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Synthesis of 1-deoxy-L-gulonojirimycin and 1-deoxy-L-talonojirimycin

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ABSTRACT

De novo synthesis of noncompetitive glycosidase inhibitors L-gulo-DNJ and L-talo-DNJ has been achieved in 9–10 steps starting from Garner's aldehyde. Key to the success of this procedure was the construction of the 2,3-unsaturated piperidine **14**, which syn dihydroxylation under Kishi's and Donohoe's conditions led to the desired iminosugars.

Iminosugars (sugar analogues having the endocyclic oxygen replaced with nitrogen) undoubtedly represent one of the most attractive classes of carbohydrate mimetics.[1] The great deal of attention developed around iminosugars lies in their powerful inhibitory aptitude towards carbohydrate processing enzymes, that is, glycosidases[2] and glycosyltransferases.[3] As these enzymes are involved in a plethora of key biochemical events, such as digestion, lysosomal catabolism of glycoconjugates and post-translational glycoprotein processing, the significant inhibitory properties of iminosugars, such as deoxynojirimycin (DNJ, **1**, Fig. 1) and its derivatives, make them excellent candidates for medical intervention, ranging from antidiabetics[4] and antivirals[5] to agents devoted to the treatment of genetic disorders.[6] In search for new, more efficient and selective inhibitors, L-iminosugars currently represent a significant breakthrough,[7] especially regarding glycosidase inhibition. Deep interference by L-iminosugars has been found against L-glycosidases[8] (i.e., fucosidases and rhamnosidases), this behaviour being related to their structural similarity with the natural substrates (L-fucose and L-rhamnose) of the corresponding enzymes. Remarkably, activity has also been extended to glycosidases belonging to D-series, often displaying considerably selective as well as potent inhibition.[9] Recent studies into the action mechanism of D-glycosidase inhibition have revealed that some L-iminosugars, especially pyrrolidines, are able to mimic the conformation of natural D-hexose substrates, by virtue of their high structural flexibility.[10] On the other hand, activity of the more rigid L-piperidines has been justified invoking a noncompetitive mode of action.[7,11] Driven by the intriguing therapeutic potential of such molecules, considerable efforts have been devoted to the synthesis of L-DNJ (*ent*-**1**) (Fig. 1) and its congeners.

In spite of the great amount of routes leading to one or some L-piperidines, just a few of them can claim to be applied to the construction of most L-epimers.[12] In this context, in a previous report we had developed a general procedure[13] for the synthesis of 1-deoxy-L-iminopyranoses by a non-carbohydrate-based route; as proof of it, iminosugars belonging to L-*manno*-, L-*altro*- and L-*allo*-configuration (**2**–**4**, Fig. 2) were prepared in high yields and stereoselective fashion. In order to widen this strategy, access to L-guloDNJ (**5**) and L-taloDNJ (**6**) (Fig. 2) has been examined in this Letter.

We began our synthesis with the coupling reaction of enol thioether[14] **7** with the Garner's aldehyde **8** in the presence of BuLi at −78 °C (Scheme 1), to achieve a mixture of diastereomers **9** (*syn*/*anti*, dr = 1:9) in good overall yield (72%). As already noticed,[13] a preference for the *anti*-adduct was found in anhydrous Et_2O, as a consequence of the poorly ionised nature of the organolithium intermediate.[15] On the other hand, no reversal stereoselection was observed in other solvents (such as THF) or after addition of several chelating[16] catalysts [$ZnBr_2$,Ti(O-*i*-Pr)$_4$, Cp_2TiCl_2]. Thus, in

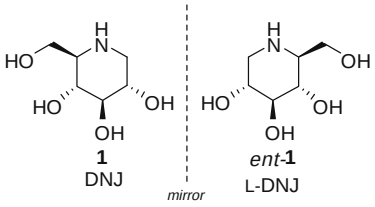

Figure 1. Deoxynojirimycin (**1**) and its enantiomer L-DNJ (**2**).

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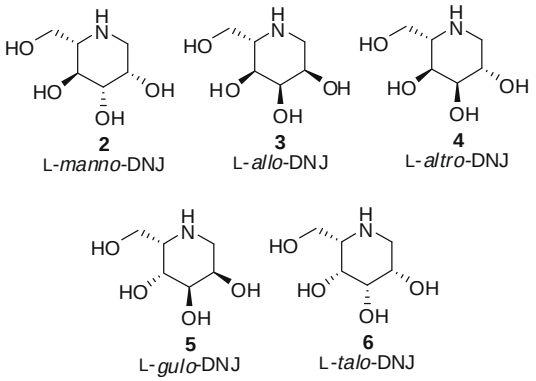
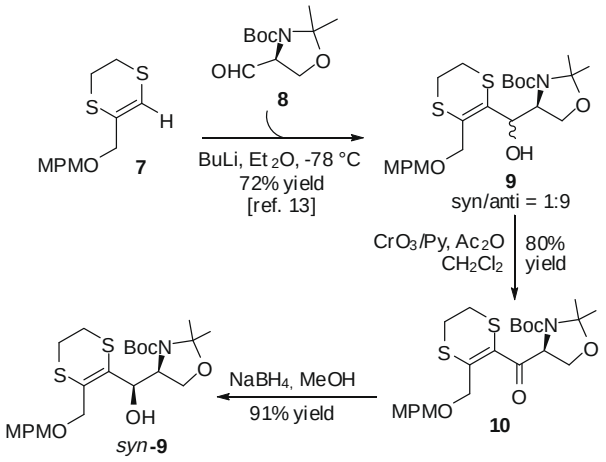


Figure 2. L-Iminosugars.

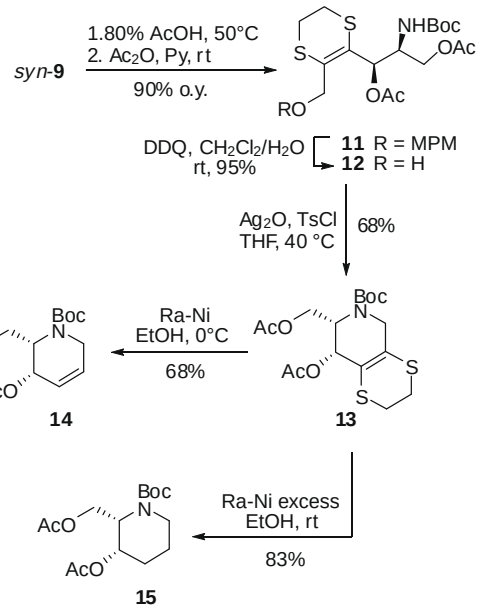
order to selectively obtain the adduct *syn*-**9** (which is the suitable precursor for L-gulo and L-taloDNJ synthesis), an oxidation/reduction procedure[17] was preferred. *sec*-Alcohols **9** were treated with in situ-generated PDC and Ac_2O in CH_2Cl_2 at room temperature, affording ketone **10** (Scheme 1). Then, reduction of **10** with sodium borohydride proceeded with full stereoselectivity, giving alcohol *syn*-**9** as the only diastereomer (73% yield over two steps).

Next, alcohol *syn*-**9** was converted into its diacetate **11** by oxazolidine ring opening (80% aq AcOH) and subsequent acetylation (90% o.y.) (Scheme 2). MPM group removal (DDQ) of **11** furnished the primary alcohol **12** in very good yield (95%). Tosylation of primary hydroxyl group (Ag_2O/TsCl) followed by in situ intramolecular attack on tosylate intermediate[18] by the amino group gave piperidine **13** (68% yield). Finally, removal of dithioethylene bridge of **13** (Raney-Ni) led to olefin **14** (68% yield). As previously reported for similar substrates,[13,19] when the desulfurisation reaction was carried out with a Raney-Ni excess (or for prolonged reaction times), the over-reduction product was obtained in a satisfying 83% yield, affording the 1,2,3-trideoxy iminosugar derivative **15** (Scheme 2).

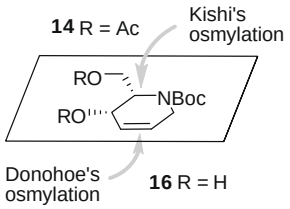
With the key unsaturated piperidine **14** in our hand, access to desired iminosugars was planned by an appropriate choice of the conditions for double-bond *syn* dihydroxylation (Scheme 3). Particularly, osmylation under Kishi's conditions[20] (OsO_4/NMO) (which is driven by steric factors) is expected to occur from the less hindered face of the olefin,[21] leading to the iminosugar with L-*gulo*-configuration. On the other hand, since access to L-taloDNJ is hampered by the difficulty to carry out osmylation from the same side of the allylic acetoxy group, synthesis of the latter was envisaged,



Scheme 1. Synthesis of *sec*-alcohol *syn*-**9**.



Scheme 2. Preparation of unsaturated L-piperidine **14**.

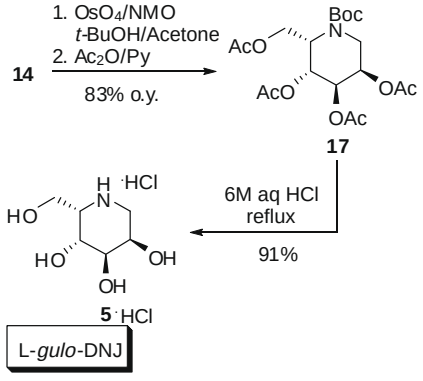


Scheme 3. Prevision of the stereoselective outcome of dihydroxylation reaction under Kishi's or Donohoe's conditions.

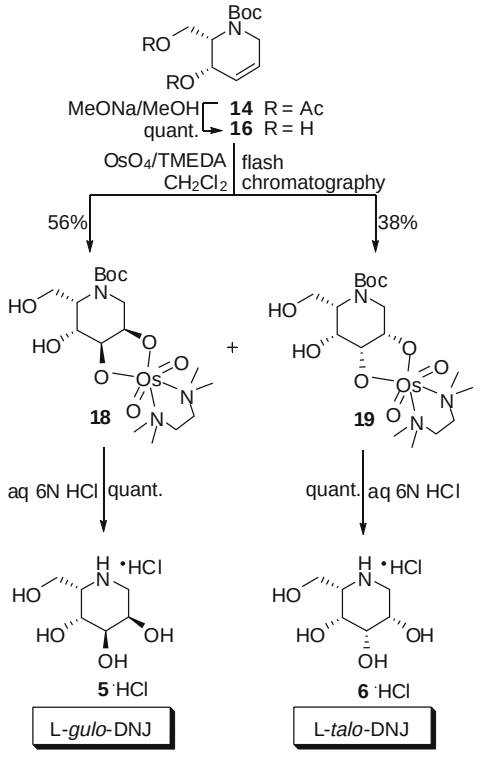
starting from the deprotected allylic alcohol **16**, using the Donohoe's conditions[22] (OsO_4/TMEDA), which usually take place as a consequence of the hydrogen bond formation between the allylic OH group of **16** and the incoming OsO_4 reagent (Scheme 3).

Thus, treatment of the diacetate **14** with OsO_4/NMO in *t*-BuOH/acetone followed by acetylation of the crude residue afforded exclusively the L-guloDNJ derivative **17**. Exposure of **17** to refluxing aq 6 N HCl furnished the pure 1-deoxy-L-gulonojirimycin (**5**)[23] in an excellent 91% yield (Scheme 4).

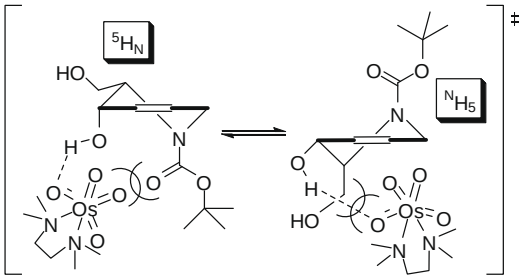
Subsequently, acetyl groups of olefin **14** were removed under common Zemplén conditions, affording diol **16**. The latter was then treated with stoichiometric OsO_4 and TMEDA in CH_2Cl_2 at −78 °C,



Scheme 4. Osmylation of **14** under Kishi's conditions.



Scheme 5. Osmylation of **14** under Donohoe's conditions.



Scheme 6. Proposed $^{N}H_5$ and $^{5}H_N$ conformers for olefin **16**.

affording a mixture of L-gulo- and L-taloDNJ derivatives **18** and **19** (dr = 6:4), which can be separated by flash chromatography ($CHCl_3$/MeOH, 8:2). Hydrolysis of osmate esters **18** and **19** along with removal of *N*-Boc protection using aq 6 N HCl[24] furnished deoxy-L-gulonojirimycin (**5**) and deoxy-L-talonojirimycin (**6**)[25] in a very good 93% overall yield (Scheme 5).

In our opinion, the low level of selectivity observed above could be due to the difficulty in the access of the incoming OsO_4/TMEDA complex to the *syn* face of allylic alcohol **16**. Indeed, even though NMR data suggest that olefin **16** exists as a mixture of conformers (presumably corresponding to $^{N}H_5$ and $^{5}H_N$),[26] it can be conjectured that entry of OsO_4/TMEDA is hampered by the presence of *t*-butoxycarbonyl group in the $^{5}H_N$ conformation, and by the axially oriented *C*-6 methylene group when **16** adopts the $^{N}H_5$ conformation (Scheme 6).

In summary, in this Letter, we have outlined a synthetic path for the preparation of non-naturally occurring L-guloDNJ (**5**) and L-taloDNJ (**6**). Studies aimed to obtain the remaining deoxyiminopyranoses belonging to L-series by *anti*-dihydroxylation reactions of olefins **14** and **16** are ongoing and will be published in due course.

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23. *Data for compound* **5**·*HCl*: $[\alpha]_D$ −2.5 (*c* 0.5 MeOH); ^{1}H NMR (500 MHz, D_2O) δ 3.13 (t, *J* = 12.2 Hz, 1H), 3.31 (dd, *J* = 4.8, 12.2 Hz, 1H), 3.55–3.59 (ddd, *J* = 1.5, 4.4, 9.3 Hz, 1H), 3.82 (dd, *J* = 9.3, 12.2 Hz, 1H), 3.91 (dd, *J* = 4.4, 12.2 Hz, 1H), 4.07 (dd, *J* = 3.0, 4.8 Hz, 1H), 4.16 (dd, *J* = 1.5, 4.8 Hz, 1H), 4.26 (ddd, *J* = 3.0, 4.9, 11.7 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 42.4, 55.5, 59.0, 62.6, 67.2, 68.5. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 43.89; H, 7.87; N, 8.70.
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25. *Data for compound* **6**·*HCl*: $[\alpha]_D$ +22.0 (*c* 0.5 MeOH); ^{1}H NMR (400 MHz, D_2O) δ 3.10 (dd, *J* = 1.6, 13.6 Hz, 1H), 3.24 (dt, *J* = 1.8, 6.7 Hz, 1H), 3.35 (dd, *J* = 2.8, 13.6 Hz, 1H), 3.65–3.74 (m, 3H), 3.99–4.04 (m, 1H), 4.02–4.08 (m, 1H). ^{13}C NMR (100 MHz, D_2O) δ 50.4, 61.1, 62.5, 68.7, 69.2, 69.9. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.45; H, 8.10; N, 8.39.
26. ^{1}H NMR (500 MHz, CD_3OD) δ 1.47 (s, 4.5H), 1.48 (s, 4.5H), 3.47–3.60 (m, 1H), 3.51 (br t, *J* = 10.8 Hz, 1H), 3.81 (br dd, *J* = 11.2, 3.3 Hz, 1H), 4.09–4.12 (m, 0.5H), 4.15–4.18 (m, 0.5H), 4.40 (br s, 1H), 4.54 (br s, 1H), 5.63 (br d, *J* = 10.2 Hz, 1H), 5.64–5.75 (m, 1H).