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Enantioselective Synthesis of Deoxymannojirimycin Based on Sharpless Asymmetric Epoxidation of a Highly Functionalized Allylic Alcohol

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Keywords: Asymmetric synthesis / Nitrogen heterocycles / Aldol reactions / Epoxidation / Total synthesis

An efficient enantioselective synthesis of deoxymannojirimicin is reported. It is based on the unusual Sharpless asymmetric epoxidation of a silyl-substituted allylic 1,4-amino alcohol coupled with a further highly stereoselective intramolecular aldolization. Both enantiomers of deoxymannojirimicin are available. An orthogonally protected polyhydroxylated piperidine was prepared, which could formally lead to other members of this piperidine family.

Introduction

Since the isolation of deoxynojirimicin in the 1970s, glycosidase inhibitors have become the subject of intense scrutiny. Besides their influences on cell–cell and cell–virus recognition processes, they present marked effects on glycoprotein processing and oligosaccharide metabolism.[1,2] Polyhydroxylated piperidines are one class of nitrogen heterocycles that can be used as potential drugs to treat diabetes, hepatitis, and several type of cancer.[3,4] 1-Deoxymannojirimycin (**1**), 1-deoxynojirimycin (**2**), and fagomine (**3**) (Figure 1) and also their *N*-alkylated derivatives have been well studied for their biological properties.[5] Due to their potential as therapeutic agents and in order to develop biologically active analogues, a large number of synthetic approaches toward piperidines have been developed.[6,7] The growing need of efficient and short access to polyhydroxylated piperidines prompted us to propose a general stereoselective synthesis to this class of molecules.[8]

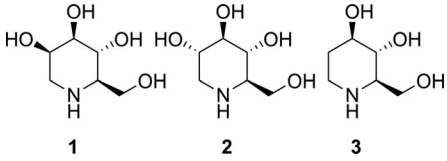
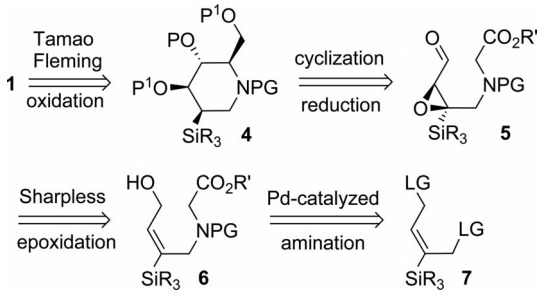


Figure 1. Structure of 1-deoxymannojirimycin (DMJ, **1**), 1-deoxynojirimycin (DNJ, **2**), and fagomine (**3**).

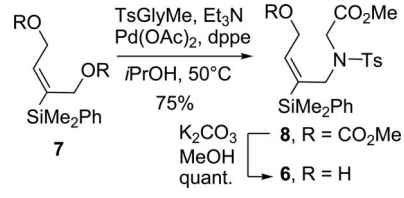
Results and Discussion

This communication deals with the de novo enantioselective synthesis of (–)-deoxymannojirimycin (**1**).[9] Scheme 1 depicts the selected synthetic pathway based on an enantioselective Sharpless asymmetric epoxidation to control the first two stereogenic centers. Polyhydroxylated piperidine **1** could be obtained from previously functionalized silylpiperidine **4**. The piperidine ring is expected to be formed during stereoselective intramolecular aldol condensation of acyclic precursor **5**. The oxirane of **5** would be formed by enantioselective Sharpless epoxidation of silylated allylic alcohol **6**.[10] The introduction of the overall chirality being controlled at that stage of the synthesis. Chemo- and stereoselective palladium-catalyzed amination of bis-allylic derivatives **7** gives target precursor **6** with the required double bond configuration.



Scheme 1. Retrosynthesis towards (–)-deoxymannojirimycin (**1**).

As depicted in Scheme 2, the reaction of bis-allylic dicarbonate **7**[11] with *N*-tosylglycine methyl ester in the presence of palladium(0) results in a highly regio- and stereoselective substitution of only one carbonate. Interestingly, performed



Scheme 2. Preparation of (*E*)-allylic alcohol **6**.

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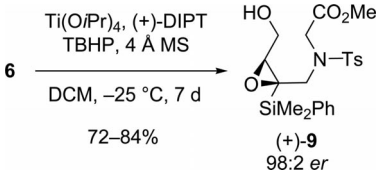
in THF, the reaction does not deliver the expected product, but instead degradation occurred.[12] In *i*PrOH, allylic amine **8** was isolated in 75% yield. Treatment of **8** with a catalytic amount of K_2CO_3 in MeOH gave corresponding allylic alcohol **6** in excellent yield.

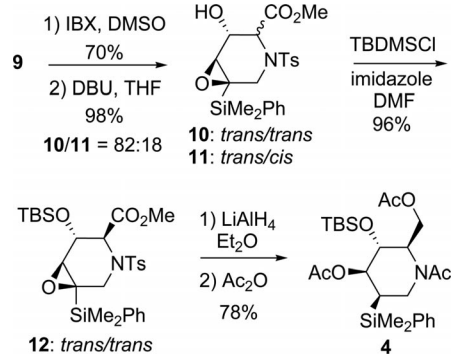
Starting from compounds **6**, a study of the enantioselectivity of the epoxidation step was performed. We first turned our attention toward the Sharpless conditions.[13] Surprisingly, only few examples have been reported concerning the Sharpless asymmetric epoxidation of alkenes bearing both amine and alcohol functions in the allylic positions.[14] These kinds of compounds seem to be challenging substrates, and a stoichiometric amount of Ti(O*i*Pr)$_4$ coupled with long reaction times have been mainly reported.[15] More challenging is the reactivity of precursor **6**, because the double bond bears three substituents and remains relatively hindered (Scheme 3).



Scheme 3. Sharpless enantioselective epoxidation of **6**.

As expected, the reaction takes place with stoichiometric quantities of Ti(O*i*Pr)$_4$ as the metal source, diisopropyltryptamine (DIPT) as the chiral inductor, and *tert*-butyl hydroperoxide (TBHP) as the co-oxidant. We observed total conversion of the starting material after 7 d in DCM at –25 °C. The optimum balance between conversion and enantiomeric excess allowed us to isolate expected epoxide **9** in an average yield of 80% after purification. The reaction was performed on various scales (0.5 to 5 g scale) and even with a large quantity of substrate, no decrease in the conversion or selectivity was observed. Under the best conditions, using (+)-DIPT, an enantiomeric ratio (*er*) of 98:2 was obtained for (+)-**9** (determined by chiral HPLC, Chiracel OD-H column; hexane/*i*PrOH, 0.45:0.05 mL). A dramatic influence of the temperature on the enantioselectivity was observed when the reaction was by performed at –20 °C with (–)-DIPT as the chiral source.[16] Epoxide (–)-**9** was isolated after 5 d in 75% yield and with a 85:15 *er*. We have no explanation for such sensitivity to the temperature. Even if stoichiometric quantities of reagent are required, this reaction using Ti(O*i*Pr)$_4$ and tartrate is not expensive and allowed the preparation of both enantiomers of precursor **6** in high yields and gram quantities.

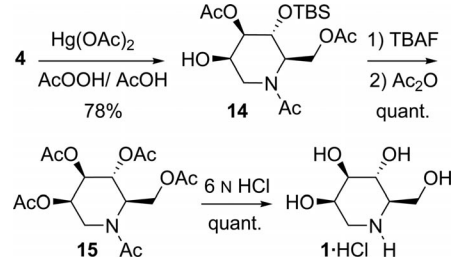
On both enantiomers of **9**, the primary alcohol function was oxidized into an aldehyde group in 70% yield by treatment with iodoxybenzoic acid. Resulting acyclic epoxy aldehyde **5** cyclized smoothly in the presence of DBU to give the desired piperidine ring in 98% yield (Scheme 4). This highly stereoselective intramolecular aldolization gave mainly one out of four possible stereoisomers. Expected *trans*/*trans* diastereomer **10** was the major compound with its *trans*/*cis* diastereomer **11** as a minor product (**10**/**11** = 82:18). In both cases, the relative configuration between the oxiranyl and the hydroxy functions was totally controlled to be *trans*.[17] Attempts to improve the diastereoselectivity by lowering the temperature with or without Lewis acids [Yb(OTf)$_3$, Mg(ClO$_4$)$_2$] were unsuccessful. However, diastereoisomers **10** and **11** could be separated by careful SiO_2 flash chromatography.



Scheme 4. Preparation of piperidine **4**.

At that point of the synthesis, **10** could be converted into the corresponding silylated ether. HPLC analysis confirmed the high enantiomeric purity of piperidines (+)-**12** and (–)-**12**. For that purpose, a racemic mixture of **10** and **11** was also converted into corresponding TBDS ethers **12** and **13** (see Supporting Information). We pursued the synthesis with enantiomer (–)-**12**. Having the correctly functionalized piperidine core in hand, we reduced both the ester and the epoxide functions with $LiAlH_4$. As expected, the opening of the oxiranyl ring is totally chemoselective and proceeds through attack of the hydride onto the carbon bearing the silicon group. The *N*-tosyl protecting group could be removed during the reduction by prolonging the reaction time to 48 h. To facilitate the purification, the acylation of the crude mixture with Ac_2O was carried out to give expected piperidine **4** in 78% yield after chromatography.

The oxidation of the C–Si bond of **4** to a C–O bond with overall retention of configuration could be conducted according to the Tamao–Fleming procedure (Scheme 5).[18,19] Upon treatment with Hg(OAc)$_2$ (1.6 equiv.) in a AcOOH/AcOH solution, **4** was oxidized into **14** in 78% yield. The use of the Fleming's buffered conditions (AcOOH, AcOH, KBr) led to only moderate



Scheme 5. Tamao–Fleming oxidation: preparation of (–)-DMJ (**1**).

conversion and the starting material was recovered in 50% yield after 15 h.

After selective removal of the TBS protecting group of **14**, the intermediate diol was acetylated to isolate pentaacetylated (–)-DMJ **15**. Finally, total deprotection with a 6 N HCl gave expected D-DMJ salt **1**·HCl after simple evaporation of the volatiles. The spectral data of this compound are in total accord with the literature data.[20] This validates our enantioselective approach for the synthesis of both enantiomers of DMJ (**1**).

Conclusions

In conclusion, we reported an alternative enantioselective synthesis of deoxymannojirimycin that rivals previously published preparations. (–)-Deoxymannojirimycin was obtained in seven steps from acyclic precursor **6** (34% yield, >96% *ee*). This approach allows differentiation of all the hydroxy groups, which we believe offers great potential for the elaboration of more complex molecules. This work illustrates that a strategy based on the Sharpless epoxidation of functionalized trisubstituted alkenes is a viable and useful synthetic approach for the enantioselective construction of polyhydroxylated heterocycles.

Experimental Section

Molecular sieves (4 Å, 5.7 g) were heated at 250 °C and dried in vacuo overnight before use. Under an atmosphere of argon, a solution of $Ti(OiPr)_4$ (4.4 mL, 15 mmol, 1.2 equiv.) in CH_2Cl_2 (93 mL) was added to the molecular sieves. The heterogeneous solution was stirred at –23 °C for 15 min. A solution of (+)-DIPT (4.32 g, 14.8 mmol, 1.2 equiv.) in CH_2Cl_2 (93 mL) was added by cannula to the cold mixture under an atmosphere of argon, and the flask was washed with CH_2Cl_2 (27 mL) The resulting mixture was stirred at –23 °C for 25 min. A solution of allylic alcohol **6** (5.5 g, 12 mmol, 1 equiv.) in CH_2Cl_2 (93 mL + 27 mL to rinse) was then added by cannula to the precedent cold mixture, followed by a solution of TBHP (6 M in octane, 6.2 mL, 37 mmol, 3 equiv.). After stirring at –23 °C for 7 d, the mixture was hydrolyzed with a saturated solution of Na_2SO_4 (30 mL) and stirred for 30 min to warm to room temperature. The thick solution was filtered through Celite. The filtrate was dried with $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography (cyclohexane/EtOAc, 7:3 to 5:5), epoxy alcohol **9** (4.1 g, 8.8 mmol, 75%) was obtained as a colorless oil. $[\alpha]_D^{20}$ = +15.9 (*c* = 0.9, $CHCl_3$). HPLC (Chiracel column OD-H, hexane/*i*PrOH = 0.45:0.05, flow rate = 0.5 mL/min, r.t.): t_R = 36.3 min, 96% *ee*. R_f = 0.25 (petroleum ether/EtOAc = 7:3). IR: $\tilde{\nu}$ = 3538, 2953, 1746, 1598, 1428, 1338, 1250, 1213, 1156, 1097, 837, 735, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.48 (s, 3 H $SiMe_3$), 0.54 (s, 3 H, $SiMe_3$), 2.42 (s, 3 H, TsMe), 2.97 (t, *J* = 5.5 Hz, 1 H, 3-H), 3.38 (s, 3 H, CO_2Me), 3.41 (d, *J* = 14 Hz, 1 H, 1-H), 3.66 (d, *J* = 18.5 Hz, 1 H, CO_2Me), 3.71 (d, *J* = 5.5 Hz, 2 H, CH_2OH), 3.92 (d, *J* = 18.5 Hz, 1 H, CH_2CO_2Me), 3.93 (d, *J* = 15 Hz, 1 H, 1-H), 7.26 (d, *J* = 8 Hz, 2 H, H_{ar}), 7.34 to 7.41 (m, 3 H, H_{ar}), 7.54 to 7.62 (m, 4 H, H_{ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.0 (CH_3), –4.9 (CH_3), 21.5 (CH_3), 47.2 (CH_2), 47.6 (CH_2), 51.7 (CH_3), 55.8 (C_q), 58.9 (CH), 60.2 (CH_2), 127.4 (2 CH), 127.9 (2 CH), 129.5 (2 CH), 129.7 (CH), 134.4 (2 CH), 135.1 (C_q), 136.0 (C_q), 143.6 (C_q), 168.9 (C_q) ppm. HRMS: calcd. for $C_{22}H_{29}NO_6SSiNa$ 486.1383; found 486.1373.

Supporting Information (see footnote on the first page of this article): HPLC data and/or optical rotation for compounds **4**, **5**, **9**, **12**, and **1**.

Acknowledgments

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