthetic methods of heterocyclic compounds with particular attention to domino processes catalyzed by transition metals (hydroformylation).