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Facile syntheses of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ)

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Abstract—1-Deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) were synthesized through a concise and practicable pathway. A strategy of using carbohydrate derivatives bearing two leaving groups in the preparation of azasugars by di-N-alkylation of amines was developed. The strategy involved the selective partial protection of dibromo alditols.

Because of their inhibition property toward glycosidase, azasugars have long been suggested as drug candidates to different kinds of carbohydrate-mediated diseases.[1] 1-Deoxynojirimycin (DNJ) **1** and 1-deoxymannojirimycin (DMJ) **2** are among the most important (Fig. 1). Their syntheses are of great importance. Although many elegant synthetic methodologies toward DNJ and DMJ have been developed,[2] only a few of them are industrially practicable. The nitrogen introduction often involved azide substitution. Heavy-metal catalysis was also widely used to install ring systems or hydroxyl groups. Based on the viewpoint to avoid these undesired processes in their syntheses, here we introduce a short and practicable synthetic pathway of DNJ and DMJ from potentially abundant carbohydrate material.

The 2,6-dibromination of sugar lactones has become a very important derivatization of sugar lactones,[3] introducing leaving groups into carbohydrate structures. The reduction of 2,6-dibromoaldonolactones generally gives 2,6-dibromoalditols.[4] Straightforwardly, di-N-alkylation of amines with 2,6-dibromoalditols by displacement of the two bromo groups should afford 2,6-iminoalditols, which are 6-membered ring azasugars. The research of Lundt's group showed that various naked 2,6-dibromoalditols react with ammonia to give 5-membered ring iminoalditiols.[4] Epoxide formation between bromo groups and neighboring –OH groups was found to be important in these reactions. The epoxide appeared to be a better alkylating group than the bromino-alkyl group.

To synthesize 6-membered ring instead of 5-membered ring azasugars, the involvement of protecting groups is inevitable. Our preliminary investigation showed that full protection of hydroxyl groups of dibromo sugars prohibits the epoxide formation between bromo group and neighboring –OH group and greatly decreases the amine N-alkylation reactivity toward bromo leaving groups. We therefore developed a synthetic strategy toward DNJ **1** and DMJ **2** from sugar lactones (Scheme 1) based on the above findings. Selective and partial protection of dibromoalditols could generate good substrates for double N-alkylation of amines. The dibromoalditols, on the other hand, could be readily obtained from sugar lactones. 1,2-Diacetal protecting group [5] was initially chosen to avoid high ring strain of the target intermediate structure by forming a [4,4,0] trans-ring system, which could also facilitate the azasugar ring cyclization.

From commercially available L-*gulono*-1,4-lactone **5**, 2,6-dibromo-2,6-dideoxy-L-iditol **6** was easily prepared by dibromination followed by reduction.[4] When **6** was treated with 2,2,3,3-tetramethoxybutane under catalysis of boron trifluoride etherate ($BF_3{\cdot}OEt_2$), a ~1:1 inseparable mixture of 3,4-*O*- and 4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl) protected dibromo-L-iditol was obtained (Scheme 2). This mixture was treated with

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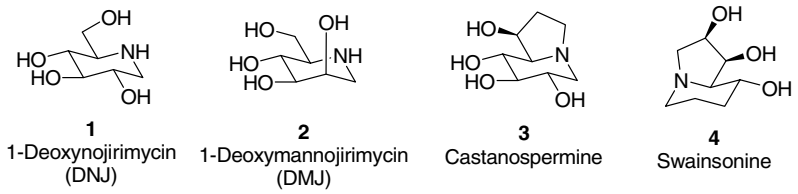
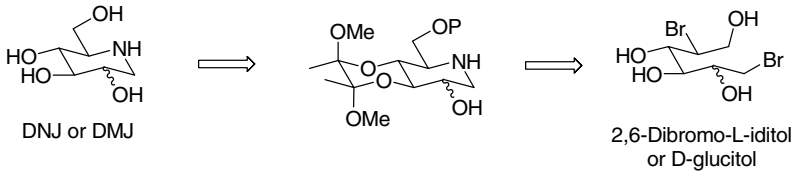
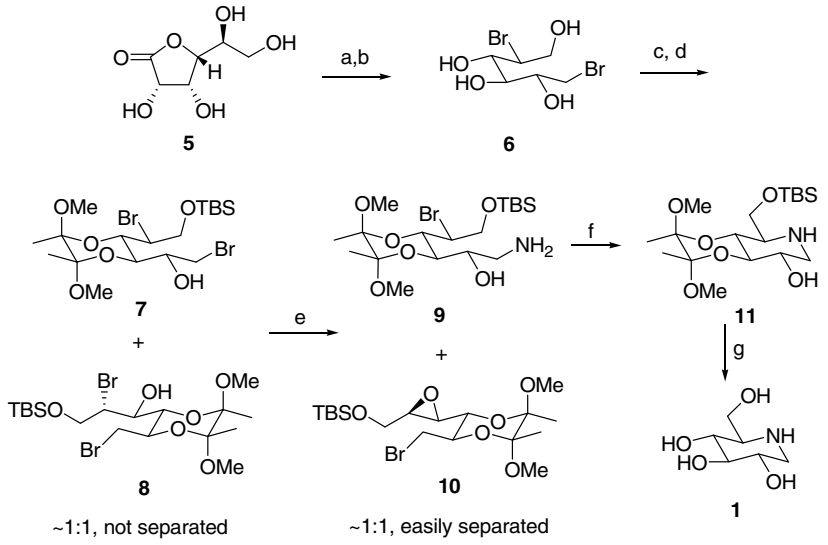


Figure 1. Several important azasugars.



Scheme 1. The retro-synthetic analysis of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ).



Scheme 2. The synthesis of 1-deoxynojirimycin (DNJ). Reagents and conditions: (a) 30% HBr in acetic acid, then MeOH; (b) $NaBH_4$, MeOH then Amberlite 120 H^+ resin; 55% over two steps; (c) 2,2,3,3-tetramethoxybutane, $BF_3{\cdot}OEt_2$, MeOH, rt; (d) TBDMSCl, Py, rt; (e) aqueous NH_3 in MeOH, rt; **9**: 28%; **10**: 26% over three steps; (f) DBU, toluene, reflux, 74%; and (g) 4 N HCl, MeOH, 95%.

t-butyldimethylsilyl chloride (TBDMSCl) to selectively protect the primary hydroxyl groups to give an inseparable mixture of **7** and **8**. After the mixture of **7** and **8** was treated with aqueous ammonia in methanol, two major products, (2′*S*,3′*S*)-6-Amino-2-bromo-1-*O*-*t*-butyldimethylsilyl-2,6-dideoxy-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-iditol **9** and (2′*R*,3′*R*)-2,3-anhydrous-6-bromo-1-*O*-*t*-butyldimethyl-silyl-6-deoxy-4,5-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-gulitol **10**, were easily separated by column chromatography. Under basic conditions, epoxides form from bromo- groups and neighboring free hydroxyl groups. A sterically unhindered epoxide is susceptible to nucleophilic attack by amines to give amino alcohols while a sterically hindered epoxide stays unchanged under mild reaction conditions. When treated with ammonia at room temperature, compound **7** transformed to a 5,6-anhydrosugar, which subsequently reacted with ammonia to yield **9**. In contrast, compound **8** transformed to 2,3-anhydrosugar **10**, which was too hindered for ammonia to attack under these reaction conditions, therefore it stayed untouched. This interesting differentiation greatly facilitated the separation process. Compound **9** was then refluxed with DBU in toluene to furnish 2,6-iminoalditol **11**, which was deprotected by hydrogen chloride in methanol to afford DNJ **1** as its hydrochloride salt.

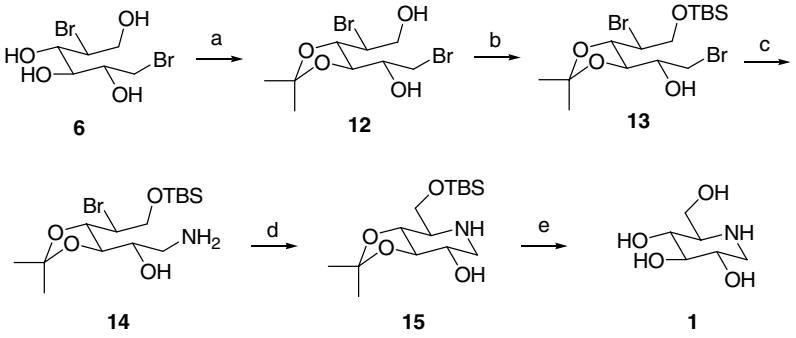
In the above synthesis, the partial protection of dibromo-L-iditol made epoxide formation possible under mild reaction conditions, which facilitated the intermolecular introduction of amine functionality. Subsequent intramolecular N-alkylation cyclized the desired 6-membered azasugar ring. Because both 3,4- and 4,5- positions of **6** have *threo*- configurations, there is no apparent selectivity between 3,4-O-diacetalation and 4,5-O-diacetalation. Fortunately, in the later steps, the inseparable isomers were further transformed and easily separated based on the different reactivity of sterically different epoxides toward nucleophilic attacks. This

process, however, decreased the efficiency of the synthesis. Isopropylidene protecting group, on the other hand, is easier to handle and frequently shows selectivity toward different vicinal –OH's. We therefore modified the synthesis with the isopropylidene protecting group.

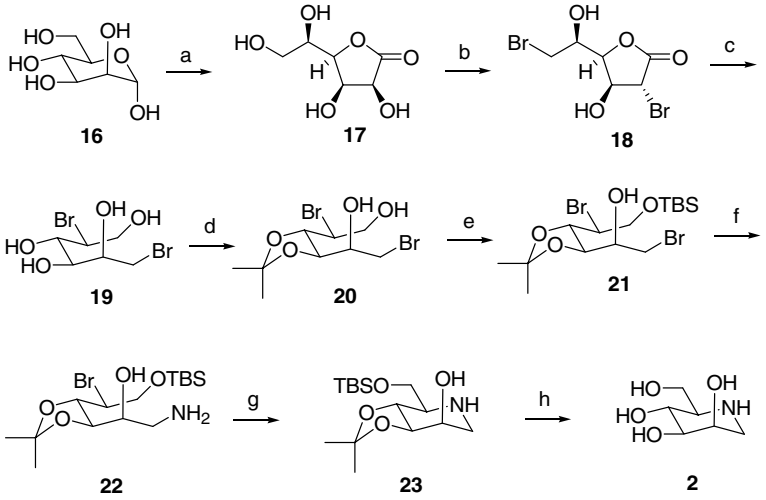
Dibromo-L-iditol **6** was treated with acetone under catalysis of *p*-toluenesulfonic acid (PTSA) for 5 min. Fortunately, the desired isomer 2,6-dibromo-2,6-dideoxy-3,4-*O*-isopropylidene-L-iditol **12** was found out to be the dominant product (Scheme 3). The ratio between **12** and 2,6-dibromo-2,6-dideoxy-4,5-*O*-isopropylidene-L-iditol was 5:1. When the reaction time was extended to 2 h, a ~1:1 ratio of these two major isomers was eventually reached. This is also due to the L-*ido* configuration of **6**. The following steps were similar to those when 1,2-diacetal was used as the protecting group except for the final cyclization step. In this case, when DBU were used as the acid scavenger, elimination reaction dominated. This suggested that the cyclization process was slower when isopropylidene protecting group was used, presumably due to the higher strain of resulted 5,6-*trans* fused ring system **15**. The problem was successfully solved by using a polar aprotic solvent with a weak base such as sodium acetate. The cyclization occurred smoothly to afford compound **15**, which after hydrolysis yielded DNJ **1**.

We then applied this methodology to the synthesis of DMJ **2** (Scheme 4). Bromine oxidation of D-mannose gave D-*manno*-1,4-lactone, which was then treated with hydrogen bromide in acetic acid. The resulted 2,6-dibromo-2,6-dideoxy-D-*glucono*-1,4-lactone was reduced by sodium borohydride to yield 2,6-dibromo-2,6-dideoxy-D-glucitol **19**. Compound **19** was treated with acetone to afford 2,6-dibromo-2,6-dideoxy-3,4-*O*-isopropylidene-D-glucitol **20**. Unlike in the case of DNJ synthesis, extension of reaction time favored the desired product **20** due to the D-*gluco* configuration (3,4-*threo* and 4,5-*erythro*). The following steps were essentially the same as above for the DNJ synthesis with similar yields.

In summary, DNJ was synthesized in five steps from 2,6-dibromo-2,6-dideoxy-L-iditol **2**. Both 1,2-diacetal and isopropylidene were employed as protecting groups. Although 1,2-diacetal protection showed to facilitate transfused ring system formation more, isopropylidene was superior for the actual synthesis. DMJ was also synthesized similarly to demonstrate the methodology



Scheme 3. Synthesis of 1-deoxynojirimycin (DNJ) using isopropylidene as the protecting group. Reagents and conditions: (a) acetone, *p*-TsOH, 72%; (b) TBDMSCl, Py; (c) aqueous NH_3 in MeOH, rt; 81% over two steps; (d) NaOAc, $MeNO_2$, reflux, 68%; and (e) 4 N HCl, MeOH, 96%.



Scheme 4. Synthesis of 1-deoxymannojirimycin (DMJ). Reagents and conditions: (a) Br_2, $NaHCO_3$, water; (b) 30% HBr in acetic acid; (c) $NaBH_4$, H^+ resin, water; (d) acetone; 52% over four steps; (e) TBDMSCl, Py; (f) aqueous NH_3 in MeOH, rt; 80% over two steps; (g) NaOAc, $MeNO_2$, reflux, 74%; and (h) 4 N HCl, MeOH, 95%.

scope. None of the above processes involved any azide or heavy-metal catalysis. Only cheap and easily available reagents were used. All these features made the synthesis not only of academic interest, but also practicable. This methodology could be expanded to the synthesis of other N-alkylated DNJ and DMJ by changing the amine source. Furthermore, intermediates **11**, **15**, and **23** are orthogonally and partially protected. They could be used as versatile building blocks for syntheses of other more complex azasugars such as castanospermine.

Acknowledgements

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Supplementary data

Experimental procedure and data are included. NMR spectra of selected compounds are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.110.

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