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New Access to 1-Deoxynojirimycin Derivatives via Azide−Alkene Cycloaddition

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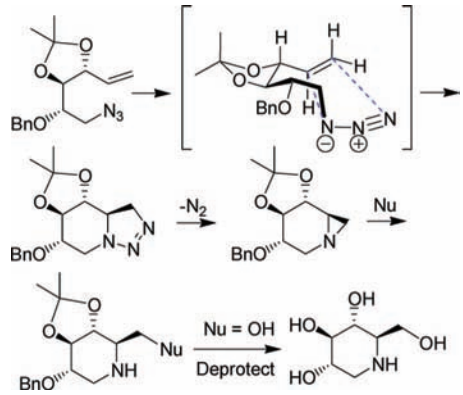
ABSTRACT



The synthesis of 1-deoxynojirimycin (DNJ) derivatives is described from D-glucono-δ-lactone. The DNJ derivatives were obtained via a sequence that included a stereoselective intramolecular Huisgen reaction, decomposition to an aziridine, and its subsequent reaction with a nucleophile. Minimization of allylic strain in the transition state accounts for the stereoselectivity of the cycloaddition reaction.

1-Deoxynojirimycin (DNJ, **1**) is a naturally occurring inhibitor of glucosidases.[1] Its derivatives have found clinical application and have potential in the therapy of HIV and hepatitis C infection.[2] DNJ derivatives also inhibit glucosylceramide,[3] and the glycosidase inhibitor **3** is a bifunctional inhibitor of angiogenesis in vitro.[4] Moreover, DNJ has potential as a scaffold in peptidomimetic research.[5] In this regard, a novel ligand for somatostatin receptors was obtained when Lys and Trp side chains were grafted to DNJ to give **2**.[6] Thus, novel synthetic strategies to DNJ[7] provide access to novel inhibitors of glycoprocessing and peptidomimetics. Herein, we describe a novel approach to DNJ derivatives from D-glucono-δ-lactone.

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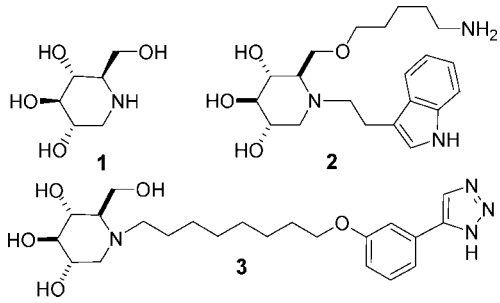
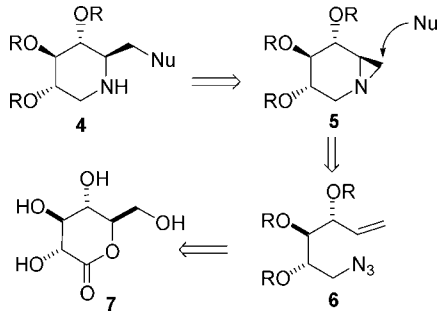


Figure 1. Structures of **1**−**3**.

The retrosynthetic analysis of DNJ derivatives **4** from D-glucono-δ-lactone **7** is shown in Scheme 1. We envisaged

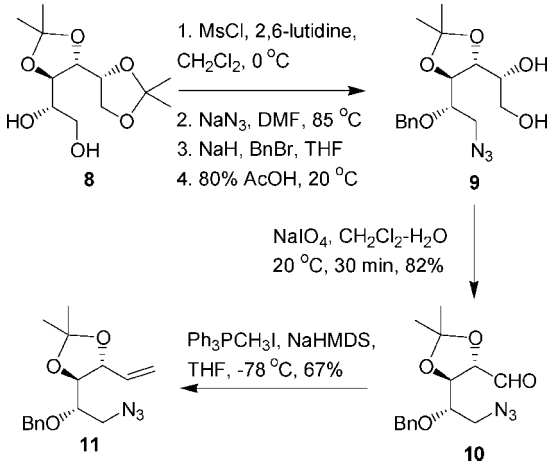
Scheme 1. Retrosynthetic Analysis



that **6** could be prepared from **7** and that intramolecular Huisgen 1,3-dipolar cycloaddition[8] and subsequent loss of nitrogen would provide access to the aziridine **5**. Subsequent reaction of **5** with nucleophiles would provide access to **4**.

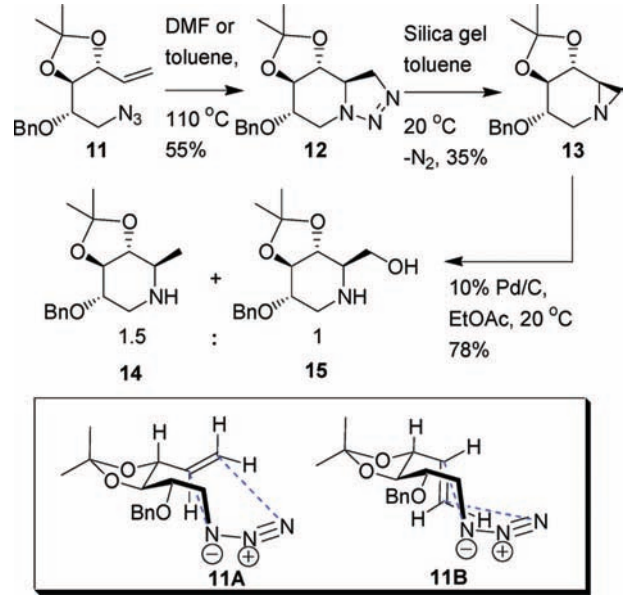
The synthesis (Scheme 2) began from **8**, which was prepared from **7** as described previously by Fleet and co-workers.[9] Regioselective mesylation of the primary hydroxyl group of **8**, followed by exchange of the mesyl group for an azide, benzylation, and the subsequent regioselective acetal cleavage, gave **9**. Oxidative cleavage of **9** using $NaIO_4$ gave aldehyde **10**, which overall was obtained in 49% yield from **7**. The alkene **11** was prepared from aldehyde **10** by a Wittig reaction (67%) using the reagent obtained after treatment of methyl triphenylphosphonium iodide with base.

Scheme 2



The thermally promoted intramolecular cycloaddition[10] of organic azide[11] **11** was investigated next. The heating of **11** at reflux in toluene gave, in a stereoselective manner, the stable 1,2,3-triazoline **12** (Scheme 3). Although the complete

Scheme 3



conversion of **11** was observed by TLC, the isolated yield of **12** was 50−60% from a number of experiments. The stereoselectivity observed in this reaction can be rationalized by comparing the relative energy of two transition states **11A** and **11B** depicted in Scheme 3. Hence, allylic strain destabilizes conformer **11B** compared with **11A** and progression of the reaction through **11A** gives **12** with an identical configuration to DNJ. A fraction containing the aziridine **13** was obtained after treatment of **12** with silica gel, suggesting

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(8) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291.

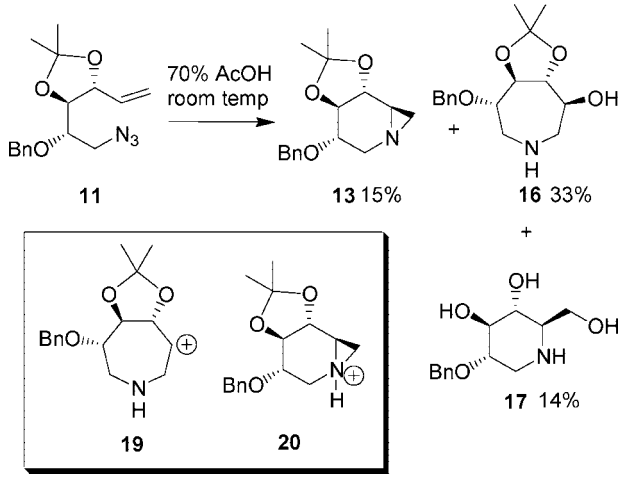
(9) Long, D. D.; Smith, M. D.; Martin, A.; Wheatley, J. R.; Watkin, D. G.; Müller, M.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1982.

(10) For reviews on intramolecular 1,3-dipolar cycloaddition in targeted synthesis, see: (a) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247–75. (b) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed; Wiley-Interscience: New York, 1984; Vol. 2, p 316.

that the acidic nature of the gel promoted loss of nitrogen. The isolation of **13**[12] was supported by mass spectrometry.[13] The fraction containing the aziridine **13** was treated with hydrogen in the presence of 10% Pd−C in ethyl acetate as solvent and this gave an inseparable mixture of DNJ derivatives **14** and **15** (78%). The formation of **14** was expected from this reduction reaction whereas the formation of **15** is explained by hydrolysis of **13** in the presence of adventitious water. These results support the proposal that **13** is formed from **12**.[14]

The possibility to carry out a one-pot conversion of **11** to DNJ derivatives was next investigated.The decomposition of the triazoline **12** and subsequent reactions of the resulting aziridine **13** were expected to be promoted in acidic conditions.The reaction of **11** in aqueous acetic acid overnight at room temperature gave a mixture of **13** (15%), azepane **16** (33%), and DNJ derivative **17** (14%) (Scheme 4). That azepane[15] **16** is obtained as the major product from

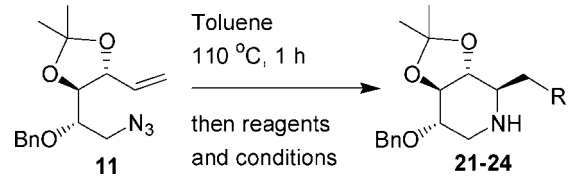
Scheme 4



this reaction where water is the nucleophile suggests that carbocation **19** is generated under these conditions.[16] An alternative explanation is that the reaction is under electronic control and C−N bond breaking in **20** is more complete when the transition state (of its reaction with water) is reached under these conditions, favoring azepane formation. The formation of **17** is explained by the reaction of water at the methylene carbon atom of **20** and acid-catalyzed hydrolysis of the acetal. It would appear that the acetal group is more stable in the azepane **16** when compared with the piperidine **15**. When this reaction was carried out at higher temperature (70 °C) a complex mixture was obtained.

The one-pot conversion of **11** with a variety of nucleophiles was next investigated, and the results are summarized in Table 1.

Table 1. One-Pot Conversion of **11** to DNJ Derivatives



entry	reagents and conditions	product (yield, %)
1	NaN_3 (5.0 equiv), AcOH (1.5 equiv), toluene, 110 °C	**21** (R = N_3, 35%)
2	MeOH, 60 °C, 1 h[a]	**22** (R = OMe, 20%), **13** (31%)
3	AcOH (5.0 equiv), toluene, 110 °C, 1 h	**23** (R = OAc, 45%)
4	PhSH, 15 h[a]	**24** (R = SPh, 57%)

[a] Toluene removed before addition of reagents.

Accordingly, **11** was first heated to reflux in toluene for 1 h, and then reagents (entries 1 and 3) were added and heating continued. Reaction of **11** with sodium azide and acetic acid in toluene by this protocol gave **21** (35%), whereas reaction with acetic acid in toluene gave **23** (45%). Interestingly, only the piperidines, and not azepane products, were isolated under these conditions, contrasting with the behavior shown in Scheme 4. This may be due to the use of the nonpolar solvent which would favor an S_N2 pathway and reaction of the nucleophile at the least hindered carbon, disfavoring the formation of **19**. An alternative explanation is that the reaction is under steric control and that C−N bond breaking in **20** has not occurred to a great extent when the transition state is reached under these conditions, favoring nucleophilic attack at the least hindered carbon of the aziridine **20**.

The second protocol involved the initial formation of the triazoline **12** in toluene, evaporation of the toluene and subsequent addition of the nucleophile. Thus, conversion of **11** to **22** (20%) and **24** (57%) was achieved by this procedure using methanol and thiophenol as nucleophiles, respectively. For the reaction with methanol the aziridine **13** was also isolated (31%).

In summary, the synthesis of a range of novel DNJ derivatives has been achieved from D-glucono-δ-lactone. The sequence has included a Huisgen cycloaddition reaction of alkene and azide in a key step. The resulting triazoline can be promoted to give an aziridine, which can be converted to DNJ derivatives in the presence of nucleophiles and DNJ

(11) For a review on applications of organic azides including alkene−azide cycloadditions, see: Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–240.

(12) Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–91.

(13) We could not obtain satisfactory NMR data as the aziridine **13** decomposed in standard deuterated solvents.

(14) Decomposition of 1,2,3-triazolines to aziridines and imines is known. For a recent example, see: Kim, S.; Lee, Y. M.; Lee, J.; Lee, T.; Fu, Y.; Song, Y.; Cho, J.; Kim, D. *J. Org. Chem.* **2007**, *72*, 4886–91.

(15) Le Merrer, Y.; Poitout, L.; Depezay, J.-C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg, Med. Chem.* **1997**, *5*, 519–33.

(16) For an example of Markovnikov addition of water to an aziridine and proposal of a carbocation intermediate, see: Hanaoka, M.; Kim, S.; Inoue, M.; Nagami, K.; Shimada, Y.; Yasuda, S. *Chem. Pharm. Bull.* **1985**, *33*, 1434–43.

itself can also be obtained by debenzylation of **17**. Although the yields from the one pot reactions are modest, **11** can, after removal of protecting groups, provide entry to a variety of DNJ derivatives for biological evaluation. Also the DNJ derivatives obtained have potential to be further exploited.For instance, "click chemistry"[17] of **21** will be possible, and **24** or a protected derivative could be oxidized to a sulfone and used to generate alkenes by Julia olefination.[18] The approach described herein will lend itself strategies to give novel compounds of interest to medicinal chemists.

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Supporting Information Available: Experimental procedures; ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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