



# 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.

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Iminosugars (sugar analogues having the endocyclic oxygen replaced with nitrogen) undoubtedly represent one of the most attractive classes of carbohydrate mimetics.<sup>1</sup> The great deal of attention developed around iminosugars lies in their powerful inhibitory aptitude towards carbohydrate processing enzymes, that is, glycosidases<sup>2</sup> and glycosyltransferases.<sup>3</sup> 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<sup>4</sup> and antivirals<sup>5</sup> to agents devoted to the treatment of genetic disorders.<sup>6</sup> In search for new, more efficient and selective inhibitors, L-iminosugars currently represent a significant breakthrough,<sup>7</sup> especially regarding glycosidase inhibition. Deep interference by L-iminosugars has been found against L-glycosidases<sup>8</sup> (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.<sup>9</sup> 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.<sup>10</sup> On the other hand, activity of the more rigid L-piperidines has been justified invoking a noncompetitive mode of action.<sup>7,11</sup> 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.<sup>12</sup> In this context, in a previous report we had developed a general procedure<sup>13</sup> for the synthesis of 1-deoxy-L-iminopyranoses by a non-carbohydrate-based route; as proof of it, iminosugars belonging to L-manno-, L-alto- 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-gulo-DNJ (**5**) and L-talo-DNJ (**6**) (Fig. 2) has been examined in this Letter.

We began our synthesis with the coupling reaction of enol thioether<sup>14</sup> **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,<sup>13</sup> a preference for the *anti*-adduct was found in anhydrous Et<sub>2</sub>O, as a consequence of the poorly ionised nature of the organolithium intermediate.<sup>15</sup> On the other hand, no reversal stereoselection was observed in other solvents (such as THF) or after addition of several chelating<sup>16</sup> catalysts [ZnBr<sub>2</sub>, Ti(O-*i*-Pr)<sub>4</sub>, Cp<sub>2</sub>TiCl<sub>2</sub>]. Thus, in

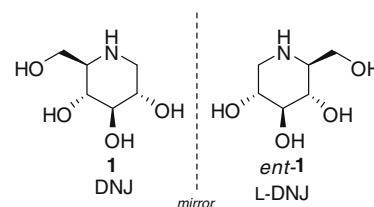


Figure 1. Deoxynojirimycin (**1**) and its enantiomer L-DNJ (**2**).

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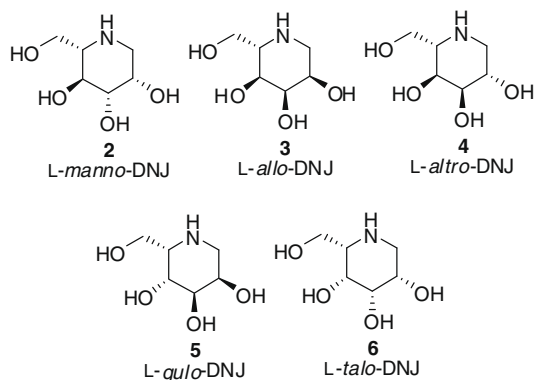
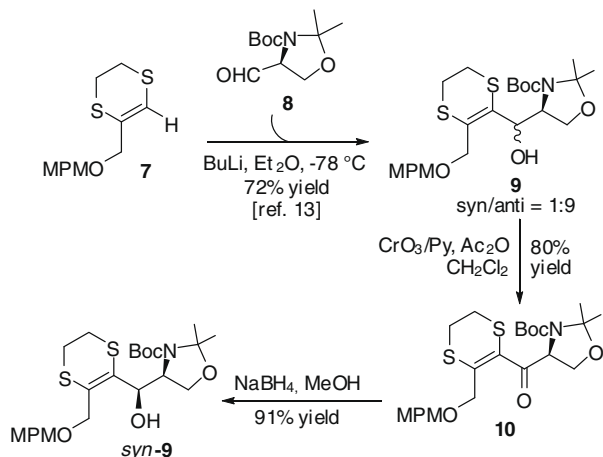
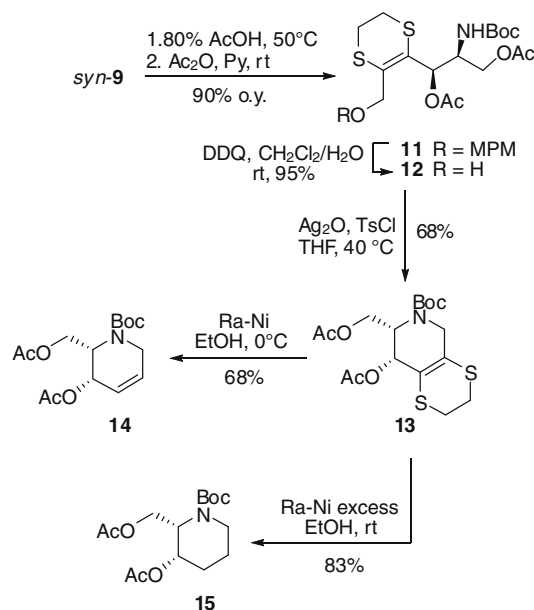
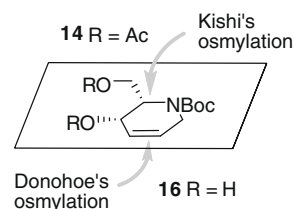


Figure 2. L-Iminosugars.

order to selectively obtain the adduct *syn*-**9** (which is the suitable precursor for L-gulo and L-taloDNJ synthesis), an oxidation/reduction procedure<sup>17</sup> was preferred. *sec*-Alcohols **9** were treated with in situ-generated PDC and Ac<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>O/TsCl) followed by in situ intramolecular attack on tosylate intermediate<sup>18</sup> 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,<sup>13,19</sup> 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<sup>20</sup> (OsO<sub>4</sub>/NMO) (which is driven by steric factors) is expected to occur from the less hindered face of the olefin,<sup>21</sup> 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,

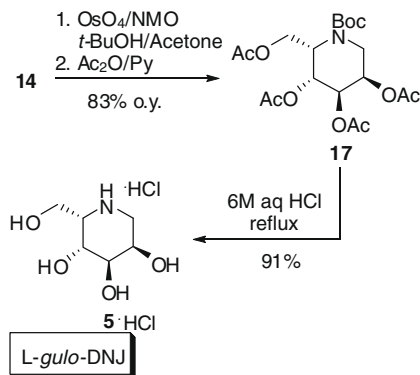
Scheme 1. Synthesis of *sec*-alcohol *syn*-**9**.Scheme 2. Preparation of unsaturated L-piperidine **14**.

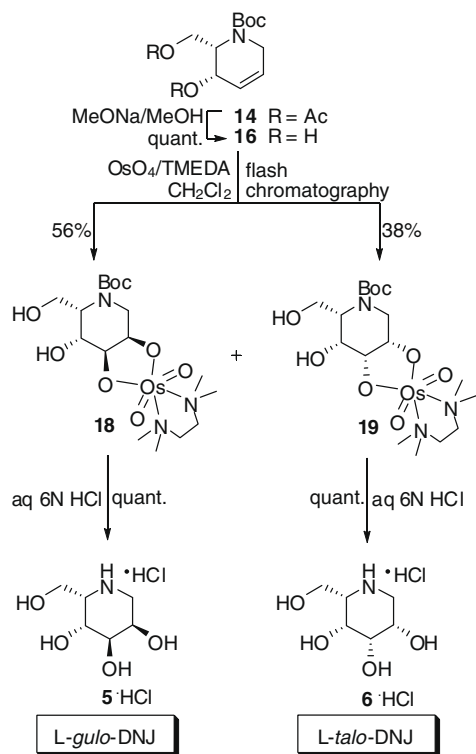
Scheme 3. Prevision of the stereoselective outcome of dihydroxylation reaction under Kishi's or Donohoe's conditions.

starting from the deprotected allylic alcohol **16**, using the Donohoe's conditions<sup>22</sup> (OsO<sub>4</sub>/TMEDA), which usually take place as a consequence of the hydrogen bond formation between the allylic OH group of **16** and the incoming OsO<sub>4</sub> reagent (Scheme 3).

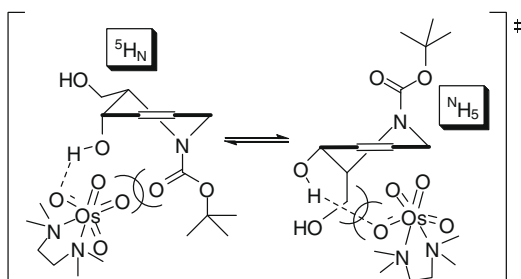
Thus, treatment of the diacetate **14** with OsO<sub>4</sub>/NMO in *t*-BuOH/acetone followed by acetylation of the crude residue afforded exclusively the L-guloDNJ derivative **17**. Exposure of **17** to refluxing aq 6 N HCl furnished the pure 1-deoxy-L-gulonojirimycin (**5**)<sup>23</sup> in an excellent 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<sub>4</sub> and TMEDA in CH<sub>2</sub>Cl<sub>2</sub> at –78 °C,

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



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



Scheme 6. Proposed  $^5\text{H}_5\text{N}$  and  $^5\text{H}_5\text{N}$  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 ( $\text{CHCl}_3/\text{MeOH}$ , 8:2). Hydrolysis of osmate esters **18** and **19** along with removal of *N*-Boc protection using aq 6N HCl<sup>24</sup> furnished deoxy-L-gulonojirimycin (**5**) and deoxy-L-talonojirimycin (**6**)<sup>25</sup> 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  $\text{OsO}_4/\text{TMEDA}$  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  $^5\text{H}_5\text{N}$  and  $^5\text{H}_5\text{N}$ ),<sup>26</sup> it can be con-

cluded that entry of  $\text{OsO}_4/\text{TMEDA}$  is hampered by the presence of *t*-butoxycarbonyl group in the  $^5\text{H}_5\text{N}$  conformation, and by the axially oriented C-6 methylene group when **16** adopts the  $^5\text{H}_5\text{N}$  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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- Data for compound **6**-HCl:  $[\alpha]_D^{25}$  +22.0 (c 0.5 MeOH);  $^1\text{H}$  NMR (400 MHz,  $\text{D}_2\text{O}$ )  $\delta$  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).  $^{13}\text{C}$  NMR (100 MHz,  $\text{D}_2\text{O}$ )  $\delta$  50.4, 61.1, 62.5, 68.7, 69.2, 69.9. Anal. Calcd for  $\text{C}_6\text{H}_{13}\text{NO}_4$ : C, 44.16; H, 8.03; N, 8.58. Found: C, 44.45; H, 8.10; N, 8.39.
- $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  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).