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Synthesis of L-*altro*-1-Deoxynojirimycin, D-*allo*-1-Deoxynojirimycin, and D-*galacto*-1-Deoxynojirimycin from a Single Chiral Cyanohydrin

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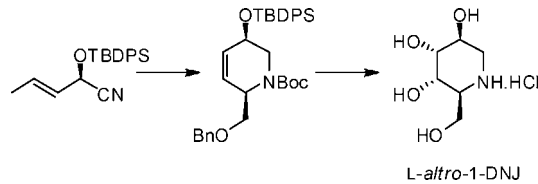
ABSTRACT



The chemoenzymatic synthesis of three 1-deoxynojirimycin-type iminosugars is reported. Key steps in the synthetic scheme include a Dibal reduction−transimination−sodium borohydride reduction cascade of reactions on an enantiomerically pure cyanohydrin, itself prepared employing almond hydroxynitrile lyase (*pa*HNL) as the common precursor. Ensuing ring-closing metathesis and Upjohn dihydroxylation afford the target compounds.

Hydroxynitrile lyases have proven their value over the last 25 years in the enantioselective synthesis of cyanohydrins. The resulting chiral cyanohydrins are valuable and highly versatile starting materials in the stereoselective synthesis of a variety of compounds with important biological or medicinal properties, including natural products.[1] Examples include, among others, α-hydroxy acids,[2] α-hydroxy esters,[3] 1,2-ethanol amines,[2,4] carbohydrates,[5] aziridines,[6] piperidinols,[7] sphingosines,[8] α-hydroxy-β-amino acids,[9] and β-hydroxy-α-amino acids.[10]

Recently we reported[7b] on the almond (*R*)-hydroxynitrile lyase-mediated conversion of *O*-TBDPS-protected cyanohydrin **1**[11] into chiral and functionalized piperidine derivative **3**. The strategy applied involved conversion of cyanohydrin

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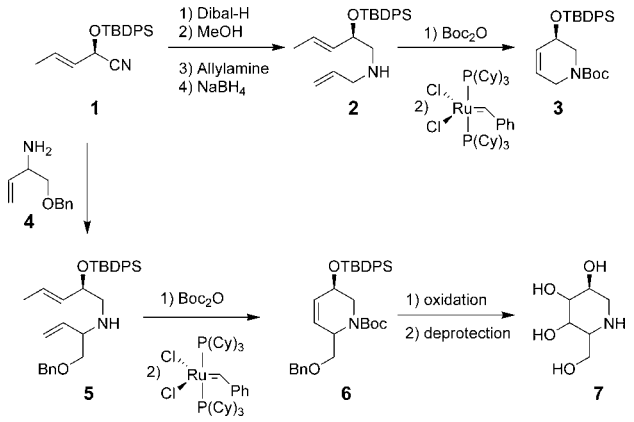
Scheme 1. Synthetic Outline

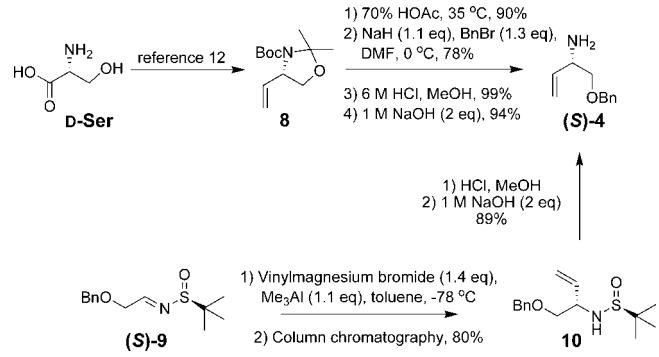


1 into allylamine **2**, followed by N-protection and ring-closing metathesis to afford **3** in high yield (Scheme 1). We anticipated that use of a more functionalized allyl amine, for instance (*S*)-**4** or (*R*)-**4**, could lead to a set of highly functionalized and orthogonally protected cyclic intermediates **6** (Scheme 1) that in turn should be readily transformed into 1-deoxynojirimycin-type iminosugars **7**. In this paper, we report on our results in the stereoselective synthesis of two new cyclic precursors **6** starting from *O*-TBDPS-protected cyanohydrin **1**, and their use in the synthesis of L-*altro*-1-deoxynojirimicin (L-*altro*-1-DNJ), D-*allo*-1-deoxynojirimicin (D-*allo*-1-DNJ), and D-*galacto*-1-deoxynojirimicin (D-*galacto*-1-DNJ).

In the first instance, we investigated the synthesis of amines (*R*)- and (*S*)-**4**. To this end, we adapted a strategy reported by Taylor *et al.*[12] for the synthesis of vinyl glycinol starting from D-serine. Selective removal of the acetonide from oxazolidine **8** with 70% acetic acid gave an intermediate alcohol that was benzylated under standard conditions (Scheme 2). Subsequent acidic removal of the Boc group afforded amine (*S*)-**4**, which was analyzed by chiral HPLC as its *N*-tosyl derivative. These analyses revealed that in multiple separate syntheses the ee's of the amines (*R*)- and (*S*)-**4** varied from 94 to 98%, and we were unable to achieve complete stereochemical control via this route. Arguably, racemization under the basic conditions in the Wittig reaction that converts Garner's aldehyde into oxazolidine **8** is at the basis of the observed loss in ee.

As an alternative, we turned our focus to a methodology for the synthesis of protected 1,2-amino alcohols starting from enantiomerically pure *tert*-butanesulfinyl aldimines (e.g., (*S*)-**9**), as described by Barrow[13] and Ellman.[14,15] Barrow and co-workers reported a diastereomeric ratio of 5.9:1 for the addition of vinylmagnesium bromide to the *O*-TBDMS-protected derivative of imine **9**. Ellman improved the diastereoselectivity of this type of reaction by changing the solvent from DCM to toluene and the addition of $AlMe_3$ as a Lewis acid. This afforded diastereoselectivities up to 97:3.

Scheme 2. Preparation of (*S*)-*O*-Benzylvinylglycinol ((*S*)-**4**)



We applied the Ellman reaction conditions[14] to the addition of vinylmagnesium bromide to imine (*S*)-**9**. The reaction afforded adduct **10** in a diastereomeric ratio of 96:4 as determined by ^{1}H NMR. After silica gel column chromatography, enantiomerically pure **10** was obtained in 80% yield. Removal of the chiral auxiliary under acidic conditions gave (*S*)-**4** in high yield and >99% ee as established by chiral HPLC on the N-tosylated derivative of (*S*)-**4**. Amine (*R*)-**4** was obtained in similar yields and >99% ee from (*R*)-**9** (Scheme 2).

With both (*S*)-**4** and (*R*)-**4** in hand, we proceeded with the conversion of **1** into secondary amine **11** via the *Dibal reduction−transimination−$NaBH_4$ reduction* sequence of reactions.[4b,7b] Initial experiments afforded amine **11** in 60−65% yields. These results correlate well with a recent report[16] in which the same sequence of events is featured as the key step en route to functionalized morpholines. With the exception of the amounts of Dibal-H applied (we apply 1.5 equiv of Dibal-H as opposed to 5 equiv applied by Rutjes and co-workers), parameters such as reaction time and concentrations were comparable. We anticipated that yields could be improved by increasing the concentration of the reaction partners of the transimination process (see Supporting Information for experimental details). Indeed, in this fashion, we were able to improve the yields to 78−80% (Scheme 3). In addition, the excess of amine (*S*)-**4** could be readily recovered by silica gel column chromatography.

With amine **11** in hand, we set out to synthesize key intermediates **12** and **14**. Boc-protection of **11**, which had to

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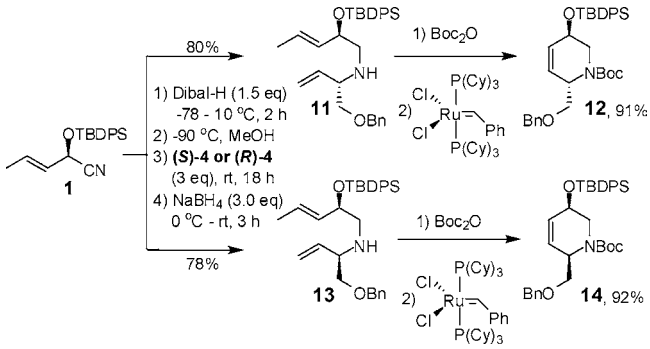
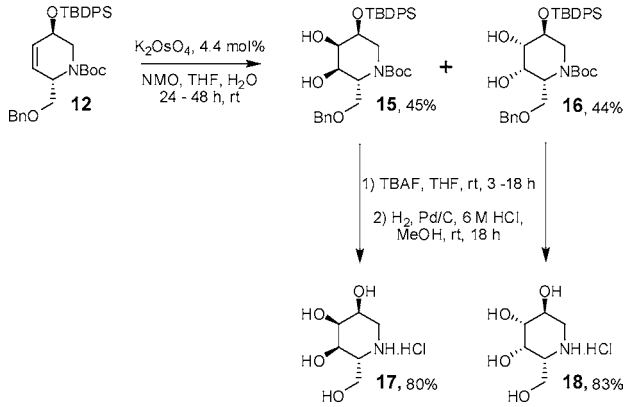
Scheme 3. Conversion of **1** into Key Intermediates **12** and **14**



be executed in THF at 50 °C in the presence of 2 equiv of triethylamine, followed by RCM with first-generation Grubbs catalyst afforded the cyclic iminosugar precursor **12** in 91% yield over two steps. In the same fashion, via amine **13**, precursor **14** was obtained in comparable yields (Scheme 3).

Next, we turned our efforts to the conversion of **12** and **14** into the target 1-deoxynojirimycin-type hydroxylated piperidines. Application of the Upjohn dihydroxylation procedure to alkene **12** gave a 1:1 mixture of compounds **15** and **16**. The diastereomeric mixture could be readily separated by column chromatography affording enantiomerically pure **15** and **16** in 45% and 44% yield, respectively. A two-step deprotection sequence comprising desilylation using TBAF followed by catalytic hydrogenation under acidic conditions to remove the Boc and benzyl protective groups afforded D-*allo*-1-DNJ (**17**) and D-*galacto*-1-DNJ (**18**) in good yields (Scheme 4).

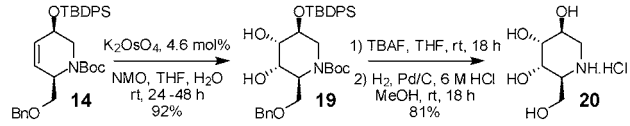
Scheme 4. Synthesis of D-*allo*-1-DNJ (**17**) and D-*galacto*-1-DNJ (**18**)



Application of the Upjohn dihydroxylation to compound **14** afforded diol **19** as the single enantiomer in 92% yield. Deprotection via the protocol described above gave L-*altro*-1-DNJ (**20**) in a good 75% overall yield from **14** (Scheme 5). The spectral and analytical data of the compounds **17**, **18**, and **20** were in complete agreement with literature data.[17]

In conclusion, we have described the syntheses of three out of sixteen possible 1-deoxynojirimicin isomers from

Scheme 5. Synthesis of L-*altro*-1-DNJ (**20**)



cyanohydrin **1**. As there are also (*S*)-hydroxynitrile lyases available (for instance *Hb*HNL from *Hevea Brasiliensis*),[1] enantiomeric **17**, **18**, and **20** should be accessible with equal ease. Alternatively, desilylation of **12** and **14**, followed by a Mitsunobu reaction should, formally, lead to the enantiomers of both **12** and **14**. The chemistry described above makes compounds **12** and **14** valuable extensions to the already known synthetic strategies toward 1-deoxynojirimycin derivatives and analogues from chiral pool carbohydrates[18] and *de novo* synthetic strategies,[19] often from chiral building blocks.[19b−e] We are currently investigating the application of orthogonally protected iminosugars **15**, **16**, and **19** in the synthesis of potential inhibitors of enzymes involved in the glucosylceramide metabolism.[20]

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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