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Synthesis of Azasugars.[1] Part 1[2] Isomerization of Polyhydroxylated Piperidines

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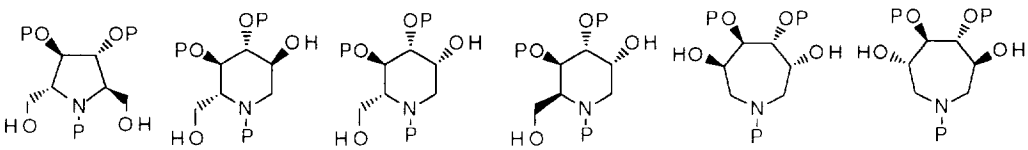
Key words : Azasugar, 1-deoxynojirimycin, 1-deoxymannojirimycin, 2,5-dideoxy-2,5-imino-D-mannitol.

Abstract : *N*-Benzyl-3,4-di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol and L-gulitol undergo easy isomerization, mainly either by ring contraction, or either by SN_2 inversion at C2. This isomerization performed by bis-hydroxyl activation allows to access to 2,5-dideoxy-2,5-imino-L-iditol, 5-epi-DNJ, DMDP, and DMJ.

Polyhydroxylated piperidines and pyrrolidines constitue a major class of glycosidase and glycosyl-transferase inhibitors.[3] Because of the potential chemotherapeutic utility of these azasugars in the treatment of diabets,[4] cancer,[5] and viral infections (especially anti HIV activity),[6] there is continuing interest in the synthesis of 2,5-dideoxy-2,5-imino-D-mannitol **1** (DMDP), 1-deoxynojirimycin **2** (DNJ), 1-deoxymanno-jirimycin **3** (DMJ), and related compounds. We recently reported a straightforward synthesis of DNJ and analogues (**4**, **5** and **6**) from D-mannitol by heterocyclization of enantiomerically pure C_2-symmetric bis-epoxides with benzyl-amine.[7]



DMDP **1** P = H **1a** P = Bn | DNJ **2** P = H **2a** P = Bn | DMJ **3** P = H **3a** P = Bn | **4** P = H **4a** P = Bn | **5** P = H **5a** P = Bn | **6** P = H **6a** P = Bn

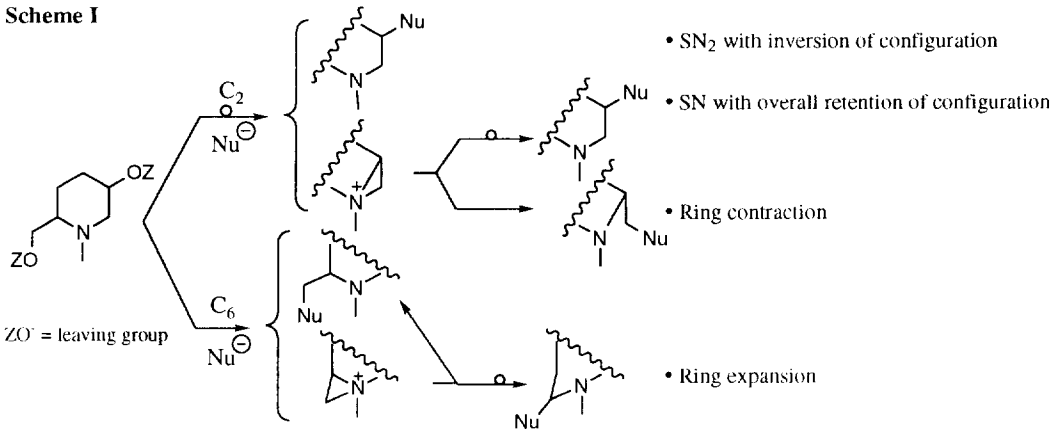
Here, we would like to report our first results concerning the isomerization of the 3,4-di-*O*-protected-polyhydroxypiperidines **2a** and **4a** which can, after bis-hydroxyl activation at C2 and C6, undergo various transformations (Scheme I). Skeletal rearrangement of β-chloro-piperidines or -pyrrolidines, *via* an aziridinium salt, has already been reported,[8] but this method has found little applications in polysubstituted heterocycles, and only few cases have been described in synthesis,[9] and more interestingly in bicyclic alkaloids such as swainsonine or castanospermine.[9c-e]

Hydroxyl groups activation has been performed either by mesylation, or by transformation into an alkoxyphosphonium salt under Mitsunobu conditions.[10]

From the L-*gulo*-piperidine **4a** : The L-*gulo*-piperidine **4a** reacts instantaneously with mesylchloride (2.3 equiv) in triethylamine at 0°C to afford the corresponding 2,6-dimesylate **7** in quantitative yield (Scheme II).[11] Nucleophilic displacement by cesium acetate in dimethylformamide at 40-50°C, followed by methanolysis in

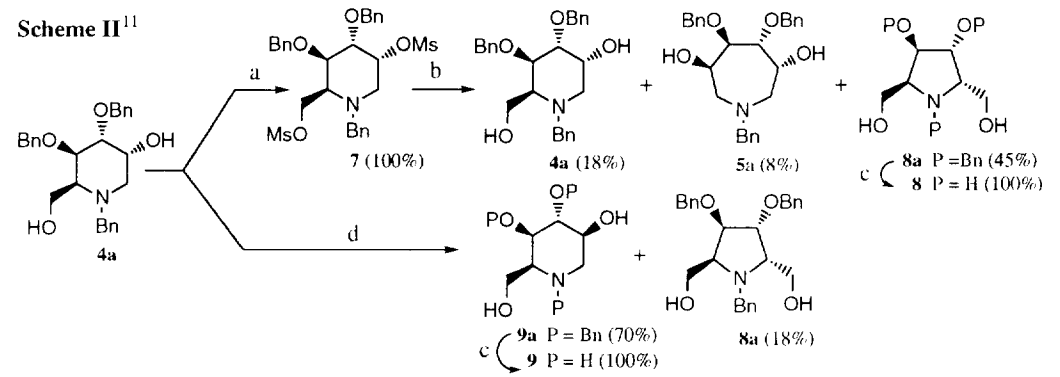
the presence of potassium carbonate gave three compounds which were easily separated by flash chromatography.

Scheme I



The first, isolated in 18% yield, has been identified to the starting L-*gulo*-piperidine **4a**, and the second (8%) to the D-*manno*-azepane **5a**. The third product **8a** (45%), which possesses a C_2 axis of symmetry in ^1H and ^{13}C NMR, has been correlated, after hydrogenolytic removal of both *N,O*-benzyl protecting groups (H_2, Pd black, AcOH) and purification by ion exchange chromatography, to the 2,5-dideoxy-2,5-imino-L-iditol **8**.[12] So, this diastereomer of DMDP, already prepared in our laboratory by another method,[12b] has been obtained in 45% overall yield from **4a** (55% based on recuperation of **4a**).

Scheme II[11]

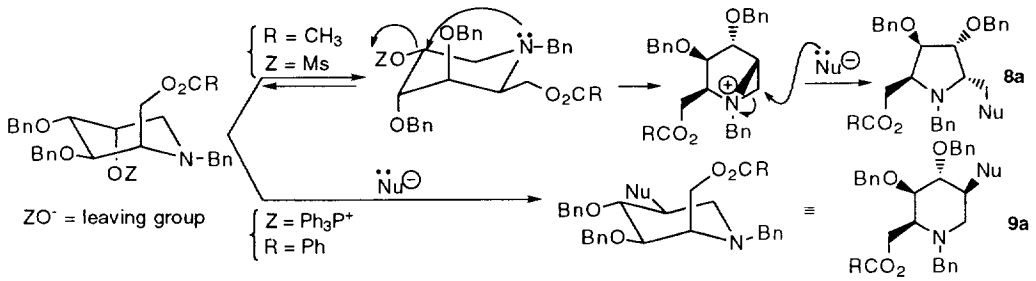


(a) MsCl (2,3 eq), Et_3N, CH_2Cl_2, 0°C, 100%. (b) AcOCs, DMF, 40-50°C then MeOH, K_2CO_3. (c) H_2, Pd black, then DOWEX®(100%). (d) 4 eq [Ph_3P-DEAD-$PhCO_2H$], THF, 0°C, then MeOH, K_2CO_3.

Moreover, treatment of **4a** with 4 equiv of triphenylphosphine-diethylazodicarboxylate-benzoic acid in THF at 0°C gave a mixture of only two products, which after methanolysis and flash chromatography separation, leads to **8a** and **9a** in 18 and 70% yield, respectively. Compound **9a**, for which the piperidinic structure was established by ^1H and ^{13}C NMR analysis, results from a S_N2 reaction at C2. By hydrogenolysis, **9a** was then converted to the new compound **9** (5-epi-DNJ).[13]

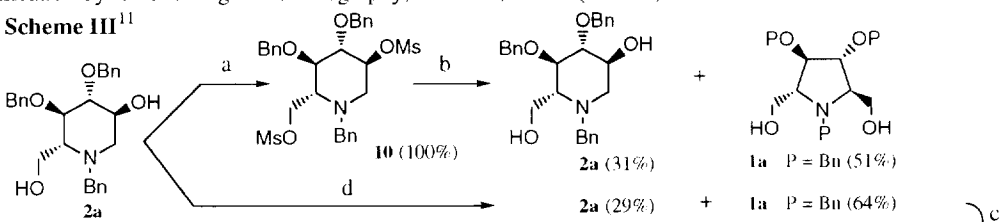
Interestingly, from the L-*gulo*-piperidine **4a**, these two procedures appear to be different and show that the normal S_N2 reaction competes with the aziridinium pathway. With the mesylate, a poorer leaving group than the alkoxyphosphonium, substitution is more difficult and requires more drastic conditions (heating, long

reaction time) which allows the aziridinium formation, followed mainly by ring contraction. In the case of Mitsunobu conditions (fast reaction at 0°C), the intermolecular S_N2 is easier than the intramolecular participation of nitrogen which requires an inversion of the chair conformation :



From the D-*gluco*-piperidine **2a** : Similar reactions were performed (Scheme III)[11] on the D-*gluco*-piperidine **2a** by treatment with mesyl-chloride (100% yield of dimesylate **10**) and then cesium acetate, or under Mitsunobu conditions (4 equiv Ph_3P-DEAD-$PhCO_2H$, THF, 0°C). In all cases, a mixture of two products has been obtained, and its methanolysis (MeOH, K_2CO_3) has furnished, after flash chromatography separation, the starting D-*gluco*-piperidine **2a** (31 and 29% overall yield from **2a**, respectively) and the pyrrolidine **1a** (51 and 64% overall yield from **2a**, respectively). The structure of the latter, which possesses a C_2 symmetry axis in ^1H and ^{13}C NMR, was further confirmed, after hydrogenolysis of both *N*,*O*-benzyl protecting groups and purification by ion exchange chromatography, as above, with **1** (DMDP).[12b, 14]

Scheme III[11]

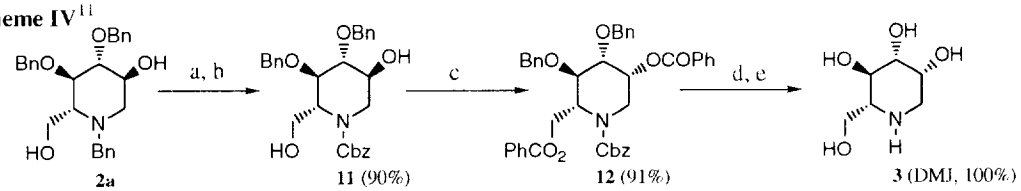


For reaction conditions of a, b, c and d, see scheme II

In this case, these two procedures mainly gave ring contraction to the pyrrolidine, due to an easy neighboring nitrogen participation, since the leaving group is in equatorial position, and subsequent ring opening of the aziridinium at the less substituted side.

In order to avoid the neighboring nitrogen participation, we have converted **2a** into the carbamate **11** (Scheme IV)[11] by selective hydrogenolysis of benzyl-nitrogen bond using Pearlman's catalyst,[15]

Scheme IV[11]



(a) H_2, $Pd(OH)_2$/C 20%, EtOH. (b) BnOCOCl, K_2CO_3, DMF, 0°C. (c) 4eq [PPh_3-DEAD-$PhCO_2H$], THF, 0°C
(d) MeOH, K_2CO_3 *in vacuo*, 40°C (e) H_2, Pd black, AcOH

followed by treatment with benzyl chloroformate (BnOCOCl, K_2CO_3, DMF). The carbamate **11** underwent substitution upon treatment under Misunobu conditions to yield only **12** (91%). To confirm the inversion of

configuration at C2, **12** was fully deprotected by methanolysis (MeOH, K_2CO_3, *in vacuo*, 40°C) and hydrogenolysis. The structure of the resulting compound **3** was further checked up by comparison with DMJ.[16]

In conclusion, the present work outlined a novel isomerization of polyhydroxylated piperidines with the unmasked 2,6-hydroxyl groups. In the case of *gulo*-configuration, substitution at C2 by a S_N2 process is relatively easy to give access to the *ido*-configuration. While in the case of *gluco*-configuration, where all substituants are in equatorial direction, the neighboring nitrogen participation occurs with mainly ring contraction to the *manno*-configuration. So, from two polyhydroxypiperidines, easily prepared from D-mannitol, we have reported the access to 2,5-dideoxy-2,5-imino-L-iditol, 5-epi-DNJ, DMDP, and DMJ in 55, 67, 64, and 82% yield, respectively. Further utilization of this methodology in the synthesis of other azasugars and related systems, as well as relevant biological data of the new compounds with several glycosidases, will be reported in due course.

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