

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 seqüência de reações de proteção e desproteção seletivas e reações de substituição nucleofílica obtivemos diversos intermediários isopropilidênicos. A formação de um epóxido intermediário e sua subsequente abertura, através de uma reação nucleofílica intramolecular, levou à obtenção do heterociclo 1,5-didesoxi-1,5-diamino-2,3-*O*-isopropilideno-6-silila-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 diacetone **4** (3%), **3** (46%) and triacetone **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 sulfonylation, 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 acetone **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,

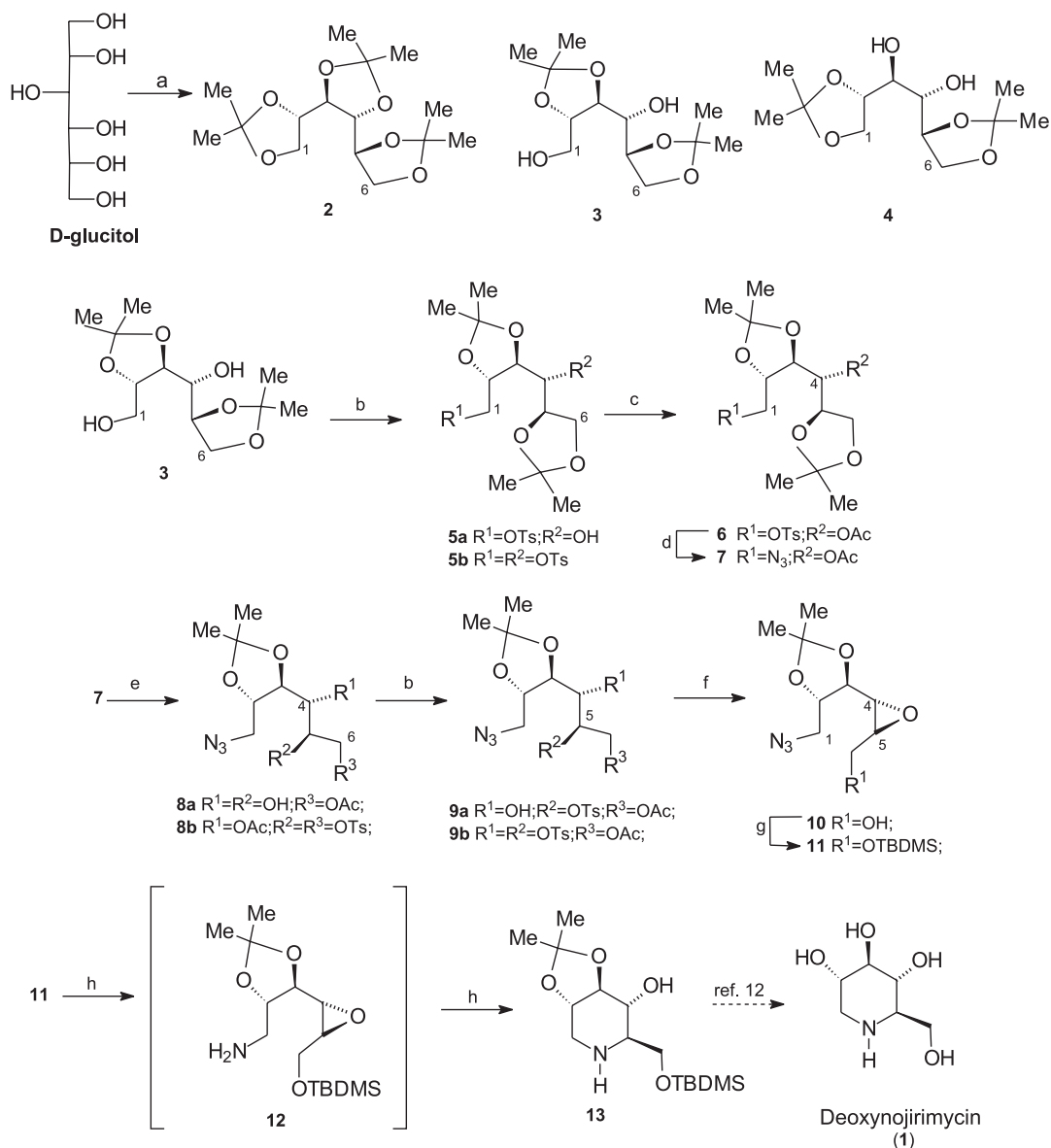
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acyl group migration is not observed. This migration protects the primary group at C-6 from tosylation during the next step. The azide epoxide **10** was obtained after sulfonation of **8a** and treatment with K_2CO_3 , followed by basic treatment 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 $NaBH_4$ 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 comparison 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.²² 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.²³ IR spectra were recorded with a Bomem 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 °C 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 and dried over anhydrous Na₂SO₄. Purification by column chromatography gave three derivatives: **4** (0.04 g, 3%); **3** (0.667 g, 46%) and **2** (0.271 g, 16%).

2. Yellowish amorphous solid; $[\alpha]_D^{25} = +7.61^\circ$ (CHCl₃); (lit.^{24,25} +7.5°), ν_{\max} /cm⁻¹: 2986, 1370, 1073 (film); ¹H NMR (CDCl₃) δ 1.34 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.39 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.43 (s, 3H, CH₃), 1.44 (s, 3H, CH₃), 3.85 (dd, *J* 8.0 and 7.3 Hz, 1H, H-1), 3.97 (dd, *J* 8.0 and 4.7 Hz, 1H, H-1'), 4.04 (dd, *J* 8.3 and 6.7 Hz, 1H, H-6), 4.00-4.20 (m, 4H, H-2, H-3, H-4 and H-5), 4.15 (dd, *J* 8.3

and *J* 2.3 Hz, 1H, H-6). ¹³C NMR (CDCl₃) δ : 25.3, 26.6, 25.7, 26.3, 26.9, 27.2, 66.1, 67.9, 76.8, 77.3, 78.1, 80.5, 109.5, 109.8, 109.8. Elem. Anal: Calc. for C₁₅H₂₆O₆: C, 59.60; H, 8.61; Found: C, 60.08; H, 8.70.

4. Colorless needles; mp 90 °C, $[\alpha]_D^{25} = +10.74^\circ$ (CHCl₃); ¹H NMR (CDCl₃) δ 1.35 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 2.65 (br, s, 1H, OH), 2.83 (br, s, 1H, OH), 3.52 (s, 1H, H-3), 3.75 (dt, *J* 4.7 and 1.4 Hz, 1H, H-4), 3.91 (dd, *J* 8.4 and 7.0 Hz, 1H, H-6), 4.02 (dd, *J* 7.5 and 4.7 Hz, 1H, H-1'), 4.09 (dd, *J* 8.4 and 6.6 Hz, 1H, H-6), 4.10-4.20 (m, 2H, H-1, H-2), 4.28 (dt, *J* 7.0, 6.6 and 4.2 Hz, 1H, H-5); ¹H NMR (CDCl₃/TMS/D₂O) δ 1.35 (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 3.51 (dd, *J* 7.5 and 1.4 Hz, 1H, H-3), 3.75 (dd, *J* 4.7 and 1.4 Hz, 1H, H-4), 3.90 (dd, *J* 8.4 and 7.0 Hz, 1H, H-6), 4.02 (dd, *J* 7.5 and 4.7 Hz, 1H, H-1'), 4.08 (dd, 8.4 and 6.6 Hz, 1H, H-6'), 4.15 (m, 2H, H-1, H-2), 4.28 (dt, *J* 7.0, 6.6 and 4.7 Hz, 1H, H-5); ¹³C NMR (CDCl₃) δ : 25.3, 25.4, 26.5, 26.9, 66.1, 67.2, 69.4, 73.9, 75.3, 78.1, 109.5, 110.0; Anal. Calc. for C, 54.96; H, 08.83; Found: C, 54.93; H, 08.46.

3. Colorless oil; $[\alpha]_D^{25} = -12.43^\circ$ (CHCl₃); (lit.^{24,25} -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 OH), 3.50 (dt, *J* 2.5 and 6.6 Hz, 1H, H-4), 3.71 (m, 1H, H-1), 3.81 (m, 1H, H-1'), 4.00-4.20 (m, 5H, H-2, H-3, H-5, H-6 and H-6'). ¹H NMR (CDCl₃/D₂O) δ : 1.35 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 1.43 (s, 6H, 2 CH₃), 3.50 (dd, *J* 2.5 and 6.6 Hz, 1H, H-4), 3.60 (dd, *J* 4.2 and 12.0 Hz, 1H, H-1), 3.81 (dd, *J* 12.0 and 3.6 Hz, 1H, H-1'), 4.00-4.20 (5H, m, H-2, H-3, H-5, H-6, H-6'). ¹³C NMR (CDCl₃) δ : 25.1, 26.6, 26.8, 27.1, 61.9, 66.9, 70.7, 76.3, 77.1, 77.4, 109.4, 109.5.

2,3:5,6-di-O-isopropylidene-1-p-toluenesulfonyl-D-glucitol (5a) and *2,3:5,6-di-O-isopropylidene-1,4-di-p-toluenesulfonyl-D-glucitol (5b)*

Method A. To a solution of diacetone **3** (1.45 g, 5.5 mmol) in Et₃N (5.0 cm³) cooled externally by an ice bath TsCl was added (1.43 g) under argon. The mixture was stirred at 0 °C 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 Et₃N (0.3 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 CH_2Cl_2 and the resulting solution was washed with saturated aqueous NaCl, dried (Na_2SO_4) 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; $\nu_{\text{max.}}/\text{cm}^{-1}$: 3512, 1371, 1170, 1070, 737 (film); $^1\text{H NMR}$ (CDCl_3) δ : 1.39 (s, 6H, CH_3), 1.33 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 2.28 (br, d, 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 8.4 Hz, 2H); $^{13}\text{C NMR}$ (CDCl_3) δ : 21.7, 25.3, 26.8, 26.9, 27.0, 67.2, 69.1, 71.3, 74.7, 76.3, 77.9, 109.8, 110.4, 128.3, 130.1, 132.1, 145.3.

5b. White amorphous solid; $[\alpha]_{\text{D}}^{25} = +7.9^\circ$ found (CHCl_3); (lit.^{24,25} $+6.8^\circ$). $^1\text{H NMR}$ (CDCl_3) δ : 1.30 (s, 3H, CH_3), 1.35 (s, 6H, CH_3), 1.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.81 (t, J 7.5 Hz, 1H, H-6), 3.95 (dd, J 3.8 and 7.5 Hz, 2H, H-4 and H-6'), 4.06-4.11 (m, 3H, H-1', H-3 and H-5), 4.25 (dd, J 11.4 and 2.3 Hz, 1H, H-1), 4.65-4.72 (m, 1H, H-2), 7.72 (d, 4H), 7.35 (m, 4H). $^{13}\text{C NMR}$ (CDCl_3) δ : 21.6, 21.7, 25.6, 26.0, 26.8, 27.0, 65.7, 67.8, 74.1, 74.9, 78.7, 78.8, 109.7, 110.8, 127.9, 128.0, 129.8, 129.9, 132.1, 133.0, 145.1, 145.5.

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

To a mixture containing monotosyl derivative **5a** (1.60 g, 3.85 mmol) and 10.0 cm^3 of Et_3N , 1.0 cm^3 of acetic anhydride was added. The mixture was stirred at room temperature for 24 h. After that, it was neutralised with aqueous NH_3 and evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with saturated aqueous NaCl and dried over Na_2SO_4 . The Et_3N was evaporated in a rotary evaporator using MeOH for the azeotropic system. Purification by a flash silica gel chromatographic column (7:3 heptane-EtOAc) gave **6** (1.34 g, 76%). $\nu_{\text{max.}}/\text{cm}^{-1}$: 2988; 1745; 1371; 1226; 1117 (film).

4-O-acetyl-1-azido-1-deoxy-2,3:5,6 di-O-isopropylidene-D-glucitol (**7**)

To a mixture containing 4.21 g (9.2 mmol) of acetyl-tosyl **6**, 10.0 cm^3 DMF and 2.0 cm^3 H_2O , 0.830 g NaN_3 (12.7 mmol) was added. The mixture was heated under reflux for 12 h. The solution was added to an ice-water mixture. The precipitate formed was filtered and washed with CH_2Cl_2 . Purification by a flash silica gel chromatographic column (7:3 heptane-EtOAc) gave **7**

(2.68 g, 86%) as an amorphous compound, white solid. $\nu_{\text{max.}}/\text{cm}^{-1}$: 2988; 2104, 1740, 1372, 1225, 1070 (film). $^1\text{H NMR}$ (CDCl_3) δ : 1.34 (s, 3H, CH_3), 1.38 (s, 6H, CH_3), 1.44 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.29 (dd, 1H, J 5.4 and 12.9 Hz, H-1), 3.59 (dd, J 12.9 and 4.3 Hz, 1H, H-1'), 3.82-3.90 (m, 1H, H-2), 3.88 (dd, J 8.6 and 12.8 Hz, 1H, H-6), 4.04 (dd, J 6.4 and 8.6 Hz, 1H, H-6), 4.13 (dd, J 2.1 and 7.5 Hz, 1H, H-3), 4.26 (q, J 6.4 Hz, 1H, H-5), 5.02 (dd, J 2.1 and 6.4 Hz, 1H, H-4). $^{13}\text{C NMR}$ (CDCl_3) δ : 20.8, 25.3, 26.5, 27.0, 51.1, 66.1, 70.4, 74.9, 75.7, 76.8, 109.5, 110.0, 170.3.

6-O-acetyl-1-azido-2,3-O-isopropylidene-D-glucitol (**8a**)

Method A. To a mixture containing acetyl azide **7** (1.10 g, 3.36 mmol) and MeOH (5.0 cm^3), TsOH (catalyst, 0.1 mmol) was added. The mixture was stirred at 0 °C for 5 h, neutralised with aqueous NH_3 (10% v/v) and evaporated. The residue was dissolved in CH_2Cl_2 , washed with aqueous NaCl and dried over anhydrous Na_2SO_4 . 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%). $^1\text{H NMR}$ (CDCl_3) δ : 1.45 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.64 (s, 1H, OH), 2.82 (d, 1H, J 4.8 Hz, OH), 3.35 (dd, 1H, J 5.0 and 13.2 Hz, H-1), 3.49 (t, 1H, H-4), 3.57 (dd, 1H, J 4.1 Hz, H-1'), 3.84 (br, s, 1H, H-5), 4.2-4.3 (m, 1H, H-2), 4.19 (dd, J 2.2 and 7.9 Hz, 1H, H-3), 4.25 (dd, J 5.5 and 12.3 Hz, 1H, H-6), 4.43 (dd, J 2.7 and 12.3 Hz, 1H, H-6'); $^1\text{H NMR}$ ($\text{CDCl}_3/\text{D}_2\text{O}$) δ : 1.45 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.35 (dd, J 5.0 and 13.2 Hz, 1H, H-1), 3.49 (dd, J 2.2 and 7.9 Hz, 1H, H-4), 3.57 (dd, J 4.0 and 13.2 Hz, 1H, H-1'), 4.20-4.30 (m, 1H, H-2), 4.19 (dd, J 2.2 and 7.9 Hz, 1H, H-3), 4.25 (dd, J 5.5 and 12.3 Hz, 1H, H-6), 4.43 (dd, 2.7 and 12.3 Hz, 1H, H-6'); $^{13}\text{C NMR}$ (CDCl_3) 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 cm^3), 4-pyridinium toluene-sulfonate (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 NH_3 (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-isopropylidene-D-glucitol (**8b**)

Colourless oil; $^1\text{H NMR}$ (CDCl_3) δ : 1.38 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.29 (dd, J 13.3 and 5.0 Hz, 2H, H-1, H-6), 3.55 (dd, J 13.3 and 7 Hz, 2H, H-1',

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 3.2 Hz, 1H, H-6'), 3.82-3.99 (m, 2H, H-2 and H-5), 4.33 (dd, 1H, *J* 8.3 and 2.2 Hz, 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 (0.486 g, 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) was added. The solution was stirred at room temperature for 1 h. The residue was purified by TLC, (1:1 heptane-EtOAc), giving compound **10** (0.029 g, 58%) as a colorless viscous oil. ν_{max} /cm⁻¹: 3425; 2107, ¹H NMR (CDCl₃) δ: 1.42 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 2.00 (br, 1H, OH), 3.15 (dd, *J* 2.2 and 4.5 Hz, 1H, H-4), 3.25 (m, 1H, H-5), 3.39 (dd, *J* 4.5 and 13.1 Hz, 1H, H-1), 3.59 (dd, *J* 4.5 and 13.1 Hz, 1H, H-1'), 3.71 (br, d, *J* 3 and 13 Hz, 1H, H-6), 3.92 (dd, *J* 2.2 and 4.5 Hz, 1H, H-3), 3.96 (dd, *J* 2.4 and 13.1 Hz, 1H, H-6'), 4.10-4.18 (m, 1H, H-2). ¹³C NMR (CDCl₃) δ: 26.6, 26.9, 51.5, 53.8, 55.6, 60.6, 77.5, 77.3, 110.6.

4,5-anhydro-1-azido-1-deoxy-2,3-isopropylidene-6-silyl-D-glucitol (11)

To a mixture containing 0.025 g (0.11 mmol) of epoxide **10** in 2.0 cm³ of DMF, tert-butyldimethylsilyl chloride (0.032 g, 0.212 mmol) and imidazole (0.02 g, 0.34 mmol) were added under an inert atmosphere. The solution was stirred at room temperature for 24 h. CH₂Cl₂ was added to the residue, and it was washed with an aqueous solution of NaCl and dried over anhydrous Na₂SO₄. Then, the solvent was removed under reduced pressure. The residue was purified by PLC (6:4 heptane-EtOAc), giving **11** (0.02 mg, 53%) and **10** (0.010 g, 42%). ¹H NMR (CDCl₃) δ: 0.06 (s, 3H, CH₃), 0.07 (s, 3H, CH₃), 0.89 (s, 9H, CH₃), 1.42 (s, 3H, CH₃), 1.45 (s, 3H, CH₃), 3.00 (dd, *J* 2.2 and 4.7 Hz, 1H, H-4), 3.09-3.14 (m, 1H, H-5), 3.35 (dd, *J* 4.6 and 13.2 Hz, 1H), 3.58 (dd, *J* 4.2 and 13.2 Hz, 1H, H-1), 3.75 (dd, *J* 4.0 and 12.1 Hz, 1H, H-6'), 3.58 (dd, *J* 4.2 and 13.2 Hz, 1H, H-1'), 3.83 (dd, *J* 3.4 and 12.1 Hz, 1H, H-6), 3.88 (dd, 1H, *J* 4.7 and 8.1 Hz, H-3), 4.10-4.16 (m, 1H, H-2). ¹³C NMR (CDCl₃) δ: -5.4, 18.3, 25.8, 26.6, 26.8, 51.5, 54.2, 55.7, 62.3, 76.6, 77.3, 110.5

1,5-dideoxy-1,5-imino-2,3-O-isopropylidene-D-glucitol (13)

To a solution of 0.02 g of epoxide **11** (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%). [α]_D²⁵ = +23.6 (CHCl₃); (lit.¹² +20.1 (CHCl₃)); ¹H NMR (CDCl₃) δ 0.08 (s, 3H, CH₃-Si), 0.10 (s, 3H, CH₃-Si), 0.91 (s, 9H, CH₃ (t-butyl)-Si-), 1.47 (s, 6H, 2 CH₃), 2.48-2.58 (m, 1H, H-5), 2.75 (dd, *J* 11.2 and 12.7 Hz, 1H, H-1_{ax}), 3.28-3.36 (m, 2H, H-1' and H-2), 3.42 (t, *J* 8.7 Hz, 1H, H-3), 3.72 (t, *J* 8.7 Hz, 1H, H-4), 3.79 (dd, *J* 4.7 and 9.8 Hz, 1H, H-6), 3.91 (dd, *J* 4.2 and 9.8 Hz, 1H, H-6'). ¹³C NMR (CDCl₃) δ: -5.5, 18.2, 25.9, 26.3, 46.7, 60.8, 63.2, 72.0, 76.0, 84.2, 110.5. HR-EIMS *m/z* [M-CH₃]⁺ found 302.167. Calc. for C₁₄H₂₈NO₄Si: 302.179.

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