Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 5, pp. 1077-1080, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00129-8

Stereocontrolled Synthesis of 1,5-Dideoxy-1,5-imino-allitol (1-Deoxy-allonojirimycin) from Serine

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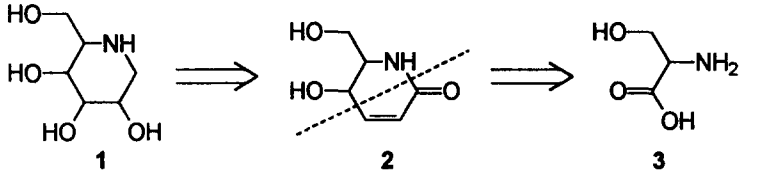
Abstract: 1-Deoxy-L-allonojirimycin was prepared from a protected L-serine aldehyde via a 5,6-dihydro-2-pyridone as a key intermediate.

Polyhydroxylated piperidine systems such as 1-deoxynojirimycin and related compounds of the general type **1** which can be regarded as 1-deoxy-azasugars have received considerable interest in recent years due to their biological activity, especially with respect to their potential application in cancer and AIDS therapy[1,2,3]. The rationale behind this hope is the fact that these sugar analogues are very often specific and potent inhibitors of glycosidases[4,5] and such inhibition has significance to both viral expression and tumor growth[6,7].

A number of synthetic routes have been developed to various azasugars in their optically active form. Besides the "chiral-pool"-approach starting particularly from sugars[8-15] or tartaric acid[16], chemoenzymatic[2,17] and asymmetric[18,19] synthetic strategies have been used as efficient entries to different systems. Looking for a generally applicable and flexible methodology for the preparation of azasugars of various configurations and substitution patterns, we found that a dihydro-pyridone system **2**[20] might be a valuable key intermediate since stereoselective hydroxylation of the double bond should lead to the desired target molecules. Intermediate **2** could be derived from serine **3** by the introduction of an appropriate C_3-building block, for which we envisioned the propiolic ester anion.



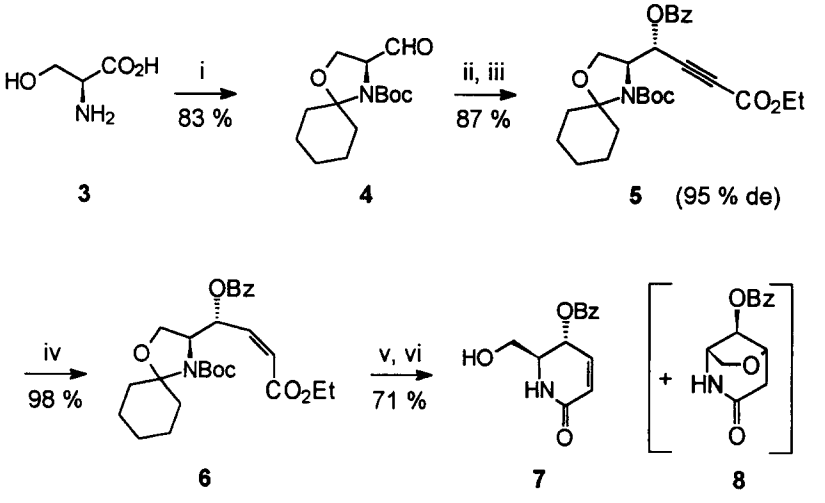
1 **2** **3**

Scheme 1

Surprisingly until now there is only one approach which relies on serine as a starting material for the synthesis of nojirimycin derivatives. Dondoni and his group applied an elegant chain extension strategy with

thiazol derivatives as homologating reagents[21]. In contrast to the present report the hydroxyl groups were introduced by acyclic stereocontrol.

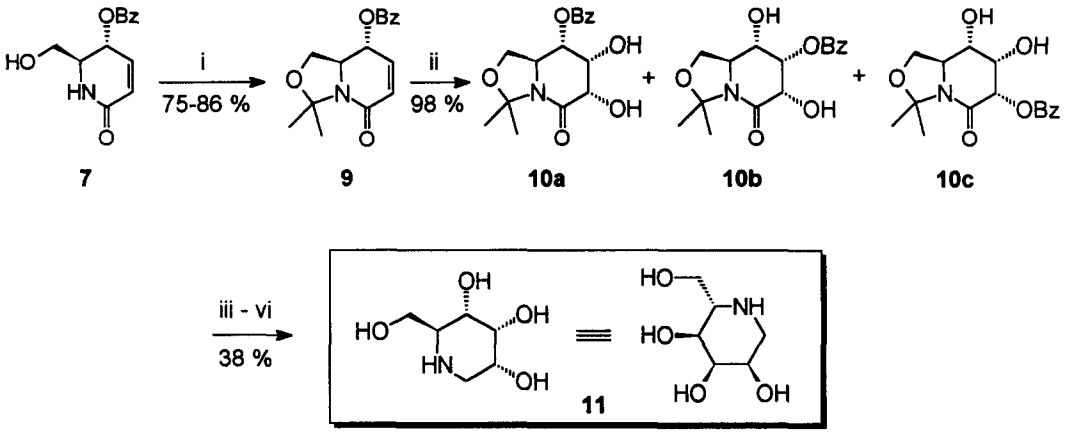
Serine was transformed into its serinal derivative **4** as described in the literature[22]. This configurationally stable α-aminoaldehyde derivative is an analogue of the well known Garner aldehyde[23] for which it has been shown that alkynyl anions can be added in a highly diastereoselective manner[24,25]. The reaction with the propargylic ethyl ester anion confirmed these results for **4**. In the presence of two equivalents hexamethylphosphoric triamide (HMPT), the diastereomeric excess was 95 % whereas without HMPT only 60 % was reached. The alkoxide anion reaction intermediate furnished **5** on addition of benzoyl chloride. The anti-diastereomer was formed preferentially consistent with a non chelation controlled reaction mechanism[24]. Partial hydrogenation of the carbon carbon triple bond could be readily accomplished using Lindlar's catalyst under normal pressure conditions. Acid labile protecting groups were removed using trifluoroacetic acid (TFA). After evaporation cyclisation was induced by stirring the residue in a two phase system consisting of saturated aqueous $NaHCO_3$ and ethyl acetate. Enone **7** was obtained in 71 % yield after chromatographical purification[26]. Interestingly the minor syn-diastereomer was found to be unstable. Intramolecular Michael addition under the cyclisation conditions led to oxazabicyclo[3.2.1]octane **8**.



Scheme 2: i: Ref. 22; ii: $HCCCO_2Et$, BuLi, THF, HMPT, -90 °C → -35 °C; iii: BzCl, -50 °C → rt; iv: Lindlar's cat., EtOAc, quinolin, rt; v: Et_2O/H_2O/TFA (1 : 1 : 3), rt, 1 h; vi: EtOAc, sat. $NaHCO_3$, rt, 15 h

Dihydropyridinone **7** was transformed into its isopropylidene acetal **9** by reacting it with dimethoxypropane (DMP) in the presence of pyridinium *p*-toluenesulfonate (PPTS)[27]. In this compound one side of the carbon-carbon double bond is shielded by a methyl group of the acetal functionality; hence reactions should preferentially take place on the other side. Dihydroxylation with osmium tetroxide gave a mixture of three products **10a-10c** differing in the position of the benzoyl group which were chromatographically separable. All three of them were shown to be allo-configurated[28]. There was no indication for formation of any manno-configurated product during the reaction[29].

Intermediate **10a** was convertable into a mixture of **10b** and **10c** by adding a few drops of triethylamine to a solution of the neat compound in methanol. Isomers **10b** and **10c** were separable by HPLC on silica gel using a mixture of hexane/isopropanol (8 : 2) as eluent. However, when pure material was allowed to stand in the solvent mixture at room temperature for a few hours, it always rearranged to give mixtures of **10b** and **10c**. **10b** and **10c** were not transformable into **10a** by the addition of triethylamine to a solution in methanol.



Scheme 3: i: PhH, DMP, PPTS, 78 °C; ii: acetone/H_2O (1 : 1), 4 % OsO_4, NMO, rt, 55 h; iii: MeOH/NEt_3 (9 : 1), rt, 18 h; iv: 2 N HCl, 50 °C, 5 h; v: TDSCl, Py, rt, 40 h; vi: BH_3*SMe_2, THF, rt, 24 h → Dowex 50X8-400 ($H^{\oplus}$)

Removal of the protecting groups was accomplished by transesterification followed by acidic cleavage of the acetal group. The primary hydroxy functionality had to be temporarily reprotected because of its tendency to react intramolecularly with the anomeric centre during the following borane reduction[30]. The thexyldimethylsilyl group (TDS) was chosen because of its high preference for the primary hydroxyl group and because of its removability during the acidic work up of the next step.

The reaction with TDSCl in pyridine gave a mixture of products which was purified by a chromatographic filtration through a small layer of silica gel. After evaporation a white solid was obtained consisting of mono and higher silylated compounds. The following borane reduction yielded the title compound **11**[31] after acidic work up and purification by ion exchange chromatography and crystallisation from ethanol. Its NMR-spectroscopic data were in good agreement with values obtained for a derivative of **11**[32,33] and allo-nojirimycin itself[18].

In conclusion a synthetic sequence starting from L-serine and leading to (*S*)-1-deoxy-allonojirimycin **11** is shown in which three chiral centres are introduced into the molecule in a highly stereocontrolled manner. As D-serine is also commercially available, the *R*-enantiomer is equally accessible.

The elaboration of 7 to different 1,5-didedoxy-1,5-iminoalditols will be described in the near future.

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(*Received in UK* 3 *April* 1995)