# First Stereocontrolled Reduction of Isoxazoline by Hydrogenolysis: A New Route to Iminosugars via Cyclic Sulfates

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**Abstract:** The synthesis of four new trihydroxylated piperidines, considered as analogues of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ), was achieved using cyclic sulfate substituted isoxazoline derivatives. The key step is the one-pot reduction of an isoxazoline to an amine which undergoes intramolecular attack on the sulfate ester with high stereoselectivity and regioselectivity. The isoxazoline precursors were obtained by the 1,3-dipolar cycloaddition reaction between 2,2-dimethyl-4-vinyl-1,3-dioxolane and 1-benzyloxy-2-nitroethane.

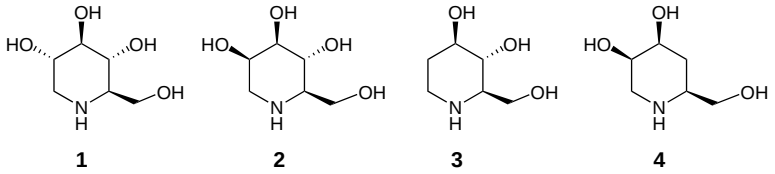
**Key words:** cyclic sulfates, iminosugars, piperidines, cycloadditions, glycosidase inhibitors

Polyhydroxylated piperidines – also known as iminosugars or azasugars - are a class of compounds of great interest, due to their extraordinary biological properties. They are potent inhibitors of glycosidase and glycoprotein-processing enzymes and are widely investigated for their antiviral (anti-HIV), antidiabetic and anticancer activities.[1,2] A large number of naturally occurring iminosugars and their synthetic analogs are known. 1-Deoxynojirimycin (DNJ) **1**, 1-deoxymannojirimycin (DMJ) **2** and fagomine **3** are typical examples (Figure). Their effectiveness has made the development of numerous glycosidase inhibitors a matter of considerable interest to the synthetic chemist.[3,4] Many such compounds have been prepared by cyclization of aminoketoses provided by aldolase catalyzed synthesis,[5,6] or by reductive amination of aldoketoses.[7,8] In other cases, the cyclization of an 2-aminopolyol with a suitable leaving group has led to the desired piperidines.[9]

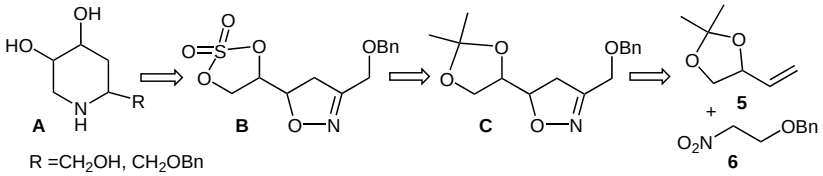
Some trihydroxylated piperidine derivatives have been synthesized and their inhibitory effects have been evaluated.[9–11] For instance, 1,4,5-trideoxy-1,5-imino-D-lyxohexitol **4** was active against α-D-glucosidase, β-D-glucosidase and β-D-galactosidase.[11]

Δ-2-Isoxazolines (**C**, Scheme 1) have proven versatile intermediates and have been fully employed for the synthesis of aminosugars.[12–19] However, very few developments for iminosugar preparation have been described in the literature.[20,21] Δ-2-Isoxazolines are usually obtained by 1,3-dipolar cycloaddition reaction of nitrile oxides (generated in situ from primary nitro derivatives) with alkenes (Scheme 1). We have already described the chemo-enzymatic synthesis of optically pure isoxazolines of type **C** and their conversion into 3-deoxyfructose by controlled reduction and hydrolysis.[22] We thought that these compounds **C** could provide a new route to polyhydroxylated piperidines.

Our retrosynthetic scheme starting from alkene **5** and nitro compound **6** is depicted in Scheme 1. The key step is the




**Figure**




**Scheme 1**

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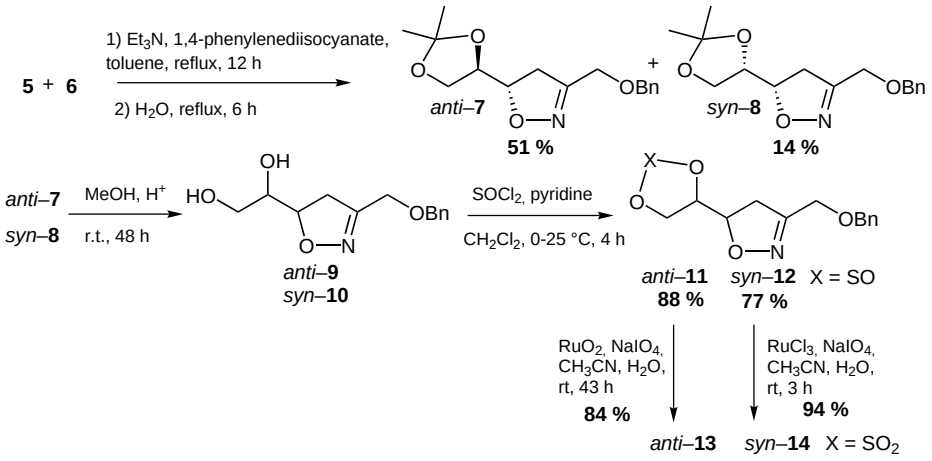
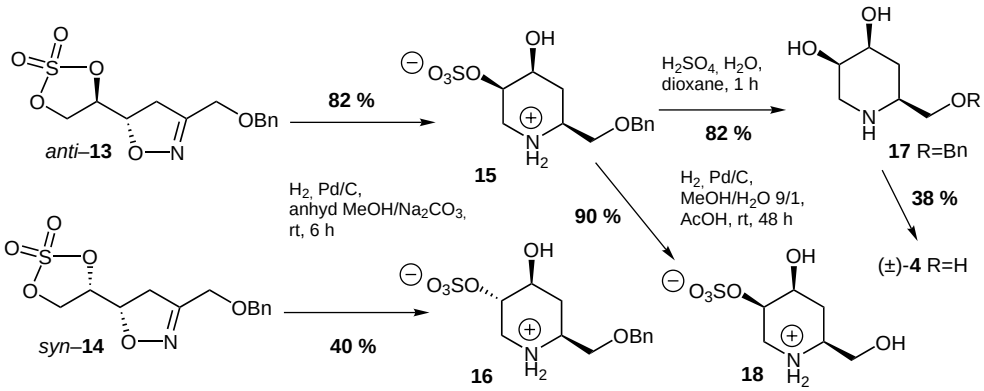
one-pot reduction and cyclization of an isoxazoline cyclic sulfate of type **B** to obtain piperidines **A**.

The first step of our synthesis involved a 1,3-cycloaddition reaction of a nitrile oxide generated in situ from nitro compound **6**[22] with the commercially available alkene **5** (Scheme 2). The improved Mukaiyama procedure[23,24] was applied and afforded isoxazolines *anti*-**7** and *syn*-**8** in 51% and 14% yield, respectively. These diastereomers were easily separated and used separately in the next steps. Complete removal of the ketal groups was achieved in methanol in the presence of Amberlyst® 15 at room temperature, to give the crude diols **9** and **10**. Following a classical procedure,[25] cyclic sulfites **11** and **12** were obtained in 88% and 77% yield, respectively (calculated from **7** and **8**). As usual, cyclic sulfites were mixtures of two isomers (not separated) having different configurations at the sulfur atom.[25] In the next step, the sulfite *syn*-**12** was oxidized into *syn*-**14** in 94% yield with catalytic $RuCl_3$[25] in the presence of $NaIO_4$ in $CH_3CN/H_2O$. However, these conditions were inappropriate in the case of *anti*-**11**, for which partial oxidation of the benzyl group was observed. This side reaction was avoided by replacement of $RuCl_3$ by ruthenium (IV) oxide[26] and sulfate **13** was isolated in 84% yield.

The reduction of the isoxazoline was performed by hydrogenolysis over 10% Pd/C in anhydrous methanol in the presence of sodium carbonate (0.5 equiv for **13** and 1 equiv for **14**) (Scheme 3). Anhydrous conditions were very important to prevent competitive hydrolysis of the imine intermediate into ketone. Furthermore, without sodium carbonate, formation of unidentified by-products was observed. In basic medium, the reduction of the isoxazoline was followed by the opening of cyclic sulfate ring by the intermediate amine and the zwitterionic piperidines **15** and **16** were obtained in 82% and 40% yield, respectively after purification by cation exchange (Dowex® 50WX8, $H^+$ form).[27] In both cases, the reaction was highly stereo- and regioselective and the benzyl group was not cleaved; this latter operation requires acidic conditions (*vide infra*). These piperidines were fully characterized and the relative configurations were established by NMR studies (NOE) and also by comparison with the already described piperidine **4** (*vide infra* (±)-**4**).[11] In the crude reaction product, only one stereomer was detected by NMR spectroscopy and isolated after purification. From the product structures, it was deduced that the hydrogen had been delivered on the side of the isoxazoline cycle, which was hindered by the cyclic sulfate group. Such a diastereoselectivity, as well as the complete regioselectivity for the cyclization, were unexpected. Piperidine **15** can be considered as an analog of 1-deoxymannojirimycin **2** and **16** (configurations described for the first time for a trihydroxypiperidine) as a 1-deoxynojirimycin **1** analog.




**Scheme 2**




**Scheme 3**

The sulfate group of piperidine **15** was removed with concentrated $H_2SO_4$ and water in dioxane[28] (Scheme 3). The piperidine **17** was isolated in 82% yield. The piperidine (±)-**4** was obtained in 38% yield (not optimized) after hydrogenolysis of the benzyl protecting group over Pd/C in the presence of acetic acid.[29] Analytical data were identical to those described for compound **4**.[11] Following the same procedure, the zwitterionic piperidine **18** was isolated in 90% yield. All piperidines were characterized and their analytical data are in agreement with the proposed structures.[30]

In conclusion, we have opened a new route to trihydroxylated piperidines with access to various configurations; four new analogs of natural compounds such as DNJ and DMJ were isolated. Our approach, with a highly stereo- and regioselective key step, offers simple procedures and acceptable chemical yields. As no racemization steps can occur in our methodology, this should lead easily to enantiomerically pure compounds starting from the already described isoxazolines **9** and **10**.[22] Preparation of such compounds and their evaluation as glycosidase inhibitors are under investigation. We plan to extend this methodology to chiral alkenes and other nitro compounds to have access to chiral piperidines and other functionalities (R group shown in structure **A**, Scheme 1).

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(27) **Typical Procedure for Preparation of 15.** A solution of **13** (1.08 g, 3.45 mmol) in anhyd MeOH (50 mL) was stirred under $H_2$ in the presence of 10% Pd/C (500 mg) and anhyd $Na_2CO_3$ (183 mg, 1.73 mmol) for 6 h. The solids were removed by filtration through a membrane filter (0.2 μm) and the filtrate concentrated under vacuum. The residue was neutralized with HCl 1N, then purified over an acidic resin (Dowex 50WX8, 200-400 mesh) using water as eluent. Compound **15** was isolated as a white solid in 82% yield (892 mg).
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(30) All new compounds reported here were racemic and gave satisfactory spectral data ($^1$H and $^{13}$C NMR, IR, mass). Selected spectral data ($^1$H and $^{13}$C), **15**: $^1$H NMR (300 MHz, $D_2O$): δ = 1.78 (ddd, 1 H, *J* = 13 Hz), 1.96 (ddd, 1 H, *J* = 13, 3.5, 3.5 Hz), 3.24 (dd, 1 H, *J* = 14, 1 Hz), 3.52 (m, 1 H), 3.63 (dd, 1 H, *J* = 11, 8 Hz), 3.71 (dd, 1 H, *J* = 11, 8 Hz), 3.81 (dd, 1 H, *J* = 14, 3 Hz), 4.03 (ddd, 1 H, *J* = 13, 3.5, 3.5 Hz), 4.61 (s, 2 H), 4.75 (m, 1 H), 7.43 (m, 5 H). $^{13}$C NMR (100 MHz, $D_2O$): δ = 30.3 ($C_4$), 48.6 ($C_1$), 57.8 ($C_5$), 66.9 ($C_3$), 71.8 ($C_6$ or $C_7$), 75.7 ($C_2$), 75.9 ($C_7$ or $C_6$), 131.3–131.6 ($C_{9\text{-}10\text{-}11}$), 139.8 ($C_8$). **17**: $^1$H NMR (300 MHz, $D_2O$): δ = 1.86 (AB, 1 H, *J* = 13 Hz), 1.91 (AB, 1 H), 3.21 (dd, 1 H, *J* = 14, 1 Hz), 3.46 (dd, 1 H, *J* = 14, 3 Hz), 3.53 (m, 1 H), 3.66 (dd, 1 H, *J* = 11, 8 Hz), 3.75 (dd, 1 H, *J* = 11, 4 Hz), 3.99 (m, 1 H), 4.17 (m, 1 H), 4.65 (s, 2 H), 7.46 (m, 5 H). $^{13}$C NMR (75 MHz, $D_2O$): δ = 29.8 ($C_4$), 50.9 ($C_1$), 57.9 ($C_5$), 67.6 ($C_3$), 69.6 ($C_2$), 72.0 ($C_6$ or $C_7$), 76.0 ($C_6$ or $C_7$), 131.4–131.7 ($C_{9\text{-}10\text{-}11}$), 140.0 ($C_8$). **18**: $^1$H NMR (300 MHz, $D_2O$): δ = 1.80 (ddd, 1 H, *J* = 13 Hz), 2.00 (ddd, 1 H, *J* = 13, 3.5, 3.5 Hz), 3.28 (dd, 1 H, *J* = 14, 1 Hz), 3.42 (dddd, 1 H, *J* = 13, 8, 4, 3.5 Hz), 3.68 (dd, 1 H, *J* = 12.5, 8 Hz), 3.81 (dd, 1 H, *J* = 12.5, 4 Hz), 3.86 (dd, 1 H, *J* = 14, 3 Hz), 4.08 (ddd, 1 H, *J* = 13, 4.5, 3.5 Hz), 4.79 (m, 1 H). $^{13}$C NMR (75 MHz, $D_2O$): δ = 30.1 ($C_4$), 48.5 ($C_1$), 59.7 ($C_5$), 64.0 ($C_6$), 68.5 ($C_3$), 75.6 ($C_2$). **16**: $^1$H NMR (400 MHz, $(CD_3)_2SO$): δ = 1.42 (ddd, 1 H, *J* = 13, 13, 13 Hz), 2.00 (ddd, 1 H, *J* = 13, 4.5, 4.5 Hz), 2.81 (dd, 1 H, *J* = 13, 11 Hz), 3.40 (m, 1 H), 3.50 (m, 1 H), 3.56–3.80 (m, 3 H), 4.12 (m, 1 H), 4.55 (AB, 2 H, *J* = 12 Hz), 7.36 (m, 5 H). $^{13}$C NMR (100 MHz, $D_2O$): δ = 32.2 ($C_4$), 44.7 ($C_1$), 53.7 ($C_5$), 68.1 ($C_3$), 69.6 ($C_6$), 72.6 ($C_7$), 74.4 ($C_2$), 127.9–128.6 ($C_{9\text{-}10\text{-}11}$), 137.9 ($C_8$).