Available online at www.sciencedirect.com
SCIENCE DIRECT
Carbohydrate Research 341 (2006) 2200–2203
Carbohydrate RESEARCH

A facile synthesis of 1,6-dideoxynojirimycin from L-sorbose

Jia-Ning An, Xiang-Bao Meng, Yun Yao and Zhong-Jun Li*

Department of Chemical Biology, School of Pharmaceutical Sciences, State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, China

Received 26 March 2006; received in revised form 30 May 2006; accepted 6 June 2006
Available online 3 July 2006

Abstract—A practical synthesis of 1,6-dideoxynojirimycin, a potent glycosidase inhibitor, starting from L-sorbose, is described.

Keywords: 1,6-Dideoxynojirimycin; L-Sorbose

1. Introduction

1,6-Dideoxynojirimycin (**7**) is a naturally occurring alkaloid that is classified as an imino sugar. Because of the structural resemblance to the sugar moiety of natural substrates for glycosidases, imino sugars are often found to be potent glycosidase inhibitors. These compounds could be potential drug candidates as antiviral, antiinfective, and antitumor agents. They might also be used to treat carbohydrate metabolism disorders or serve as glylcosphingolipid lysosomal storage disease therapeutics.[1–5] Therefore, the synthesis of 1,6-dideoxynojirimycin has been studied by different groups.[6] However, many of these methods either started from rare materials or required long synthetic approaches with limited stereospecificity. A noted exception is the efficient approach described by Pistin and Hollingsworth from D-glucose.[6d]

For further investigation into both bioactivity and synthetic methodology, our group has developed a novel and practical synthetic approach for 1,6-dideoxynojirimycin from relatively inexpensive and accessible L-sorbose. With the fixed chiral centers of the starting material and the almost quantitative stereoselectivity in the reductive amination step,[6a] the enantiochemistry of this approach is fully guaranteed.

2. Results and discussion

L-Sorbose was converted to 2,3-*O*-isopropylidene-L-sorbofuranose **1** by treating the sugar with concd H_2SO_4 in acetone.[7] The triol **1** reacted with *p*-toluenesulfonyl chloride in pyridine to afford the distosylate **2**. Regioselective azide displacement of the 6-*O*-tosylate was successfully accomplished by treating **2** with sodium azide in anhydrous DMF at 75 °C for 30 h to obtain the desired product **3** in high yield. Similar regioselective nucleophilic substitution in the reaction of 1,6-distosylated fructose[8a] and sorbose[8b] with nucleophiles like sodium iodide or sodium chloride was reported. The regioselectivity of these substitutions should be caused by the steric hindrance of isopropylidene and the electron-withdrawing effect of 2-ketal. Converting the 1-*O*-tosylate of **3** to a methyl group, together with the reduction of the 6-azido group to the amine, was hindered by the slow reductive process. We found that the tosylate and azide could be reduced with $LiAlH_4$ in refluxing THF in only low yield,[9] and the workup was tedious and time consuming. The 1-*O*-tosylate of **3** was finally substituted by I_2/NaI in DMF, followed by hydrogenation in the presence of $Pd(OH)_2$, to afford the 1-methyl product **5**.

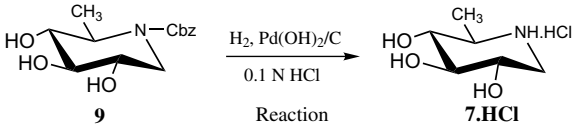
The amine **5** was adsorbed onto Dowex 50 (H^+) resin, and the acetonide was hydrolyzed to give the unstable intermediate **6**, which underwent intramolecular reductive amination in the presence of hydrogen and $Pd(OH)_2$ to give 1,6-dideoxynojirimycin **7**. No 5-epimer was

* Corresponding author. Tel.: +86 10 82801504; fax: +86 10 62367134; e-mail: zjli@bjmu.edu.cn

0008-6215/$ - see front matter
doi:10.1016/j.carres.2006.06.002

detected by TLC in the reaction mixture. Due to the difficulty of purifying the product through chromatography, the crude product was treated with CBzCl and then subjected to flash chromatography. Along with the expected final products **9**, small amount of side product **10** was obtained. The structure of **9** was fully assigned by NMR spectroscopy and mass spectrometry. The structure of **10** was deduced based on NMR and MS data, and the observed aromatization in the reductive amination in our early unpublished study. Therefore, the undetermined side product of reductive amination could be assumed to be **8** (Scheme 1).

Finally, the purified 1,6-dideoxynojirimycin hydrochloride was obtained after hydrogenation of **9**, followed by the addition of 0.1 N HCl and lyophilization to give the product in 70% yield (based on **5**).



9 **7.HCl**

3. Experimental

3.1. General

Melting points were measured on an X 4 melting point apparatus. Optical rotations were measured at room temperature (rt) using an AA-10 R automatic polarimeter in a 0.1-dm cell. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR 300 spectrometer. The HRESIMS mass spectra were obtained using a Bruker APE IV FTMS instrument. Reagents were either dried by standard techniques or used as purchased.

3.2. Preparation of 2,3-*O*-isopropylidene-1,6-bis-*O*-(*p*-toluenesulfonyl)-α-L-sorbofuranose (2)

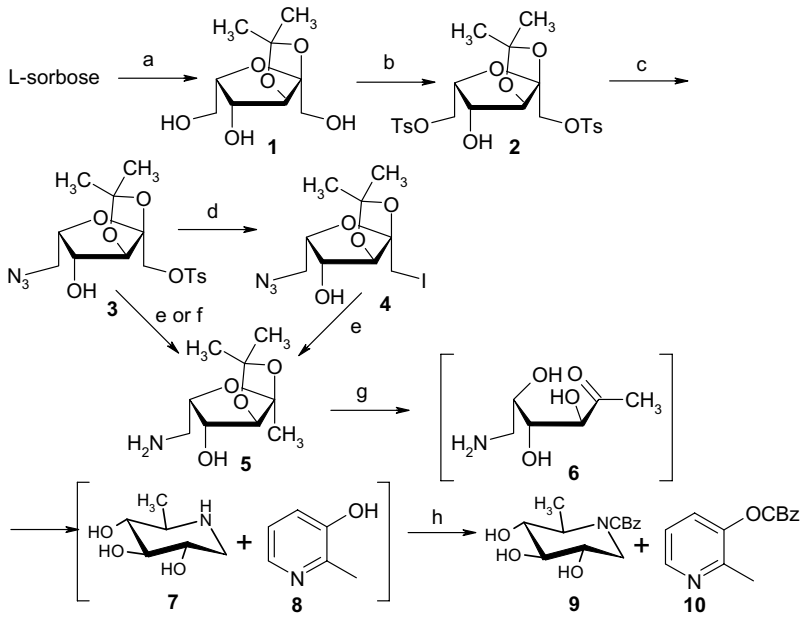
To a solution of 2,3-*O*-isopropylidene-α-L-sorbofuranose (10.0 g, 45.0 mmol) in anhyd pyridine (25 mL) was added *p*-toluenesulfonyl chloride (21.67 g, 114.0 mmol) in batches, and the mixture stirred for 5 h at rt. The mixture was concentrated, and the resulting yellow syrup was dissolved with a large amount of $CHCl_3$ (600 mL). The organic layer was washed with satd aq $CuSO_4$ (75 mL) and water (35 mL), dried ($MgSO_4$), and evaporated to a yellow syrup. The crude syrup was purified by flash chromatography using 10:1 petroleum–EtOAc to give compound **2** as a white solid (23.52 g, 98.0%): mp 128–130 °C, lit.[10] 131 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H, $(CH_3)_2C$), 1.43 (s, 3H, $(CH_3)_2C$), 2.45 (s, 6H, $2CH_3$–Ph), 4.04–4.16 (m, 3H, 2H-6, H-1), 4.23–4.28 (m, 2H, H-1, H-3 or H-4), 4.38 (ddd, *J* 2.7 Hz, 1H, H-5), 4.44 (s, 1H, H-3 or H-4), 7.35 (d, 4H, *J* 8.1 Hz, H–Ph), 7.78 (dd, 4H, *J* 5.7, 8.1 Hz, H–Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.63 × 2 (CH_3–Ph), 26.04 ((CH_3)$_2$C), 27.17 ((CH_3)$_2$C), 66.52, 67.92, 74.24, 84.99, 89.18, 111.44, 113.14 ((CH_3)$_2$C quart, C-2 quart), 127.96 × 4, 129.96 × 4 (Ph), 132.30 × 2, 145.20 × 2 (Ph quart).

3.3. 6-Azido-6-deoxy-2,3-*O*-isopropylidene-1-*O*-(*p*-toluenesulfonyl)-α-L-sorbofuranose (3)

To a solution of compound **2** (10.0 g, 18.9 mmol) in anhyd DMF (40 mL) was added NaN_3 (1.85 g, 28.4 mmol), and the suspension was heated at 75 °C for 30 h. The mixture was concentrated, and the resulting mixture was added to water (200 mL) and extracted with EtOAc (800 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated to give a crude yellow product that was purified by flash chromatography. Elution with 14:1 petroleum–EtOAc afforded a white solid (6.72 g, 89%): mp 90–92 °C; $[\alpha]_D^{20}$ +57.7 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H, $(CH_3)_2C$), 1.49 (s, 3H, $(CH_3)_2C$), 2.46 (s, 3H, CH_3–Ph), 3.44–3.56 (m, 2H, H-6), 4.15 (d, 2H, $J_{1,1'}$ 10.5 Hz, H-1), 4.21 (br s, 1H,), 4.26 (d, 2H, $J_{1,1'}$ 10.5 Hz, H-1′),4.31–4.37 (ddd, 1H, H-5) 4.50 (s, 1H), 7.37 (d, 2H, *J* 8.4 Hz, H–Ph), 7.80 (d, 2H, *J* 8.4 Hz, H–Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.67 (CH_3–Ph), 26.07 ((CH_3)$_2$C), 27.15 ((CH_3)$_2$C), 49.2 (C-6), 68.37 (C-1), 75.01, 80.07, 85.50, 111.29, 113.02 ((CH_3)$_2$C quart, C-2 quart), 128.00 × 2, 130.02 × 2(Ph), 132.29, 145.45 (Ph quart). HRESIMS: Anal. Calcd for $C_{16}H_{21}N_3O_7S$: *m*/*z* 400.1184 $[MH]^+$. Found: *m*/*z* 400.1186.

3.4. 6-Azido-1,6-dideoxy-1-iodo-2,3-*O*-isopropylidene-α-L-sorbofuranose (4)

To a solution of compound **3** (2.5 g, 6.27 mmol) in anhyd DMF (20 mL) was added NaI (11.65 g, 62.7 mmol), and the mixture was heated for 15 h at 110 °C (bath temperature). TLC with 2:1 petroleum–EtOAc then showed that the reaction was almost complete. The mixture was then cooled and the solvent was evaporated. The residue was dissolved in water (50 mL), extracted with $CHCl_3$ (400 mL), and the $CHCl_3$ layer was dried ($MgSO_4$), and evaporated to give a yellow syrup. The crude product was purified by silica gel chromatography using 15:1 petroleum–EtOAc to give a white solid (1.77 g, 79.7%): mp 53–55 °C; $[\alpha]_D^{20}$ +40.6 (*c* 1.28, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 3H, $(CH_3)_2C$), 1.51 (s, 3H, $(CH_3)_2C$), 3.51–3.67 (m, 4H, 2H-6, 2H-1), 4.28 (d, 1H, *J* 3 Hz,), 4.40 (ddd, 1H, H-5), 4.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.37 (CH_3-1), 26.43 (CH_3)$_2$C), 27.45 (CH_3)$_2$C), 49.22 (C-6), 75.58, 79.90, 86.51, 112.36 × 2 (CH_3)$_2$C quart, C-2 quart); HRESIMS: Anal. Calcd for $C_9H_{15}IN$: *m*/*z* 328.0051 $[MH-N_2]^+$. Found: *m*/*z* 328.0053.



Scheme 1. Synthesis of 1,6-dideoxynojirimycin from L-sorbose. Reagents and conditions: (a) Ref. 7; (b) TsCl/pyridine, rt, 5 h, 98%; (c) NaN_3, DMF, 75 °C, 30 h, 89%; (d) KI, DMF, 110 °C, 15 h, 79.7%; (e) H_2 (60 psi), $Pd(OH)_2/C$ (10%), CH_3OH, H_2O, rt, 20 h, 79.5%; (f) $LiAlH_4$, reflux, 30 h, 40.3%; (g) Dowex H^+, H_2 (60 psi), $Pd(OH)_2/C$ (10%), $MeOH/H_2O$, rt, 30 h, 87.1%; (h) CBzCl, aq satd $NaHCO_3$, acetone, toluene, rt, 14 h, 100%.

3.5. 6-Amino-1,6-dideoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (5)

(a) To a solution of compound **3** (0.75 g, 1.88 mmol) in anhyd THF (20 mL) was carefully added $LiAlH_4$ (0.28 g, 7.52 mmol) in small portions, and the mixture was refluxed for 30 h. TLC with 10:1 $CHCl_3$–MeOH showed that the reaction was almost complete. Excess $LiAlH_4$ was decomposed by the careful addition of water (3 mL), and the suspension was filtered and washed with MeOH. The filtrate and MeOH were then combined and concentrated, providing a pale-yellow syrup that was chromatographed on silica gel column by elution with 20:1 $CHCl_3$–MeOH to give **5** (0.15 g, 40.3%). (b) To a solution of compound **4** (1.00 g, 2.82 mmol) in 1:1 MeOH–satd aq K_2CO_3 (60 mL) was added $Pd(OH)_2/C$ (10%) (200 mg), and the mixture was hydrogenated at 60 psi for 20 h. The suspension was filtered when TLC with 4:1 $CHCl_3$–MeOH showed that the reaction was complete, and the filtrate was concentrated, giving a crude white solid. The crude product was subjected to separation on a silica gel column with 17:1 $CHCl_3$–MeOH to give **5** as a pale-yellow syrup (0.45 g, 79.5%): $[\alpha]_D^{20}$ −75.0 (*c* 0.32, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H, $(CH_3)_2C$), 1.47 (s, 3H, $(CH_3)_2C$), 1.71 (s, 3H, CH_3-1), 3.15 (d, 2H, $J_{6,6'}$ 13.2 Hz, H-6), 3.32 (br s, 2H, $-NH_2$), 3.50 (dd, 1H, $J_{5,6'}$ 3.6 Hz, $J_{6,6'}$ 13.2 Hz, H-6′), 4.17 (s, 1H), 4.22 (s, 1H), 4.31 (d, 1H, $J_{5,6'}$ 3.6 Hz, H-5); ^{13}C NMR (75 Hz, $CDCl_3$): δ 24.61 (CH_3-1), 26.08 ($(CH_3)_2C$), 27.17 ($(CH_3)_2C$), 40.97 (C-6), 76.58, 79.18, 88.46, 110.36, 113.18 ($(CH_3)_2C$ quart, C-2 quart). HRESIMS: Anal. Calcd for $C_9H_{18}NO_4$: *m*/*z* 204.1241 $[MH]^+$. Found: *m*/*z* 204.1236.

3.6. *N*-Benzyloxycarbonyl-1,5,6-trideoxy-1,5-imino-D-glucitol (9)

To a solution of compound **5** (0.30 g, 1.48 mmol) in water (30 mL) was added Dowex 50 (H^+) resin to adjust the pH to pH 3–4. Immediately $Pd(OH)_2/C$ (10%) (150 mg) was added, and the reaction was subjected to 60 psi of hydrogen with agitation for 30 h. The resin (containing 1,6-dideoxynojirimycin) was slurried in satd anhyd ammonia–MeOH (pH 9–10) for 30 min and filtered. The solids were washed with water, followed by methanol. The filtrate and washes were combined and concentrated by rotary evaporation at rt. The residue was dissolved in water and lyophilized to provide crude 1,6-dideoxynojirimycin. Subsequent chromatography proved to be unsuccessful. Therefore, a benzyloxycarbonyl group was introduced to facilitate the separation. To a solution of crude 1,6-dideoxynojirimycin (0.189 g, 1.29 mmol) in 15 mL of satd aq $NaHCO_3$ was added dropwise benzyl chloroformate (0.32 g, 1.93 mmol) in 7:1 acetone–toluene (4 mL). After stirring for 14 h at rt, the suspension was concentrated, and the resulting solid was dissolved in water (20 mL), and extracted with EtOH (80 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow syrup that was purified by flash chromatography with elution of 24:1 $CHCl_3$–MeOH to afford a colorless syrup (0.29 g,

79.6%): $[\alpha]_D^{20}$ +95.0 (*c* 0.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, 3H, $J_{5,6}$ 6.9 Hz, CH_3), 3.36 (d, 1H, $J_{1a,1e}$ 13.8 Hz, H-1a), 3.53 (br s, 1H), 3.73 (br s, 2H), 3.92 (d, 1H, $J_{1a,1e}$ 13.8 Hz, H-1e), 4.18 (br d, 2H, *J* 3.6 Hz), 5.09 (dd, 2H, *J* 12.6, 17.4 Hz, Bn–CH_2), 7.26–7.31 (m, 5H, Ph); ^{13}C NMR (75 Hz, $CDCl_3$): δ 15.62 (CH_3), 41.74 (C-1), 53.84, 67.41, 70.09, 71.54, 72.67, 127.56 × 2, 127.99, 128.48 × 2 (Ph), 136.33 (Ph quart), 156.80 (C═O). HRESIMS: Anal. Calcd for $C_{14}H_{20}NO_5$: *m*/*z* 282.1347 $[MH]^+$. Found: *m*/*z* 282.1357. Along with the **9**, a pale-yellow syrup of **10** (0.05 g, 17.4%) was also obtained: ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 5.30 (s, 2H, Bn–CH_2), 7.19 (dd, 1H, *J* 4.8, 8.1 Hz, H-pyridine), 7.36–7.49 (m, 6H, H-pyridine, H–Ph), 8.40 (d, 1H, *J* 3.9 Hz, H-pyridine). HRESIMS: Anal. Calcd for $C_{14}H_{14}NO_3$: *m*/*z* 244.0979 $[MH]^+$. Found: *m*/*z* 244.0973.

3.7. 1,5,6-Trideoxy-1,5-imino-D-glucitol hydrochloride (7·HCl)

To a solution of **9** (0.29 g, 1.03 mmol) in 2:1 H_2O–MeOH (30 mL) was added $Pd(OH)_2/C$ (10%, 250 mg), and the hydrogenolysis was carried out at 59 psi for 6 h. The mixture was filtered and washed with water. The filtrate and washes were combined and concentrated at rt, and then 0.1 N HCl (10.5 mL) was added to the residue. The mixture was lyophilized to give a colorless resinous product (0.15 g, 100%): $[\alpha]_D^{20}$ +17.1 (*c* 0.70, H_2O), lit.[6d] $[\alpha]_D^{20}$ +13 (*c* 1.0, H_2O); ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, $J_{5,6}$ 6.6 Hz, CH_3), 2.77 (t, 1H, $J_{1a,1e} = J_{1a,2} = 12$ Hz, H-1a), 2.96–3.06 (m, 1H, H-5), 3.18–3.35 (m, 3H, H-4, H-1e, H-3), 3.58–3.67 (m, 1H, H-2); ^{13}C NMR (75 Hz, $CDCl_3$): δ 15.14 (CH_3), 46.44 (C-1), 55.73, 67.62, 72.99, 76.47. HRESIMS: Anal. Calcd for $C_6H_3NO_3$: *m*/*z* 148.0979 $[MH]^+$. Found: *m*/*z* 148.0979.

Acknowledgements

This work is supported by the National Sciences Foundation of China (Nos. 30000031 and 30330690).

Supplementary data

Supplementary data (NMR spectra) associated with this article can be found in the online version at doi:10.1016/j.carres.2006.06.002.

References

1. Afarinkia, K.; Bahar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1239–1287.
2. Pearson, M. S. M.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159–2191.
3. Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541–560.
4. Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *3*, 561–574.
5. Nishimura, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 575–591.
6. (a) Kajimoto, T.; Liu, K. K.-C.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, J. A.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6187–6196; (b) Defoin, A.; Sarazin, H.; Streith, J. *Helv. Chim. Acta* **1996**, *79*, 560–567; (c) Dhavale, D. D.; Saha, N. N.; Desai, V. N. *J. Org. Chem.* **1997**, *62*, 7482–7484; (d) Pistia, G.; Hollingsworth, R. I. *Carbohydr. Res.* **2000**, *328*, 467–472; (e) Rani, S.; Agarwal, A.; Vankar, Y. D. *Tetrahedron Lett.* **2003**, *44*, 5001–5004.
7. Paulsen, H.; Sangster, I.; Heyns, K. *Chem. Ber.* **1967**, *100*, 802–815.
8. (a) Guthrie, R. D.; Jenkens, I. D.; Yamasaki, R. *Aust. J. Chem.* **1982**, *35*, 1003–1018; (b) Mueller, H.; Reichstein, T. *Helv. Chim. Acta* **1938**, *21*, 267–272.
9. El Fangour, S.; Guy, A.; Desprse, V.; Vidal, J.-P.; Rossi, J.-C.; Durand, T. *J. Org. Chem.* **2004**, *69*, 2498–2503.
10. Lee, C.-K. *Carbohydr. Res.* **1987**, *170*, 255–262.