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IMINO-SUGARS BY STEREOSELECTIVE PROCESSES EMPLOYING PYRROLINE N-OXIDES

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The total synthesis of natural products requires selective methods to adapt to the structural complexity the nature has introduced in natural compounds. From this challenge derives the impetus to find new reactions, new reagents and new catalysts to run reactions in a chemoselective, regioselective and stereoselective way. Recently, domino or multicomponent,¹ combinatorial² or enzymatic³ processes, have expanded the synthetic tools available to researchers, and topics like atom economy⁴ and environmentally friendly syntheses became the concern of organic chemists. Having in mind all these points we approached the synthesis of natural products like glycosidase inhibitors,⁷ belonging to the classes of indolizine⁵ and pyrrolizine⁶ alkaloids, which are attracting growing interest from synthetic chemists for their various and essential biological activities (Chart 1).

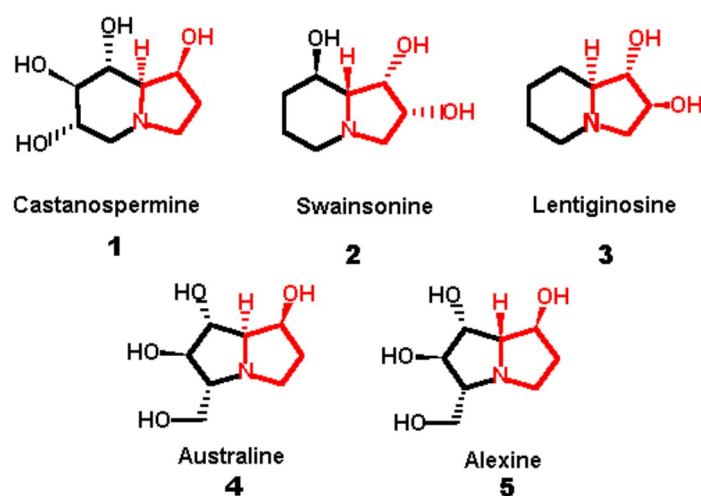
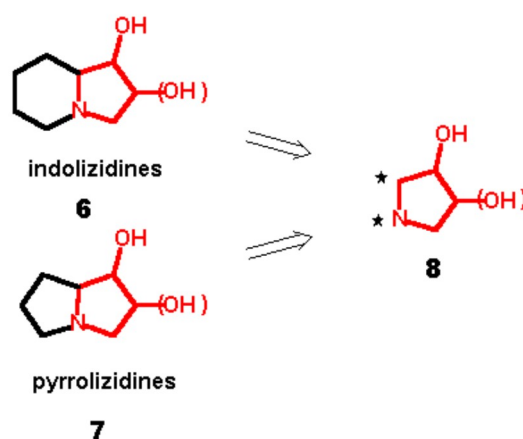


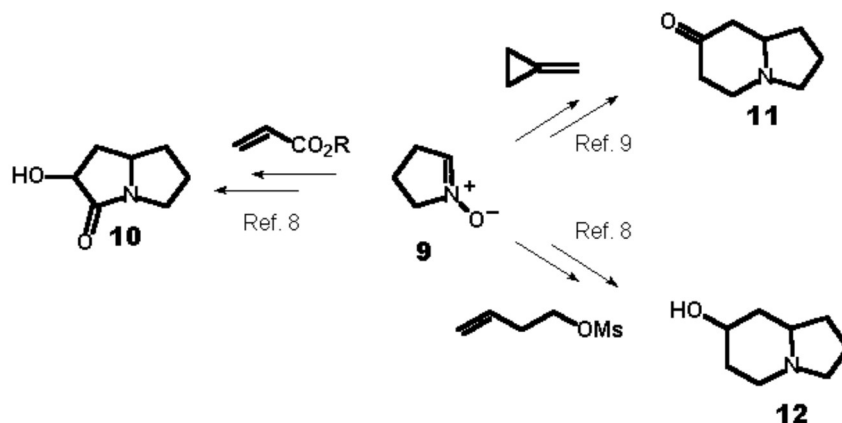
Chart 1.



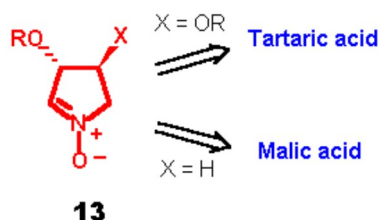
Scheme 1.

A structural analysis of these polyhydroxylated structures showed that they might be synthesized in a general way starting from a common five membered pyrroline synthon **8** bearing one or two hydroxy functions on the 3 and 4 position of the ring (Scheme 1).

The choice of the appropriate reaction partner should provide the direct entry to indolizidine or pyrrolizidine skeletons. Pyrroline-*N*-oxides appeared to us excellent synthons for this purpose, as they can afford these ring systems by 1,3-dipolar cycloadditions processes followed by simple elaboration of the cycloadducts. The whole process can fulfill all the requirements of a modern synthetic methodology like chemoselectivity, stereoselectivity and high atom economy. Many strategies were described in the literature for the synthesis of these ring skeletons^{8,9} starting from pyrroline-*N*-oxide **9**, the most common pathways being summarized in Scheme 2.



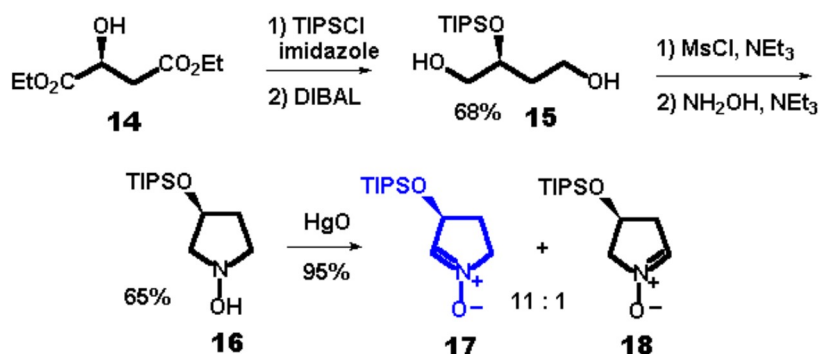
Scheme 2.



Scheme 3.

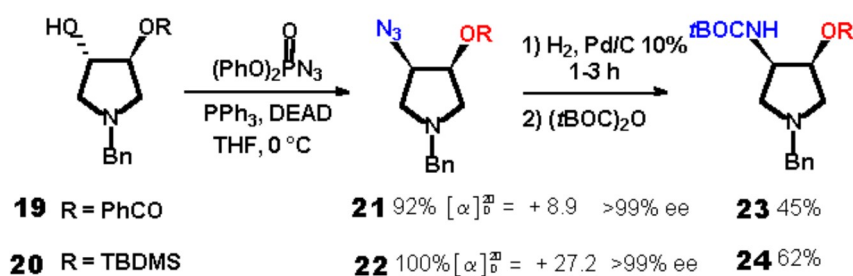
Hydroxylated pyrrolidine-*N*-oxides **13** in both enantiomeric forms can be conveniently synthesized from malic and tartaric acids. Complementary syntheses were developed to allow the synthesis of alkyl and silyl protected 3-hydroxy- and 3,4-dihydroxy pyrrolidine-*N*-oxides.¹⁰

Whereas the synthesis of *O*-alkyl protected nitrones takes place directly from chiral pool reagents via formation of a cyclic hydroxylamine, the synthesis of *O*-silyl protected nitrones requires a preformed chiral 3,4-dihydroxy-*N*-benzyl pyrrolidine.¹¹ Recently the use of TIPS as a *O*-substituent in the malic acid series allowed the use of the standard cyclic hydroxylamine procedure also for a silyl protected nitrone **17** (Scheme 4).¹²



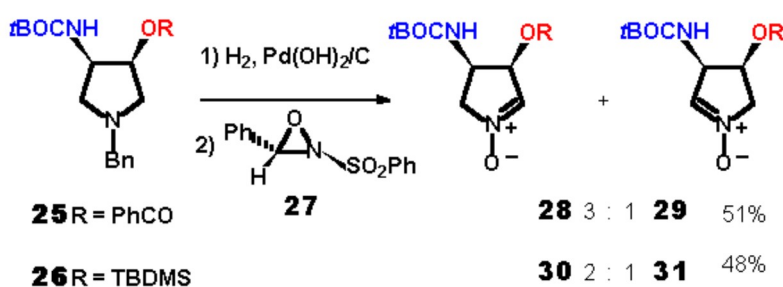
Scheme 4.

A *cis*-OH relationship on the pyrrolidine oxide is necessary to address the synthesis of swainsonine **2** and its analogues. This goal was fulfilled through a Mitsunobu reaction which inverted the configuration of the stereogenic center bearing the unprotected hydroxyl function in **20** (scheme 5).¹³ In order to obtain enantiopure aza-analogues, with a protected amino group in a *cis* relationship with the vicinal hydroxyl group, we modified the previous procedure using diphenylphosphoryl azide as reagent in the Mitsunobu reaction (scheme 5).¹⁴



Scheme 5.

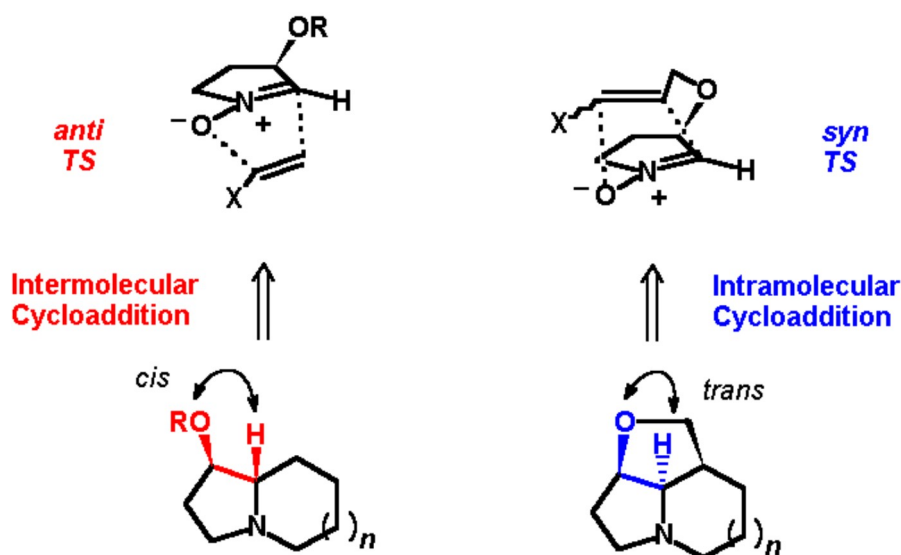
The azido compounds **21** and **22** were reduced to amino derivative and protected prior to the oxidation step.



Scheme 6.

Debenzylation and oxidation with oxaziridine **27** affords mixtures of the two regioisomeric nitrones **28-29** and **30-31**, which can be separated by chromatography (Scheme 6). The regioisomeric ratio obtained was expected on the basis of previous observations which showed the role of the most electronwithdrawing group in driving the selectivity.^{10c}

The success of a synthetic methodology consists of the possibility to fulfill different stereochemical requirements of the products starting from the same precursors. A general outlook of glycosidase inhibitors structures shows that one main stereochemical feature is represented by the relative stereochemistry between the hydroxy group at C1 and the bridgehead proton, which is relevant to the biological activity of these compounds. A *cis*-{OH,H} relationship originates from a highly favoured *anti* transition state approach of the reactants in an intermolecular cycloaddition (Scheme 9). To induce the inversion of the stereochemistry and a *trans*-{OH,H} relationship like in castanospermine (**1**), swainsonine (**2**), australine (**4**), the dipolarophile has to approach *syn* to the 3-alkoxy substituent on the nitron, and this is possible quantitatively only if the dipolarophile is directly linked to the substituent in an intramolecular process.

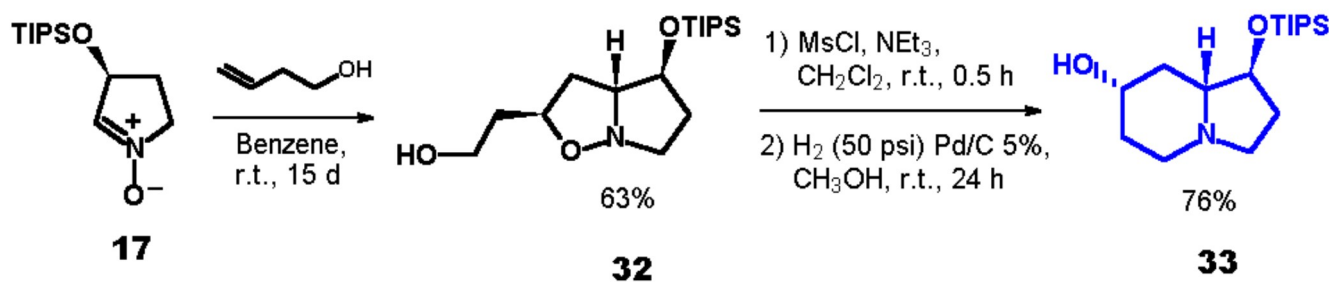


Scheme 7.

Both these approaches were successfully employed in the synthesis of polyhydroxy-indolizidines and pyrrolizidines with a strict control of the stereochemistry of this substitution pattern.

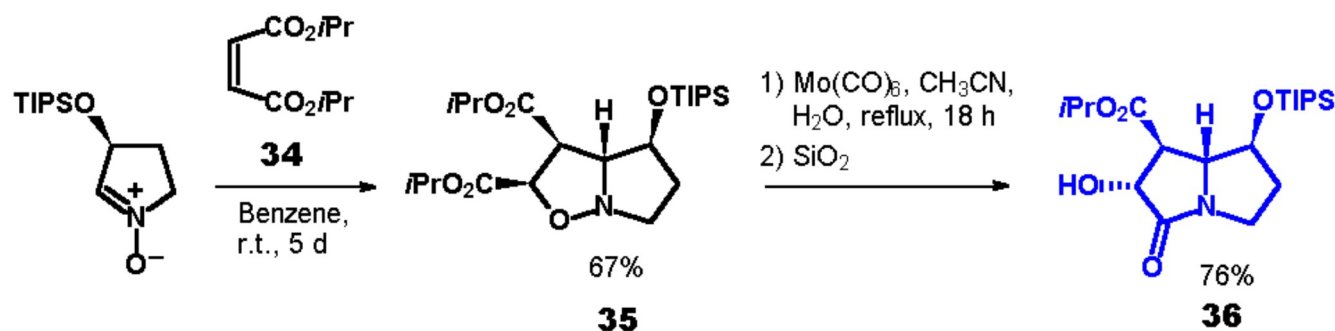
The intermolecular approach has been extensively applied with many of the previously presented nitron to afford natural products as Lentiginosine¹¹ (**3**) or analogues.¹⁵

Recently nitron **17** has been used to afford 1-*O*-silyl protected 7-hydroxy indolizidine **33** through cycloadditions to butenol and further elaboration of the adduct (Scheme 8).¹²

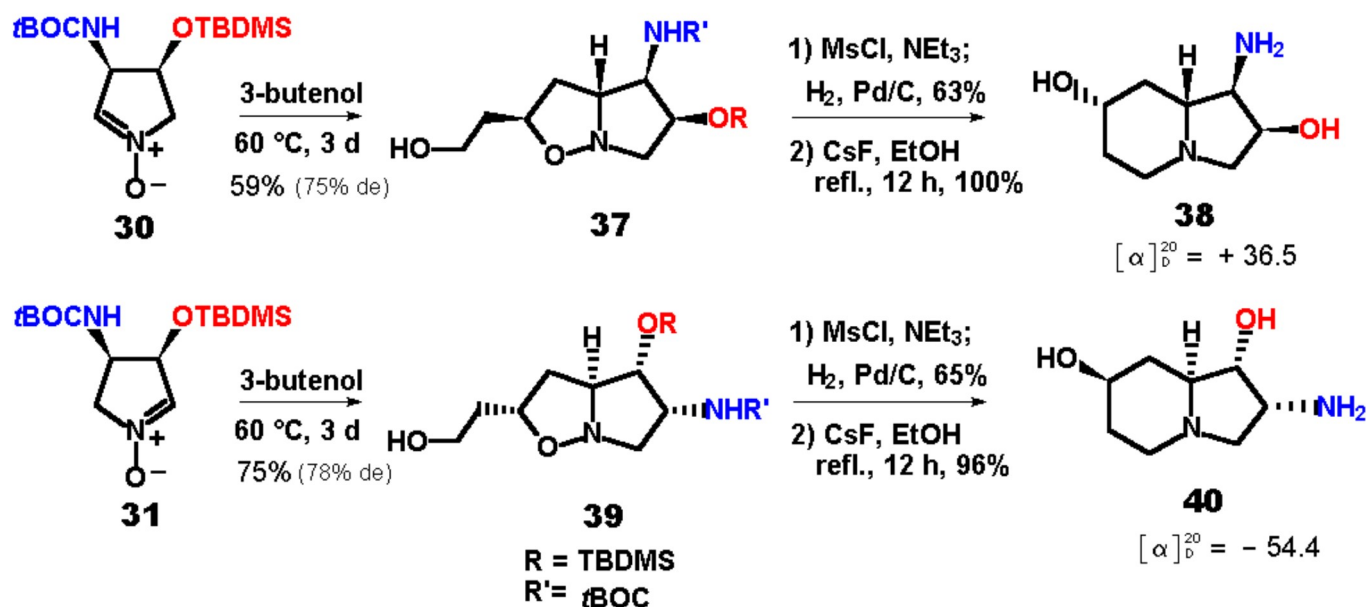


Scheme 8.

Cycloaddition with diisopropyl maleate afforded, with high diastereoselectivity, compound **35** which was transformed in the correspondent pyrrolizidinone **36** (Scheme 9).



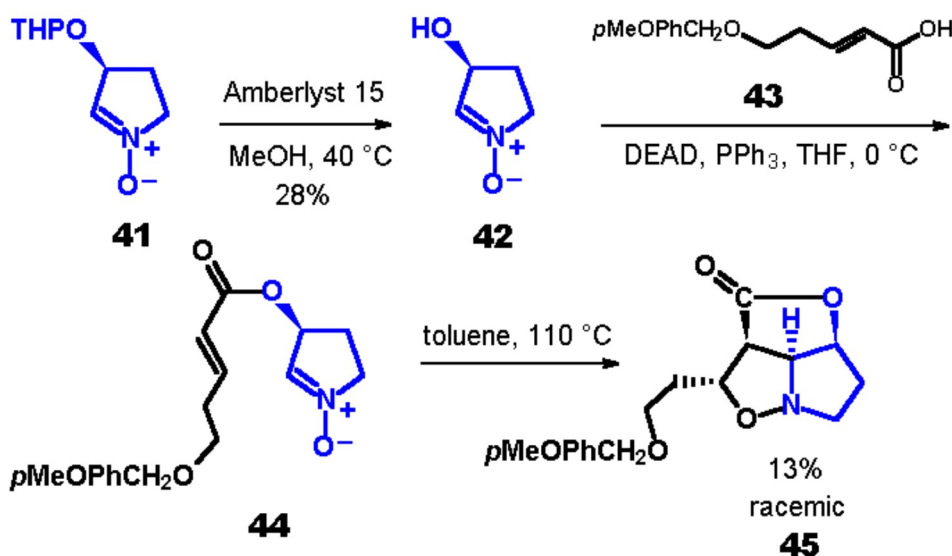
Scheme 9.



Scheme 10.

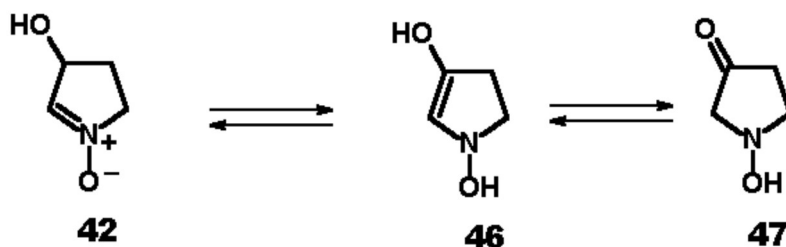
With the same procedure amino-hydroxy substituted nitrones **30–31** were transformed in the corresponding aminodihydroxyindolizidines **38** and **40**, the first examples of diaza-analogues of monosaccharides with indolizidine structure.¹⁴

The intramolecular approach requires the presence of both reacting function on the same molecule and we envisioned the possibility to use the hydroxyl group, transformed as ester, as the linker between the 1,3-dipole and the dipolarophile. Since the synthetic sequence for the obtention of this group of nitrones does not allow the presence of a double bond activated by an electron withdrawing group, we planned to deprotect the hydroxyl function on nitron **41** (scheme 11) and use it to insert the pentenoic acid derivative **43** as dipolarophile.

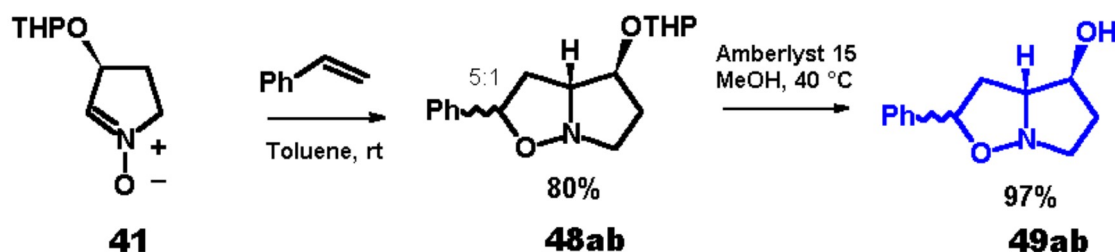


Scheme 11.

This synthetic approach revealed inefficient due to extensive racemization of nitron **42**, even in very mild conditions. This behaviour is probably inherent to nitron **42** due to its possible tautomeric equilibrium with hydroxylamine **47**.

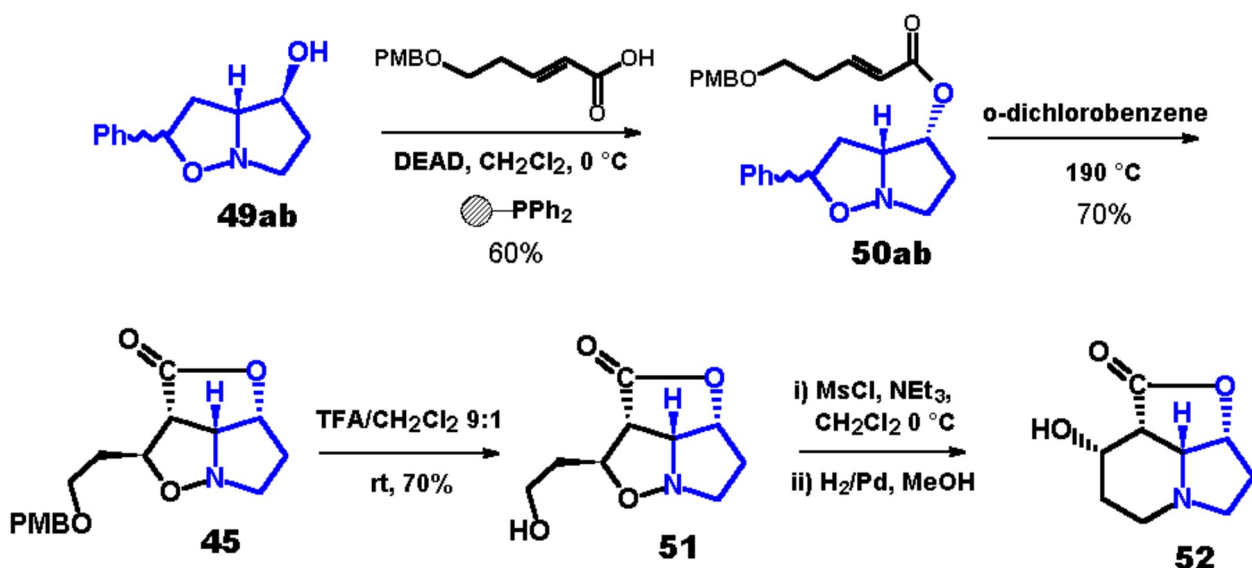


Scheme 12.



Scheme 13.

The solution of the problem was found by “masking” the nitron functionality through a 1,3-dipolar cycloaddition with styrene, affording isoxazolidines **48a,b** as mixtures of isomers which were efficiently deprotected preserving the stereochemical integrity of the OH substituted stereogenic center.



Scheme 14.

Subsequent insertion of a pentenoic acid derivative through a Mitsunobu reaction afforded compound **50**, which now contains an activated dipolarophile and a masked dipole. Heating at high temperature caused the retro-cycloaddition of styrene and the formation of the favored intramolecular adducts.¹⁶

Although the use of the 1,3-dipolar cycloaddition-retrocycloaddition process was already known as method of protection of nitrones,¹⁷ this is the first example of application to the synthesis of an indolizidine skeleton and appears to be a general method for the stereoselective synthesis of this class of compounds.

CONCLUSIONS

Hydroxylated pyrroline-*N*-oxides provide a general entry to the synthesis of polyhydroxylated pyrrolizidine and indolizidine alkaloids. Their use appears attractive for many aspects that are a major topic in modern organic synthesis. They allow a high “atom economy” in the overall process as all the skeleton atoms are kept intact from reagents to products. All the key steps occur by simple thermal induction without any need of added catalyst. This feature allow to carry out several steps in one pot as a domino process, another appealing aspect for environmentally friendly syntheses. Finally, the described methodology allows the multiplication of stereogenic centers in the indolizidine skeleton, with complete control of enantiomeric and diastereomeric relations, starting from the same stereogenic nitron precursor.

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