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A Stereoselective Route toward Polyhydroxylated Piperidines. A Total Synthesis of (±)-Deoxymannojirimycin

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Abstract : A chemo- and stereoselective palladium-catalyzed amination of silylated butenediol dicarbonates has allowed for the introduction of a glycine moiety to obtain a desired functionalized epoxysilane. A stereoselective aldolization then delivered the piperidine ring which may be used as a precursor for the synthesis of a variety of polyhydroxylated azasugars. This efficient approach has been illustrated by the synthesis of 1-deoxymannojirimycin including a stereoselective reduction with LAH and a Tamao–Fleming oxidation of a C–SiMe₂Ph bond.

For nearly half a century, glycosidase inhibitors have been the subject of intense interest.¹ Polyhydroxylated derivatives of nitrogen heterocycles are one class of active compounds that can be used as potential drugs to treat diabetes, hepatitis, or various cancers.² At physiological pH, their ammonium salts have been recognized to act as transition-state analogues of the enzymes. Moreover, as has been pointed out by Bols,³ “The best glycosidase inhibitors are compounds that have a nitrogen in place of the exo- or endocyclic oxygen or anomeric carbon...It is more important to mimic the charge development in the transition state than the shape.” Some polyhydroxylated piperidines which have been well studied for their inhibiting properties are 1-deoxymannojirimycin (**1**), 1-deoxynojirimycin (**2**), and fagomine (**3**) (Figure 1).

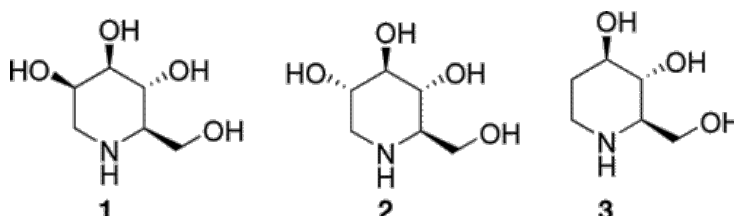
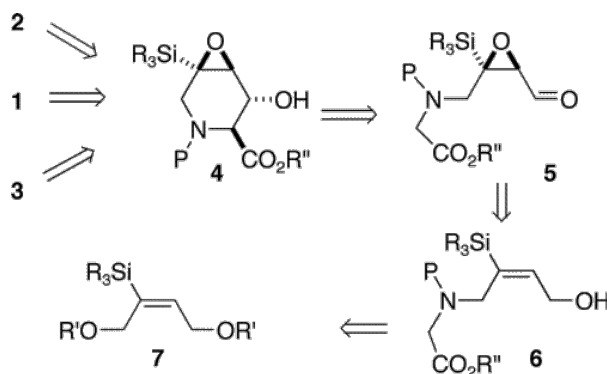


Figure 1. Structure of 1-deoxymannojirimycin (DMJ) (**1**), 1-deoxynojirimycin (DNJ) (**2**), and fagomine (**3**).

Substituted piperidines, in general,⁴ and polyhydroxylated derivatives,⁵ more precisely, have been the targets of a large number of synthetic approaches⁶ due to their potential as therapeutic agents and the need to find efficient access to biologically active analogues. Herein, we propose a general approach for the synthesis of 1-deoxyazasugars as well as some silylated derivatives.⁷

Scheme 1 illustrates our retrosynthetic analysis. Access to the desired polyhydroxylated piperidines could be achieved in a divergent way from the bicyclic system **4**. The nitrogen heterocycle bearing the epoxysilane function was considered to be of great interest, as it could be functionalized following selected reactions such as nucleophilic attacks on the epoxysilane⁸ or Brook-type rearrangements,⁹ with or without migration of the silicon group.¹⁰ For example, from **4**, chemoselective reduction of the ester and epoxysilane functionalities should deliver the silyl analogue of DMJ. Further reaction utilizing a Tamao–Fleming oxidation of the C–Si bond should yield the protected form of **1**.¹¹ On the other hand, direct oxidation of the epoxysilane¹² should give a keto alcohol, which can be stereoselectively reduced to yield DNJ **2**. Our synthetic approach to the piperidine skeleton would be

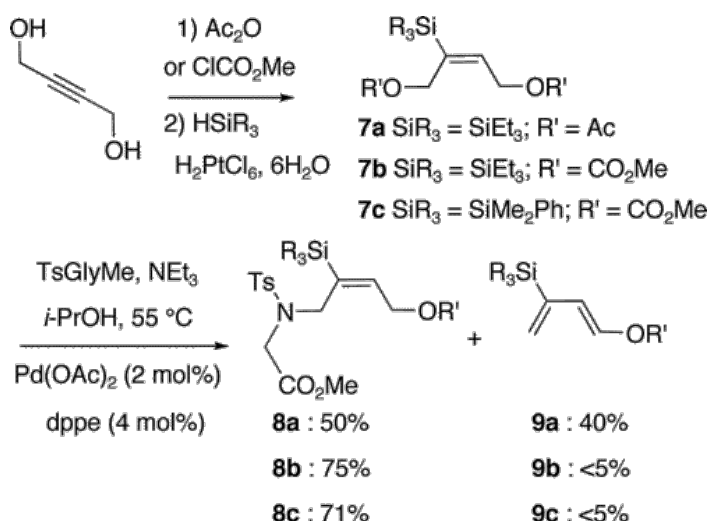
based on an intramolecular aldol condensation of the acyclic precursor **5**.¹³ Previously, we reported a strategy for the enantioselective preparation of silylated epoxy cyclopentanols via a stereoselective aldolization to build the five-membered cycle.¹⁴ We expected the same high level of stereoselectivity in **5** due, in part, to the presence of the three-membered ring.



Scheme 1. Retrosynthetic Analysis of Polyhydroxypiperidines

Finally, the preparation of the desired allylamine **6** from the easily accessible silylated bis-allylic derivatives **7** would nicely illustrate the chemo- and stereoselective silicon directed palladium-catalyzed alkylation we have recently published.¹⁵

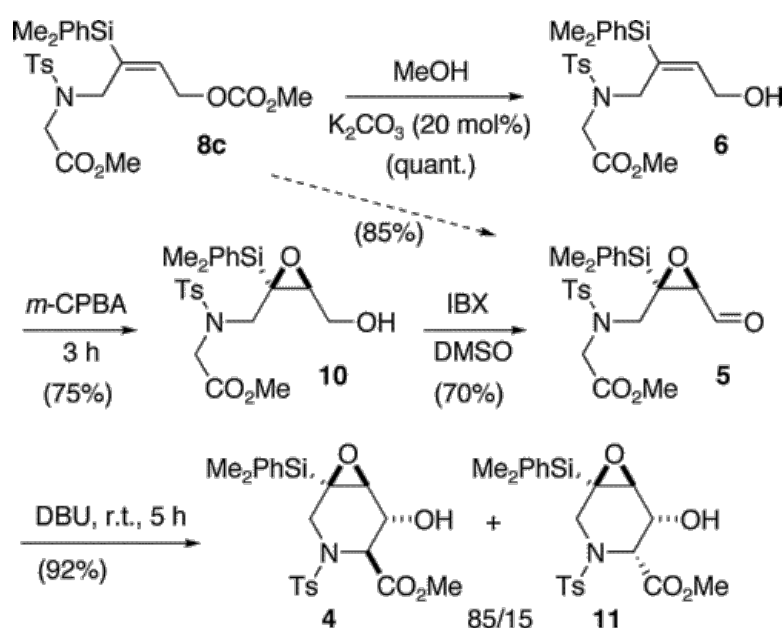
Our synthesis began with the preparation of the model diacetate **7a** bearing the triethylsilyl group. We found it to react with *N*-tosylglycine methyl ester in the presence of palladium catalyst and *i*-PrOH as solvent (Scheme 2).^{16,17} Unfortunately, due to the low reactivity of the intermediate π -allylic palladium complex, a competing β -elimination also occurred to give the corresponding diene **9a** in 40% yield. We therefore prepared a more reactive precursor **7b** having two allylic carbonate functionalities. This turned out to be advantageous, the desired product **8b** being produced in 75% yield with only a trace amount of the diene **9b**. Careful control of the reaction temperature was required for good reproducibility. We noticed similar reactivity with the bis-carbonate **7c**, bearing a functionalizable Me_2PhSi group. In this instance, we were able to isolate the allylic amine **8c** in 71% yield as a 95/5 mixture of two stereoisomers.



Scheme 2. Preparation and Palladium-Catalyzed Amination of Silylated Allylic Derivatives **7**

Treatment of **8c** with a catalytic amount of potassium carbonate in MeOH allowed for a smooth deprotection to provide the corresponding allylic alcohol **6** in excellent yield (Scheme 3). Epoxidation was next performed in a classic manner with 2 equiv of *m*-CPBA. The epoxy alcohol **10**, so obtained

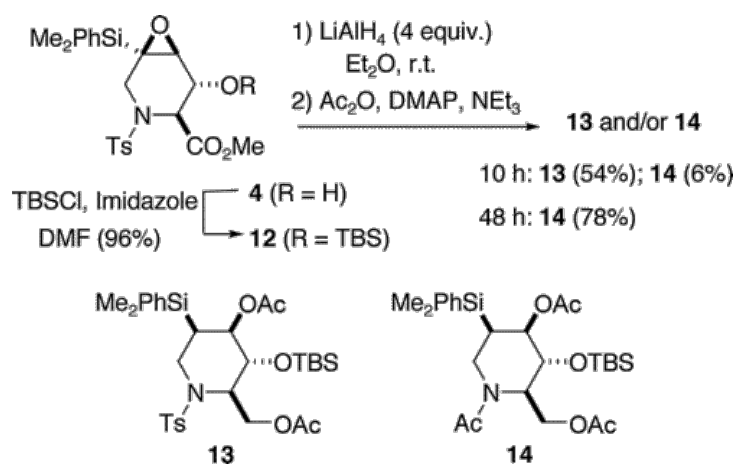
was isolated in 75% yield after purification. However, the crude product was sufficiently pure to be used directly for the next step.



Scheme 3. Preparation of the Piperidine Skeleton

Based on some of our past work, we used the iodoxybenzoic acid (IBX) to oxidize the primary alcohol. We also tested SIBX,¹⁸ a stabilized form of IBX, and obtained the desired aldehyde **5** in a comparable yield of 65%. Significantly, these three consecutive steps could be performed without purification of the intermediates to give **5** from **8c** in 85% yield. The acyclic epoxy aldehyde **5** reacted smoothly in the presence of DBU to give the piperidine ring in 92% yield.¹⁹ This aldolization proved highly stereoselective, giving mainly one of the four possible diastereomers (Scheme 3). As expected, the *trans* relationship between the oxirane and the created hydroxyl was totally controlled.¹⁴ The two diastereomers **4** and **11**, obtained in an 85/15 ratio, corresponded to the two epimers at the C- α of the cyclic amino-ester. In the major product **4**, the ester functionality was *trans* relative to the hydroxyl group. Attempts to improve the diastereoselectivity by lowering the temperature, with or without catalytic Yb(OTf)₃, were unsuccessful. The two diastereomers **4** and **11** could be separated by careful SiO₂ flash chromatography. However, we reasoned that under our basic conditions **11** could give the corresponding dehydroamino ester by dehydration. Indeed, from **5** after a reaction time of 12 h, we obtained an 85/15 mixture of **4** and the expected dehydroamino ester deriving from **11**. This allowed for an easy isolation of pure **4** in 78% yield.

With the piperidine ring system in hand, we attempted reduction of both the ester and the epoxide functionalities. At first, the use of an excess of lithium aluminum hydride reduced both the ester and the epoxide in moderate yield (46%). We reasoned that the free hydroxyl might first be chelating to the reducing agent, thus diminishing the regioselectivity of the reduction of the epoxysilyl function. Thus, we protected the alcohol **4** as its TBDMS ether **12** in 96% yield. To our delight, this protection proved to be beneficial for the reduction. After one night in Et₂O at rt, we observed the clean formation of two compounds. Direct conversion of the crude mixture to the corresponding acetates greatly simplified the purification (Scheme 4).



Scheme 4. Chemoselective Reduction of the Ester and Epoxide and *N*-Tosyl Functions

We isolated the expected diacetate **13** in 54% yield, as well as 6% of the triacetate **14** resulting from the removal of the *N*-tosyl protecting group. The formation of **14** was quite surprising in view of past literature.²⁰ Indeed, the *N*-Ts bond is usually cleaved under more drastic conditions such as DIBAL in refluxing toluene, or by the use of various radical anions, such as sodium naphthalemide. Finally, we took advantage of this result and were able to cleanly convert **12** into the triacetate **14** in 78% yield (Scheme 4).

To explain the clean deprotection of the secondary amine, we propose that the ester of **12** is first reduced into an aluminate, which then assists in the cleavage of the *N*-Ts bond. The resulting aluminato-amino-alcoholate could form a stable 5-membered cycle **A** (Figure 2). This proposition is supported by the fact that we never observed *N*-Ts bond cleavage for **4**. For this compound, the aluminum is complexed by the initially free alcohol early before any reductions and finally gives the stable intermediate **B**.

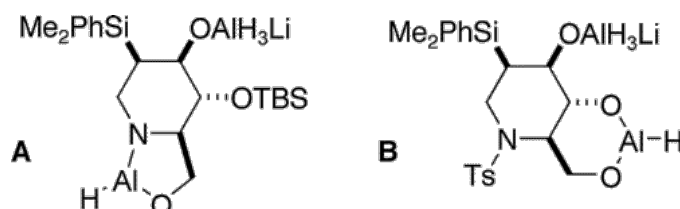
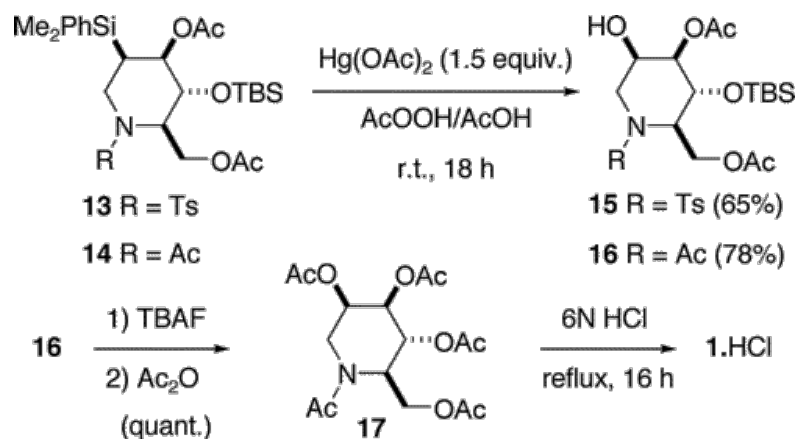


Figure 2. Proposed intermediates during the reduction of **4** and **12**

Final oxidation of the C-Si bond in **13** and **14** was performed according to the Tamao-Fleming procedure^{21,22} (Scheme 5). Initial attempts at oxidation with the KBr/AcOOH mixture in a buffered AcONa/AcOH solution gave the desired secondary alcohols **15** in a moderate conversion of 50% after 15 h. Upon treatment with 1.6 equiv of $\text{Hg}(\text{OAc})_2$ in a AcOOH/AcOH solution, both **13** and **14** were oxidized into **15** and **16** in 65 and 78% yield, respectively.



Scheme 5. Tamao–Fleming Oxidation of the C–Si Bond

Interestingly, these polyhydroxylated piperidines are orthogonally protected, which could be helpful for further modifications. Finally, after selective removal of the TBS protecting group, we acetylated the intermediate diol to isolate in a quantitative yield, the known penta-acetylated form of (\pm)-DMJ **17**. Our ^1H NMR spectrum was not in accordance with the one described by O'Doherty, but quite similar to the description of Hutchinson.²³ We fully deprotected **17** with 6 N HCl aqueous solution and obtained the expected product in a quantitative yield. The ^1H and ^{13}C NMR spectra were in perfect accordance with the descriptions of Han.²⁴ Finally, the stereochemical assignment of the formed compounds have been confirmed by an X-ray structure analysis of **15** (Figure 3).²⁵

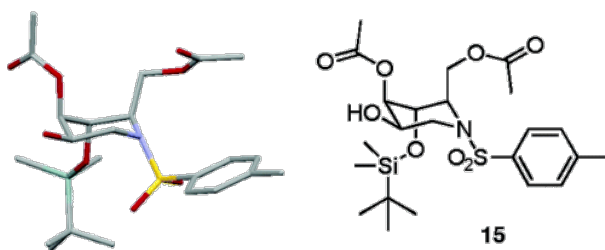


Figure 3. X-ray Analysis of **15**.

In conclusion, we have reported a complementary, highly selective, and efficient synthesis of polyhydroxylated piperidines that rivals previous preparations (36%, 7 steps from the acyclic precursor **8c**). Our approach allows for the differentiation of all the hydroxy groups, which we believe offer a great potential for the elaboration of more complex racemic molecules. A task which is under active investigation in our laboratory, as well as an asymmetric version of this synthetic approach.²⁶

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