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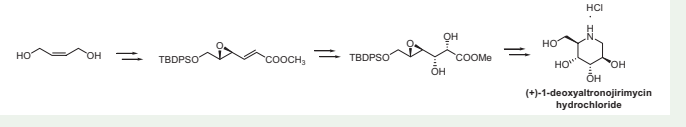
Stereoselective synthesis of (+)-1-deoxyaltronojirimycin

Giuliana Righi[a], Emanuela Mandic'[b‡], Ilaria Tirotta[b], Gaia Clara Mercedes Naponiello[b], Carla Sappino[b], Cristina Marucci[b], Michela Tomei[b] and Paolo Bovicelli[a]

[a]Department of Chemistry, CNR-IBPM, Sapienza University of Rome, Rome, Italy; [b]Department of Chemistry, Sapienza University of Rome, Rome, Italy

ABSTRACT

A stereocontrolled, facile and high-yield approach for producing (+)-*altro*DNJ, has been developed starting from the inexpensive commercial *cis* 2-butene-1,4-diol. Sharpless epoxidation and a subsequent dihydroxylation were used for the introduction of all stereocentres; finally, the ring closure under basic conditions afforded the piperidine heterocycle.



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1. Introduction

Iminosugars, carbohydrate analogues in which the endocyclic oxygen is replaced by a nitrogen atom, are nowadays the most attractive class of sugar mimics because of their high glycosidase and glycosyltransferase inhibitor activity and hence their therapeutic potential in a vast array of diseases, such as diabetes, glycosphingolipid storage disorders and viral infections (e.g. HIV, hepatitis B and C) (Compain & Martin 2007).

Usually the main problem is the lack of selectivity towards the target enzyme, causing several adverse effects. In order to increase the binding affinity to a particular substrate, many studies have been carried out and several different substitution patterns have been designed and tested. The understanding of the complicated metabolism of glycoconjugates is a challenge for modern medicine and will allow to design iminosugars specific for a particular molecular target.

Two different derivatives of 1-deoxynojirimicin are currently in the market: miglitol (Glyset®), a drug for treating type II diabetes mellitus (Fattorusso & Scafati 2008) and miglustat (Zavesca®) used for the treatment of Gaucher desease (Cox et al. 2000) (Figure 1).

CONTACT Giuliana Righi giuliana.righi@cnr.it
‡This author contributed equally to this work.
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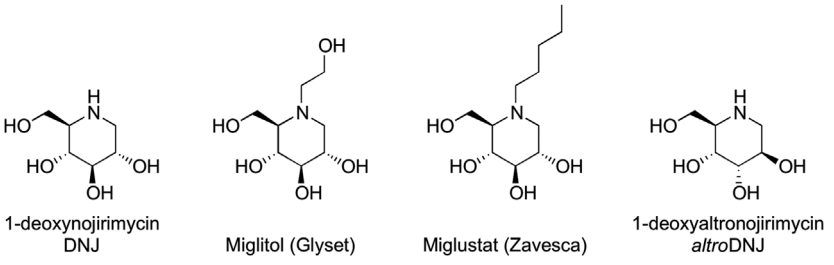


Figure 1. 1-Deoxynojirimycin and several of its derivatives.

Herein we wish to describe a new route to (+)-1-deoxyaltronojirimycin, a nojirimicin analogue having altrose stereochemistry (Figure 1), isolated from *Angylocalyxpynaertii* (Leguminosae) (Asano et al. 2001) and endowed with modest glycosidase inhibition activity (Kato et al. 2005)

2. Results and discussions

Some of the already reported syntheses of deoxynojirimycin and its various isomers (Compain & Martin 2007) employ chiral pool as starting material: carbohydrates as D-glucose derived (Dhavale et al. 2004), amino acids as the Garner aldehyde (Karjalainen & Koskinen 2011; Singh et al. 2014) or pyroglutamic acid (Ikota et al. 1997).

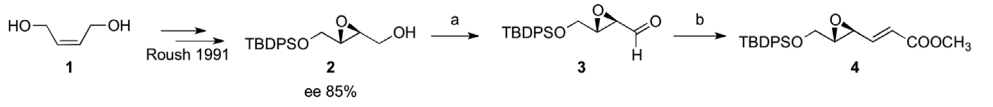
Other approaches are based on total synthesis starting from open chain precursors, achieving the goal through chemoenzymatic methods (van den Nieuwendijk et al. 2012; Soler et al. 2014), or through racemic resolution (Bagal et al. 2010) or asymmetric reaction such as asymmetric dihydroxylation (Somfai et al. 2003) or asymmetric aminohydroxylation (Singh & Han 2003; Chacko & Ramapanicker 2015).

Our approach, based on both our experience on stereo and regiocontrolled opening of oxirane ring (Antonioletti et al. 2000; Righi et al. 2011) and the results we recently obtained on dihydroxylation reaction of optically active *trans* α,β-unsaturated epoxy esters (Righi et al. 2012), starts from a suitable optically active 2,3-epoxy alcohol **2**, easily obtained from the commercially available *cis* 2-butene-1,4-diol (Roush et al. 1991).

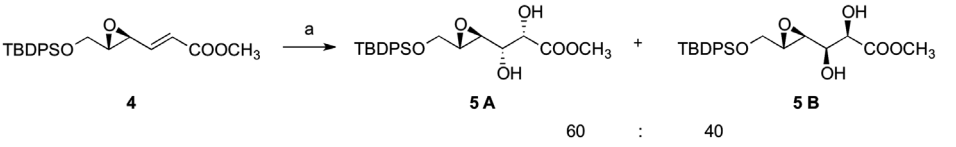
The oxidation to aldehyde of epoxy alcohol **2** followed by a Horner–Emmons reaction afforded the corresponding *trans* α,β-unsaturated epoxy ester **4**, substrate of choice for the dihydroxylation reaction (Scheme 1).

Osmium-catalysed dihydroxylation of **4** provided a diastereomeric mixture (60:40 dr) of chromatographically inseparable epoxy diols **5A** and **5B** in nearly quantitative yield (VanRheenen et al. 1976, Scheme 2). The ratio has been calculated by integration of the signals of the CHOH in α of the ester moiety on the ^{1}H NMR spectra of the crude mixture. The correct stereochemistry was assigned comparing the data of the final iminosugar with those reported in literature (Singh & Han 2003; van den Nieuwendijk et al. 2012).

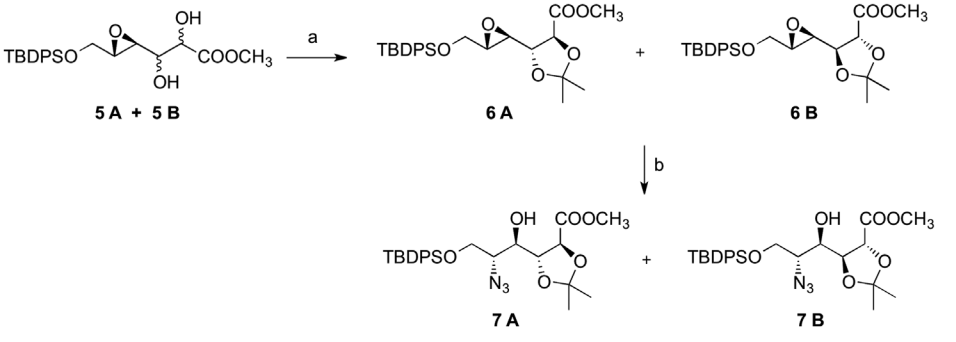
In order to protect the diolic moieties and to achieve a simpler separation, the mixture of **5A** and **5B** was transformed in the corresponding acetonides (Hermitage et al.1998). Unfortunately, also **6A** and **6B** proved to be extremely difficult to separate and consequently the subsequent opening with azide of the epoxide ring was performed on the diastereomeric mixture.



Scheme 1. (a)TEMPO (2,2,6,6-tetramethylpiperidinyloxy), IBDA (iodobenzene I,I-diacetate), CH_2Cl_2, rt, 2 h; (b) LiOH, TMPA (trimethylphosphonoacetate), THF, 70 °C, 77% from **2.**



Scheme 2. (a) OsO_4, NMO(*N*-methylmorpholine-*N*-oxide), acetone/H_2O 8:1, rt, >95% (60:40 dr).



Scheme 3. (a) DMP (2,2-dimethoxypropane), *p*TsOH, acetone, rt; (b) NaN_3, NH_4Cl, MeOH, 70 °C, 58% **7A** + **7B** from **4**, 31% of isolated **7A**).

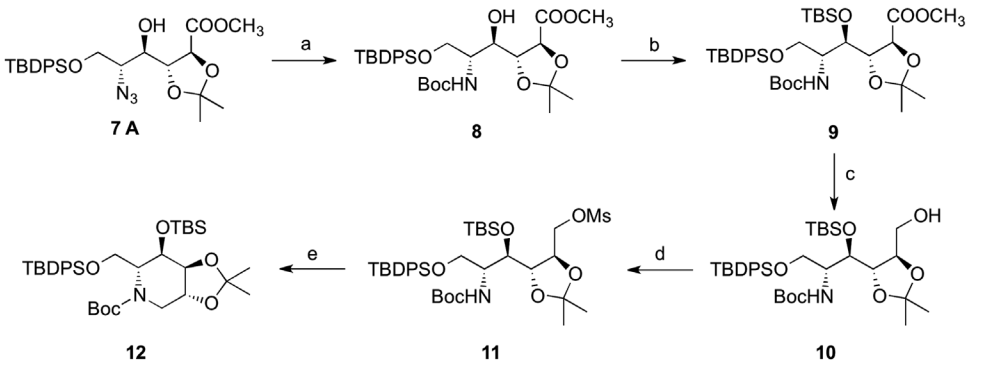
The regioselectivity of the attack is hardly predictable, as the epoxide ring is functionalised with two ether moieties. However, the use of the system NaN_3/NH_4Cl in methanol at 70 °C (Behrens et al. 1985) led exclusively to the attack on C-5 (Scheme 3).

After this reaction, the major diastereomer **7A** was isolated via chromatographic purification, while **7B** was obtained only as mixture with **7A**. Consequently, from this step the synthesis was carried out only from **7A**.

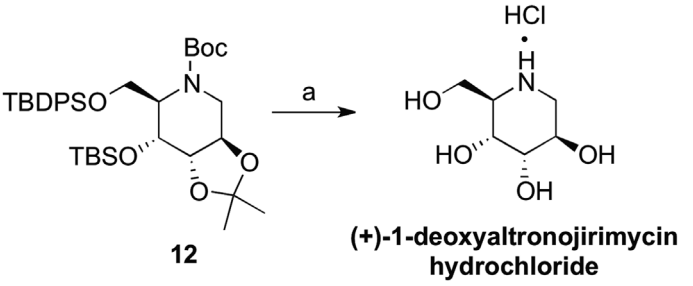
Hydrogenation of azido derivative **7A** in the presence of di*tert*-buthyldicarbonate afforded carbamate **8**. The free alcoholic moiety was then protected as *tert*-buthyldimethylsilyl ether in 80% yield from **7A**, followed by the nearly quantitative reduction of the ester to alcohol **10**.

After mesylation of the just obtained alcoholic function, the ring closure was accomplished with potassium *tert*-butoxide (Wang & Liu 2009), giving the totally protected (+)-1-deoxyaltronojirimicin **12** in good yield (Scheme 4).

Finally, the total deprotection was achieved by treatment with 37% HCl aq. in methanol at 70 °C (Somfai et al. 2003), affording the (+)-1-deoxyaltronojirimicin in nearly quantitative yield (Scheme 5).



Scheme 4. (a) H_2, Pd/C 10%, $(Boc)_2O$, AcOEt, rt, 1 atm; (b) TBDMSOTf (tert-butyldimethylsilyltrifluoromethanesulfonate), 2,6-lutidine, CH_2Cl_2, rt, 80% from **7A**; (c) $NaBH_4$, THF/H_2O 10:1, 0 °C, rt, 94%; (d) MsCl, Et_3N, DMAP, CH_2Cl_2, rt; (e) *t*-BuOK, THF, 0 °C, rt, 62% from **10**.



Scheme 5. (a) 37% HCl aq, MeOH, 70 °C, 92% yield.

3. Conclusions

In summary, through stereocontrolled, facile and high-yield reactions, we have developed a new approach for producing (+)-*altro*DNJ hydrochloride starting from the inexpensive commercial *cis* 2-butene-1,4-diol. Moreover, even if the number of steps is comparable to that of some already reported syntheses, in our sequence only few chromatographic purifications were required, making the route accessible and efficient.

It is noteworthy that, the regio and stereoselective control of the key steps allows achievement of the enantiomer (–)-1-deoxyaltronojirimicin simply using (–)-DET instead of (+)-DET in the Sharpless asymmetric epoxidation, following the same synthetic pathway.

Disclosure statement

No potential conflict of interest was reported by the authors.

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