Synthesis of 5-amino-α-D-*gluco*-hept-6-enfuranose as usefull 1-deoxynojirimycin precursor using [3,3]-sigmatropic aza-Claisen rearrangement

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Abstract

Iminosugars are one of the most interesting discoveries in the field of natural products recent years due to their promissing biological activity. We report synthesis of 1-deoxynojirimycin building block using D-glucose as the starting material and the [3,3]-sigmatropic aza-Claisen rearrangement as the key step of our synthesis.

Key words: 1-deoxynojirimycin, azasugars, aza-Claisen rearrangement

Introduction

Azasugars (also known as iminosugars) present compounds with structure similar to "normal" sugars, in which the endocyclic oxygen is replaced by a nitrogen atom. Interest in this type of compounds dates from 1966, when the effective α- and β-glucosidase inhibitor, nojirimycin, was discovered.[1,2] Azasugars bearing a hydroxyl group at C-1 were found to be relatively difficult to isolate and handle due to the unstable aminal functionality. Therefore the deoxy-derivative, 1-deoxynojirimycin (DNJ) was first prepared from L-sorbofuranose by Paulsen[3], later by reduction of nojirimycin.[2] However it was soon afterwards isolated from Mulberry trees as well as *Streptomyces* cultures.[4]

Azasugars bind specifically to the active sites of glycosidases by mimicking the corresponding natural substrates. Glycosidases are involved in a wide range of important biological processes, such as intenstinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates. Certain sugar mimics have aroused increasing interest as potential antiviral, anticancer, antidiabetic and antibacterial agents, and agrochemicals. Most of these effects can be shown to result from the direct or indirect inhibition of glycosidases.[5]

We present here stereoselective synthesis of 5-amino-α-D-*gluco*-hept-6-enfuranose as usefull DNJ precursor using D-glucose as the starting material. [3,3]-sigmatropic aza-Claisen rearrangement is used as the key step of our synthesis.

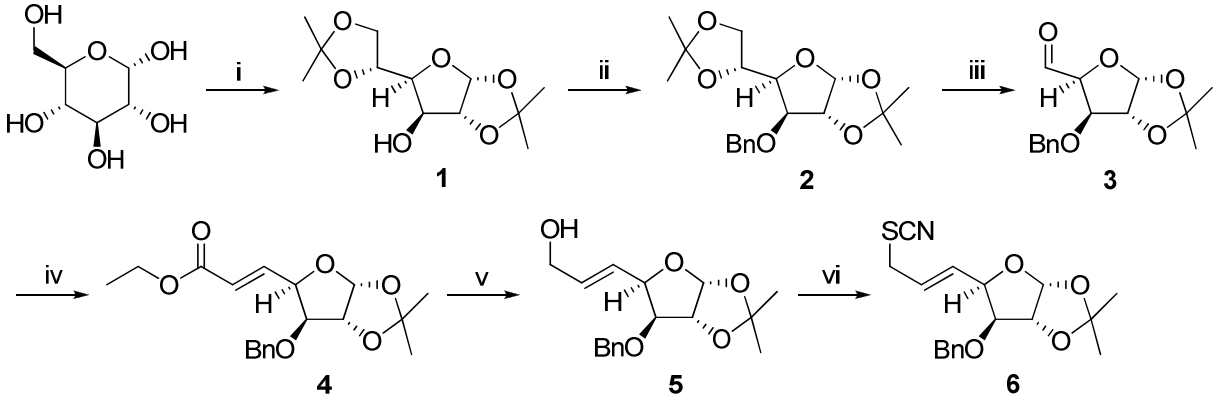
Results and discussion

We chose chiral pool starting material - D-glucose, which present precursor with good chirality. It was converted into protected derivative **1**, using acetone and iron (III) chloride (Scheme 1).[6]

Compound **1** was treated with BnBr, NaH, and TBAI as catalyst to give product **2** benzylated at the C-3 position.[7] Selective deprotection of the isopropylidene group at the C-5 and C-6 position and subsequent oxidative cleavage of resulting diol afforded aldehyde **3** in god yield.[8]

The formation of double bond was carried out by Wadsworth-Horner-Emmons reaction. Reaction of aldehyde **3** with triethyl phosphonoacetate led to ester **4** as a single product, and configuration of the double bond was determined as *E* on the basis of ^{1}H NMR spectra.

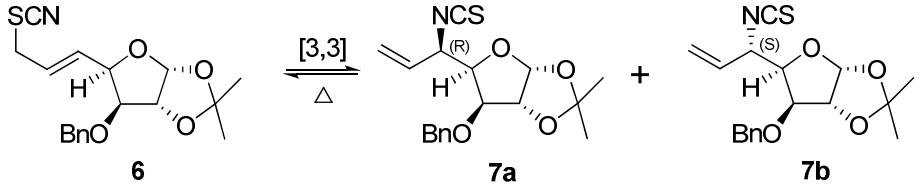
Reduction of ester **4** using diisobutylaluminium hydride in dry CH_2Cl_2 provided corresponding allylic alcohol **5**. Alcohol **5** was converted into mesylate using CH_3SO_2Cl and triethylamine as base and the crude product was subsequently treated with KSCN in dry acetonitrile to give allylic thiocyanate **6**.



Reaction conditions: i) acetone, $FeCl_3$, 78%; ii) BnBr, NaH, TBAI, THF, 80%; iii) H_5IO_6, AcOH, 90%; iv) $(EtO)_2POCH_2COOEt$, NaH, THF, 85%; v) DIBAL-H, CH_2Cl_2, 83%; vi) 1. MsCl, Et_3N, CH_2Cl_2, 2. KSCN, CH_3CN, 77%

Scheme 1. Synthesis of thiocyanate **6**

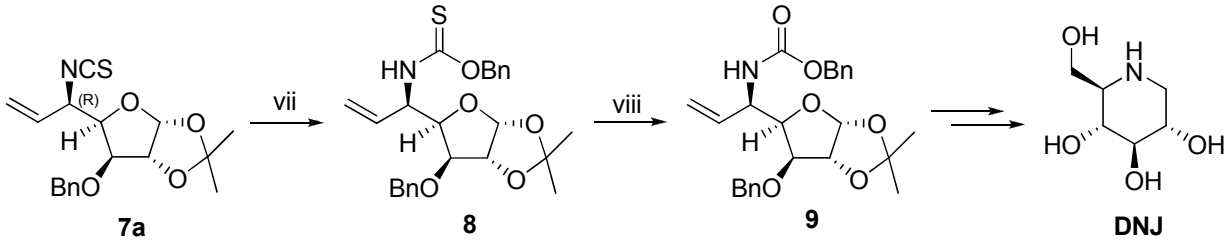
In order to inbuilding nitrogen functionality into C-5 of the furanose ring the [3,3]-sigmatropic aza-Claisen rearrangement was performed in n-heptane, using conventional heating in oil bath at 90 °C for 21 h.[9] The ratio of diastereomers 7a and 7b (3:1) was determined on the basis of ^{1}H NMR spectra from the mixture of diastereomers. The diastereomers were separated by the column chromatography on silica gel.



Reaction conditins: 90°C, 21h, (*R*):(*S*) 3:1

Scheme 2. Aza-Claisen rearrangement of thiocyanate **6** to isothiocyanates **7a** and **7b**

The pure (*R*) stereoisomer **7a** was used to the next reaction. After 24 h of stirring thiocarbamate **8** was obtained in good yield. The reaction of **8** with mesitylnitrile oxide in dry acetonitrile afforded carbamate **9** which can be transformed into 1-deoxynojirimycin (Scheme 3).



Reaction condtions: vii) BnOH, NaH, THF, 65%; viii) MNO, CH_3CN, 80%

Scheme 3. Synthesis of DNJ precursor **9**

Experimental

1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 1[7]

5.0 g (27.75 mmol) of D-glucose was dissolved in dry acetone (250 mL). Then 2.7 g of $FeCl_3$ was added and the mixture was stirred for 24 h at the room temperature. The reaction was quenched with addition of 10% K_2CO_3 solution (50 mL). Solvent was evaporated under reduced pressure, and residue was extracted with $CHCl_3$ (3x100 mL). The combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography on silica gel (hexane/ethyl acetate, 2:1) afforded 5.63 g (78%) of protected glucopyranose as white crystals.

3-*O*-Benzyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 2[8]

To a solution of known 1,2:5,6-di-*O*-isopropylidene-*α*-D-glucofuranose (5.63 g, 21,63 mmol) in dry THF (100 mL) was added NaH (1.67 g, 43,26 mmol, 60% dispersion in mineral oil, washed free of oil with anhydrous THF) at 0 °C. The reaction was stirred for 15 min at 0 °C and then BnBr (3.88 mL, 32.44 mmol) and TBAI (0.08 g, 0.22 mmol) were added at the same temperature. The mixture was allowed to warm to room temperature and stirred for 2 h and then partitioned between diethyl ether (100 mL) and ice water (50 mL). The aqeous phase was extracted with further portion of Et_2O (50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. Chromatography of the residue on silica gel (hexane/ethyl acetate, 13:1) afforded 6.06 g (80%) of benzylated product **2** as a colourless oil.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose 3

To a solution of **2** (6.06 g, 17.29 mmol) in 200 mL of glacial acetic acid was added 35 mL of 12% aqueous solution of H_5IO_6. After 25 min stirring at room temperature 400 mL of 5% aqueous solution of CH_3COONa was added. The aqueous phase was extracted with CH_2Cl_2 (2x50 mL). Combined organic layers were concentrated under reduced pressure affording oil, which was partitioned between Et_2O and water. Organic layer was washed with $NaHCO_3$, dried over Na_2SO_4 and solvent was evaporated. Chromatography on silica gel (hexane/ethyl acetate, 3:1) afforded 4.33 g (90%) of oily product **3**.

Ethyl (*E*)-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enfuranuronate 4

To a solution of NaH (0.9 g, 23.33 mmol, 60% dispersion in mineral oil, washed free of oil with anhydrous THF) in THF (33 mL) was added triethyl phosphonoacetate (3.42 mL, 17.11 mmol) in THF (22 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then the solution of aldehyde **3** (4.33 g, 15.56 mmol) was added dropwise under nitrogen atmosphere at the same temperature. The resulting solution was left under stiring for 30 min at 0 °C, and then quenched with saturated aqueous solution of NH_4Cl (30 mL). The mixture was allowed to warm to room temperature and the product was extracted with ethyl acetate (2x50 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 7:1) to afford 4.6 g (85%) of unsaturated ester **4** as a colourless oil.

(*E*)-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hept-5-enfuranose 5

To a solution of ester **4** (4.6 g, 13.2 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAL-H (38,2 mL, 46.21 mmol of 1.2 M toluene solution) at -13 °C. The resulting mixture was stirred at -13 °C for 50 min and then quenched with methanol (3 mL). The mixture was allowed to warm to room temperature and poured into 30% aq K/Na tartrate (196 mL). After being stirred for 50

min the product was extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified on silica gel (hexane/ethyl acetate, 2:1) to afford 3.35 g (83%) of allylic alcohol **5**.

(*E*)-3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-7-thiocyanato-α-D-*xylo*-hept-5-enfuranose 6

To a solution of alcohol **5** (3.35 g, 10.93 mmol) in dry CH_2Cl_2 (40 mL) were added Et_3N (2.27 mL, 16.4 mmol) and MsCl (1 mL, 13.12 mmol) at0 °C. The reaction mixture was stirred for 15 min at 0 °C and then for further 1.5 h at room temperature. The solvent was removed under reduced pressure and the residue was diluted with diethyl ether (50 mL). The solid was removed by filtration and the solvent was evaporated under reduced pressure. The crude mesylate was used in the subsequent reaction directly without further purification.

To a solution of crude mesylate in dry acetonitrile (40 mL) was added KSCN (1.59 g, 16.4 mmol). Stirring was continued for 2.5 h at room temperature. The solvent was evaporated under reduced pressure and the residue was diluted with diethyl ether (50 mL). The solid was filtered and the solvent was evaporated under reduced pressure. The resulting residue was purified by chromatography on silica gel (hexane/ethyl acetate, 5:1) to afford 3.12 g (77%) of thiocyanate **6** as colourless oil.

3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-isothiocyanato-α-D-*gluco*-hept-6-enfuranose 7a and 3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-isothiocyanato-β-L-*ido*-hept-6-enfuranose 7b

A solution of thiocyanate **6** (3.12 g, 8.40 mmol) in dry heptane (20 mL) was heated for 21 h at 90 °C under an atmosphere of nitrogen. The solvent was removed under reduced pressure and crude product was purified by chromatography on silica gel (hexane/ethyl acetate, 10:1) to give 1.40 g (45%) of isothiocyanate **7a** and 0.5g (16%) of isothiocyanate **7b**.[9]

3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(benzyloxythiocarbonylamino)-α-D-*gluco*-hept-6-enfuranose 8

To a NaH (0.01g, 4.16 mmol) in dry THF was added BnOH (0.43 mL, 4.16 mmol) at 0 °C. Mixture was stirred for 30 min at the same temperature and then solution of isothiocyanate **7a** (1.40 g, 3.78 mmol) in dry THF was added. Mixture was allowed to warm to room temperature and stirred for 24 h. The solvent was evaporated under reduced pressure and product was purified by column chromatography on silica gel (hexane/ethyl acetate, 5:1) to give 1.46 g (65%) of thiocarbamate **8**.

3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-5-(benzyloxycarbonylamino)-α-D-*gluco*-hept-6-enfuranose 9

To a solution of thiocarbamate **8** (1.46 g, 3.2 mmol) in dry acetonitrile was added mesitylnitrile oxide (0.57 g, 3.52 mmol). The reaction mixture was stirred for 3.5 h at room temperature. Removal of the solvent under reduced pressure gave a product, which was purified on silica gel (hexane/ethyl acetate, 3:1) to afford 1.23 g (80%) of carbamate **9**.

NMR spectra of all prepared compounds were consistent with their structures.

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