A Formal Total Synthesis of Deoxynojirimycin from D-Glucitol

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Descrevemos a síntese formal da desoxinojirimicina usando D-glucitol como material de partida economicamente atraente. Através de uma sequência de reações de proteção e desproteção seletivas e reações de substituição nucleofilica obtivemos diversos intermediários isopropilidênicos. A formação de um epóxido intermediário e sua subsequente abertura, através de uma reação nucleofilica intramolecular, levou à obtenção do heterociclo 1,5-didesoxi-1,5-diamino-2,3-O-isopropilideno-6-sílica-D-glucitol, que é um precursor da desoxinojirimicina (DNJ).

This report deals with the formal synthesis of deoxynojirimycin using D-glucitol as an inexpensive starting material. Through a sequence of several selective protection/deprotection and nucleophilic substitution reactions, many isopropylidene derivatives were obtained. Formation of an epoxide intermediate and its subsequent ring opening, via intramolecular nucleophilic substitution, leads to the synthesis of heterocyclic 1,5-dideoxy-1,5-diamine-2,3-O-isopropylidene-6-silyl-D-glucitol, which is a precursor of deoxynojirimycin (DNJ).

Keywords: D-glucitol, glycosidase inhibitors, isopropylidene derivatives, deoxynojirimycin

Introduction

Imino sugars,1 sometimes called azasugars, are compounds that have been shown to selectively inhibit oligosaccharide processing enzymes (i.e., glycosidases or glycotransferases).2-5 Because of the potential chemotherapeutic applications of such compounds, there is a continuing interest on the synthesis of imino sugars. Deoxynojirimycin (DNJ, 1,5-dideoxy-1,5-imino-D-glucitol) is an inhibitor for several glycosidases, and, additionally, it shows antidiabetic and antiviral activities, including anti-HIV activity.6-8 Its importance is disclosed by the large number of publications devoted to its preparation.

After Paulsen et al.9 have obtained 1-deoxynojirimycin and disclosed its potent glucosidase inhibitor effects, it has been synthesized by a variety of methods. Kinast et al.10 obtained 1-deoxynojirimycin in four steps from D-glucose through an enzymatic oxidation. Behling et al.11 described a synthesis of DNJ (1) from L-sorbose that requires the isolation of only two intermediates and the use of only one protection/deprotection protocol. Setoi et al.12-14 described a synthesis of DNJ (1) from D-mannose by a multi-step approach with protecting/deprotecting group manipulation. To date several syntheses of DNJ (1) and analogues have been described.7,15-18

This report deals with the formal total synthesis of DNJ (1) using D-glucitol, an inexpensive starting material, through a sequence of several selective protection/deprotection and nucleophilic substitution reactions.19

Results and Discussion

Treatment of D-glucitol with THF, 2,2-dimethoxypropane (DMP) and p-toluenesulfonic acid (TsOH) resulted in diacetonides 4 (3%), 3 (46%) and triacetonide 2 (16%), as shown in Scheme 1.

The 4-O-acetyl-1-azido-1-deoxy-2,3:5,6-di-O-isopropylidene-D-glucitol (7) was obtained from 3 in 37% overall yield by the sequence of sulfonation, acetylation and azidation (3 → 5a → 6 → 7). Selective cleavage of the terminal acetonide group was accomplished using p-toluenesulfonic acid in methanol at 0 °C for 5 h. The resulting mixture of acetonides 7 (51%) and 8a (34%) was purified by flash column chromatography. Under the applied conditions, acyl group migration from C-4 to C-6 was observed. Acyl group migration in non-acidic aqueous media or in dichloromethane containing triethylamine was also observed by Kilonda et al.6 When this reaction is carried out using pyridinium 4-toluenesulfonate as catalyst,
acyl group migration is not observed. This migration protects the primary group at C-6 from tosylation during the next step. The azide epoxide 10 was obtained after sulfonation of 8a and treatment with K₂CO₃, followed by basic treatment to promote deacetylation. The trans stereochemistry of the resulting epoxide 10 is confirmed by the coupling constant (J 2.2 Hz) between H₄ and H₅.²⁰,²¹

The intermediate 11 is obtained by protection with TBDMSCl. Treatment of the epoxide azide 11 with NaBH₄ in boiling methanol gave 13 a protected form of DNJ (1). The intermediate epoxide amine 12 could not be isolated (Scheme 1) and this reaction afforded a single piperidine heterocycle. In summary, 13 was obtained in 9 steps and 0.4% overall yield from D-glucitol.

Setoi et al.¹²-¹⁴ have obtained DNJ (1) by treatment of 13 a protected form of DNJ (1) with aqueous TFA for 12 h, which has been prepared from D-mannose in 14 steps and 0.4% overall yield.

¹H NMR, ¹³C NMR, 2D proton-proton homocorrelated and C-H heterocorrelated spectra and comparation with literature data confirmed the structure of intermediates.²¹

Scheme 1.
Experimental

General procedures

Thin-layer chromatography (TLC) was carried out on plates precoated with silica gel 60 F254 (E. Merck). Detection was by UV at 254 nm, followed by charring with a solution of ammonium molybdate or Dragendorff reagent. Column chromatography was carried out on silica gel (230-400 mesh) and, unless otherwise stated, mixtures of heptane-EtOAc or CH2Cl2-MeOH were used as eluent. All reactions were conducted under an argon atmosphere. Anhydrous Na2SO4 was used to dry organic solution and the removal of the solvent was done under vacuum with a rotary evaporator. Solvents were dried and purified using standard methods. IR spectra were recorded with a Bomen FTIR spectrometer using KBr pellets or NaCl cells. Elemental analyses were performed on a model 2400 CHN-Perkin Elmer instrument. Nuclear magnetic resonance spectra were obtained using Varian 300 MHz or Bruker AC-300 MHz spectrometers in CDCl3 solutions with (CH3)4Si as internal reference (300 MHz for 1H and 75 MHz for 13C). The assignments were confirmed by proton-proton homocorrelated and carbon-proton heterocorrelated spectra. HREIMS (70 eV, direct probe) experiment was performed using a VG Auto Spec-Fisions Instrument using electron ionisation at 70 eV (linked scan from 8 keV collisions with helium). Optical rotations were measured with a Jasco model J-720 digital polarimeter.

1,2,5,6-di-O-isopropylidene-D-glucitol (4), 2,3,5,6-di-O-isopropylidene-D-glucitol (3) and 1,2,3,4,5,6-tri-O-isopropylidene-D-glucitol (2)

To a mixture containing 3 cm3 of THF and 1.03 g (5.7 mmol) of D-glucitol, 1.5 cm3 of DMP and TsOH were added. The mixture was stirred at 0 oC for 1 h and left to stand at room temperature for 12 h. The mixture was neutralized with aqueous NH3 and evaporated. The residue was dissolved in CH2Cl2 and the solution was washed with saturated aqueous NaCl, dried over anhydrous Na2SO4 and evaporated. The residue was purified using column chromatography (6:4 heptane-EtOAc) to give 4 (0.04 g, 3%); 3 (0.667 g, 46%) and 2 (0.271 g, 16%).

2. Yellowish amorphous solid; [α]D25 = +7.61° (CHCl3); (lit.22 -15.15°). 1H NMR (CDCl3): δ 1.35 (s, 3H, CH3), 1.41 (s, 3H, CH3), 1.43 (s, 6H, 2 CH3), 2.60 (m, 2H, 2 OCH2), 3.50 (dd, 8.4 and 7.0 Hz, 1H, H-1), 3.81 (m, 1H, H-1´), 4.00-4.20 (m, 5H, H-2, H-3, H-5, H-6). 13C NMR (CDCl3) δ: 25.3, 25.4, 26.5, 26.9, 66.1, 67.2, 73.8, 75.3, 78.1, 109.5, 110.0.; Anal. Calc. for C, 54.96; H, 08.83; Found: C, 54.93; H, 08.46.

Method A. To a solution of diacetonide 3 (1.45 g, 5.5 mmol) in Et2N (5.0 cm3) cooled externally by an ice bath TsCl was added (1.43 g) under argon. The mixture was stirred at 0 oC for 6 h and left to stand at room temperature for 14 h. The mixture was dissolved in CH2Cl2 and the solution was washed with saturated aqueous NaCl, dried over anhydrous Na2SO4 and evaporated. The residue was purified by column chromatography (6:4 heptane-EtOAc) to give 5a (1.03 g, 45%), a monotosyl derivative and the ditosyl 5b (1.09 g, 35%).

Method B. In a procedure similar to the one described above, a mixture containing 3 (0.60 g, 2.29 mmol), CH2Cl2 (3.0 cm3), and Et2N (0.5 cm3) was added to TsCl (0.43 g), under an inert atmosphere while being cooled externally by an ice bath. The reaction was then kept in the refrigerator.
for 14 h. The mixture was dissolved in CH2Cl2 and the resulting solution was washed with saturated aqueous NaCl, dried (Na2SO4) and evaporated. The residue was purified by column chromatography (6:4 heptane-EtOAc) to give 5a (0.60 g, 63%), 5b (0.07 g, 2%) and 3 (0.15 g, 10%).

5a. Colourless oil; νmax/cm−1: 3512, 1371, 1170, 1070, 737 (film); 1H NMR (CDCl3) δ: 1.39 (s (6H, CH3), 1.33 (s, 3H, CH3), 1.35 (s, 3H, CH3), 1.43 (s, 3H, CH3), 1.46 (s, 3H, CH3), 1.46 (s, 3H, CH3), 1.48 (s, 3H, CH3), 2.43 (s, 3H, CH3), 2.28 (br, d, J, 1H, OH), 3.45 (t, J, 3.0 and 7.6 Hz, 1H, H-4); 3.9-4.3 (m, 7H, H-1, H-1!, H-2, H-3, H-5, H-6 and H-6'), 7.38 (d, J, 8.4 Hz, 2H); 7.81 (d, J, 8.6 Hz, 1H, H-6); 13C NMR (CDCl3) δ: 21.6, 21.7, 25.3, 25.6, 26.8, 27.0, 65.7, 67.8, 74.1, 74.9, 78.2, 78.8, 82.5, 85.1, 109.8, 109.9, 110.0, 110.4, 128.3, 130.1, 132.1, 145.3.

5b. White amorphous solid; [α]D25= +7.9° found (CHCl3); (lit.24,25 +6.8°). 1H NMR (CDCl3) δ: 2.46 (s, 3H, CH3), 3.81 (t, J, 3.0 and 7.6 Hz, 1H, H-4); 3.9-4.3 (m, 7H, H-1, H-1!, H-2, H-3, H-5, H-6 and H-6'), 7.38 (d, J, 8.4 Hz, 2H); 7.81 (d, J, 8.6 Hz, 2H); 13C NMR (CDCl3) δ: 21.7, 25.3, 26.0, 26.8, 27.0, 65.7, 67.8, 71.3, 74.7, 76.3, 77.9, 109.8, 110.4, 128.3, 130.1, 132.1, 145.3.

4-Acetyl-2,3:5,6-di-O-isopropylidene-1-p-toluenesulfonyl-D-glucitol (6)

To a mixture containing acetyl azide 7 (1.10 g, 3.36 mmol) and MeOH (5.0 cm3), TsOH (catalyst, 0.05g) was added. The mixture was stirred at 0 °C for 5 h, neutralised with aqueous NH3 (10% v/v) and evaporated. The residue was dissolved in CH2Cl2, washed with aqueous NaCl and dried over anhydrous Na2SO4. Filtration and evaporation of the solvent gave a residue that was purified on a chromatography column (1:1 heptane-EtOAc) giving 8a (0.33 g, 34%) and 7 (0.56 g, 51%). 1H NMR (CDCl3/OH) δ: 1.45 (s, 3H, CH3), 1.48 (s, 3H,CH3), 2.11 (s, 3H, CH3), 2.64 (s, 1H, OH), 2.82 (d, 1H, J 4.8 Hz, OH), 3.35 (dd, 1H, J 5.0 and 13.2Hz, H-1), 4.25 (dd, 1H, J 5.0 and 13.2Hz, H-1), 4.25 (dd, 1H, J 5.0 and 13.2Hz, H-1), 3.48 (t, 1H, H-4), 3.57 (dd, 1H, J 14.1 Hz, H-1'), 3.84 (br, s, 1H, H-5), 4.2-4.3 (m, 1H, H-2), 4.19 (dd, 1H, J 2.2 and 7.9 Hz, 1H, H-3), 4.25 (dd, 1H, J 5.5 and 12.3 Hz, 1H, H-6), 4.43 (dd, 1H, J 2.7 and 12.3 Hz, 1H, H-6); 13C NMR (CDCl3/D2O) δ: 20.8, 26.9, 51.5, 66.21, 68.9, 71.8, 75.9, 76.6, 110.1, 171.7.

Method B. To a mixture containing 7 (0.53 g, 1.62 mmol) and MeOH (5.0 cm3), 4-pyridinium toluenesulfonate (0.05g) was added. The mixture was stirred at room temperature for 12 h. Then, it was heated at 50 °C. The reaction was stopped when TLC indicated the presence of a third compound. The solution was neutralised with aqueous NH3 (10% v/v) then purified using a silica gel chromatographic column (1:1 heptane-EtOAc) giving 8a (0.02g, 4%), 8b (0.13g, 28%) and 7 (0.20g, 38%).

4-O-acetyl-1-azido-2,3:5,6-di-O-isopropylidene-D-glucitol (8b)

Colourless oil; 1H NMR (CDCl3): δ 1.38 (s, 3H, CH3), 1.42 (s, 3H, CH3), 2.10 (s, 3H, CH3), 3.20 (dd, J 13.3 and 5.0 Hz, 2H, H-1, H-6), 3.55 (dd, J 13.3 and 7Hz, 2H, H-1', 2.68 g, 86%) as an amorphous compound, white solid.
H-6'), 3.63 (br, s, 2H, 2 OH), 3.8-3.9 (m, 2H, H-2 and H-5), 4.29 (dd, J 8.2 and 2.2 Hz, 1H, H-3), 4.88 (dd, J 8.0 and 2.3 Hz, 1H, H-4). 1H NMR (CDCl3, D2O): δ: 1.42 (s, 3H, CH3), 1.38 (s, 3H, CH3), 2.10 (s, 3H, CH3), 3.34 (dd, J 13.2 and 5.1 Hz, 1H, H-1), 3.53 (dd, J 12.0 and 5.1 Hz, 2H, H-6'), 3.60 (dd, J 13.2 and 3.5 Hz, 1H, H-1'), 3.69 (dd, J 12.0 and 3.2Hz, 1H, H-6'), 3.82-3.99 (m, 2H, H-2 and H-5), 4.33 (dd, 1H, J 8.3 and 2.2Hz, H-3), 4.91 (dd, 1H, J 8.1 and 2.1 Hz, H-4). 13C NMR (CDCl3) δ: 21.4, 27.2, 27.6, 51.8, 63.4, 70.6, 71.2, 76.2, 77.0, 110.6, 171.7.

6-O-acetyl-1-azido-1-deoxy-2,3-isopropylidene-5-p-toluenesulfonyl-D-glucitol (9a) and 6-O-acetyl-1-azido-1-deoxy-2,3-isopropylidene-5,6-di-p-toluenesulfonyl-D-glucitol (9b)

To a mixture containing acetyl azide 8 (0.25 g, 0.87 mmol) and 5.0 cm3 of Et3N, under an inert atmosphere, cooled externally by an ice bath, TsCl (0.486g, mmol) was added. The reaction was kept in the refrigerator for 12 h. The filtrate was evaporated under reduced pressure to give crude 9a and 9b that were purified by a silica gel chromatographic column: (7:3 heptane-EtOAc) to yield 9a (0.14 g, 36%) and 9b (0.10 g, 19%).

9a. 1H NMR (CDCl3) δ: 1.33 (s, 3H, CH3), 1.39 (s, 3H, CH3), 2.01 (s, 3H, CH3), 2.45 (s, 3H, CH3), 2.66 (d, J 9.8 Hz, 1H, -OH), 3.24 (dd, J 13.3 and 4.4 Hz, 1H, H-1), 3.54 (dd, J 13.3 and 4.0 Hz, 1H, H-1'), 3.62 (t, J 9.4, 1.0 Hz, 1H, H-4), 3.86 (dd, 1H, J 8.3 and 1.1 Hz, H-3), 4.10-4.16 (m, 1H, H-2), 4.32 (dd, J 12.7 and 2.5 Hz, 1H, H-6), 4.50 (dd, J 12.7 and 5.1 Hz, 1H, H-6'), 4.66-4.74 (m, 1H, H-5), 7.32 (d, J 8.1 Hz, 2H), 7.82 (d, J 8.1 Hz, 2H). 13C NMR (CDCl3) δ: 20.9, 21.7, 27.0, 26.8, 50.9, 62.5, 67.0, 75.6, 75.7, 79.0, 111.8, 129.3, 131.3, 144.3, 167.8.

4,5-anhydro-1-azido-1-deoxy-2,3-isopropylidene-D-glucitol (10)

To a mixture containing the tosyl azide 9a (0.10 g, 0.22 mmol) and 5.0 cm3 of MeOH, K2CO3 (0.114 g, 0.82 mmol) and 5.0 cm3 of Et3N, under an inert atmosphere, 0.22 mmol) and 5.0 cm3 of MeOH, K2CO3 (0.114 g, 0.82 mmol) and 5.0 cm3 of Et3N, under an inert atmosphere, the mixture was then washed with an aqueous solution of NaCl and dried over anhydrous Na2SO4. Then, the solvent was removed under reduced pressure.

To a solution of 0.02 g of epoxide 10 (0.057 mmol) in 5.0 cm3 of EtOH, NaBH4 was added (0.002 g). The reaction was stirred at room temperature for 12 h. As no reaction was observed, the mixture was heated to 40 °C. After 24 h of reaction, more NaBH4 (0.003 g) was added and the solution was stirred at 40 °C for next 12 h. CH2Cl2 was added to the mixture, which was then washed with aqueous NaCl, dried over anhydrous Na2SO4 and the solvent was removed under reduced pressure.

The residue was purified by TLC (1:1 heptane-EtOAc), affording 13 (0.008 g, 48%). 1H NMR (CDCl3), δ: 25.8, 26.3, 46.7, 60.8, 63.2, 72.0, 76.0, 84.2, 110.5. HR-EIMS m/z [M+Na]+ found 302.167. Calc. for C14H22NO6Si: 302.179.

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References