Synthesis of Iminosugars and Analogues from Pyrrole

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Introduction

Pyrrolidine derivatives are widely found in natural products, i.e. five membered iminosugars. In contrast to the situation with six membered rings, five membered rings usually do not adopt a single well defined conformation. They exist as a rapidly interconverting mixture of envelope and twist conformations, which makes difficult the stereoselective synthesis of pyrrolidine derivatives, comparing with the corresponding six membered analogues (piperidines).

As a part of a research program that deals with new strategies for the stereoselective synthesis of five membered iminosugars, we have proposed the preparation of complexfive membered iminosugars.

[schematic diagram of pyrrolidine derivatives]

Previous results

We have previously reported that when the racemic 7-azanorbornenone 4 was passed through a chromatography column (SiO₂, CH₂Cl₂-MeOH), the pyrroline by-product 5 could be isolated in variable amounts depending on the chromatographic conditions [3]. The formation of this pyrroline can be explained through a retro-Dieckman reaction induced by the high ring strain of the unsaturated bicyclic skeleton.

New results and discussions

1. Exploiting the ring strain in 7-azanorbornenes: Synthesis of 2,5-difunctionalized 3-pyrroline scaffolds

The strained bicyclic compounds 4 and 6 can be opened under very mild conditions to give versatile 3-pyrroline scaffolds, such as 7 and 8.

- Synthesis of 2,5-difunctionalized 3-pyrroline scaffolds

2. Functionalization of the bicycle & ring opening: Stereoselective synthesis of functionalized iminosugar scaffolds

The ring strain induced by the double bond is not essential for the ring opening.

- Functionalization of the bicycle & ring opening

References

[1] This name was chosen by analogy with the previously developed “naked” sugar methodology on the azanorbornenes, see: (a) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. Tetrahedron 1999, 55, 13521; (b) Vogel, P. Curr. Org. Chem. 2000, 4, 455.


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Method a:
- NaOMe(cat)/MeOH, r.t., quant.
- (retro-Dieckman reaction)

Method b:
- AcOH(cat)/MeOH, r.t., quant.
- (retro-Dieckman reaction)

- Wittig definition (C=C bond formation)
- Reductive amination (C-N bond formation)
- Reduction / Oxidation...

Pyrrolidine 8 can be obtained in both enantiomerically pure forms using the previously reported resolution of racemic alcohol 6 [3].

Versatile scaffold