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An Improved Synthetic Method for *N*-Butyl-1-Deoxynojirimycin

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Abstract

N-butyl-1-deoxynojirimycin (NB-DNJ) based on imino sugars Deoxynojirimycin (DNJ) has been approved for treatment of Gaucher's disease. Here, an improved synthetic procedureof NB-DNJ was described. High yields can be achieved during the introduction steps of n-butyl by combining a strong nucleophilicity of imine in the iminosugar andan easy leaving group methanesulfonatein butyl, which is much higher than the similar reported procedures. This method can be served as an excellent solution to the synthesis of various *N*-alkyl substituted chain DNJ, even applied to large-scale production.

Keywords: Synthesize; Improve; DNJ; NB-DNJ; Gaucher disease

Introduction

Iminosugars are a class of sugar mimics in which the endocyclic oxygen of monosaccharides was substituted with a nitrogen atom [1]. Representing the most common iminosugars, 1-deoxynojirimycin (DNJ, **1**), is a naturally occurring piperidine 1-deoxyglucose mimic from the mulberry tree, which exhibits potent α- and β-glucosidases inhibition [2]. Based on its high therapeutic potential, there are two approved iminosugar medicines, Zavesca® (NB-DNJ, miglustat, **2**) and Miglitol® (**3**), which were used for the treatment of Gaucher's disease (GD) and type II diabetes respectively [3,4]. GD is a progressive lysosomal storage disorder caused by the insufficient activity of the β-glucocerebrosidase (GCase, acid β-glucosidase, EC 3.2.1.45), which isresponsible for the hydrolysis of the glucosylceramide (GC) in lysosome. Mutant GCase with low catalytic activity results in the accumulation of un-degraded substrates, which ultimately leads to bone lesions, hepatosplenomegaly and any other diseases. Two primary therapeutic approaches for GD patients are enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). In 2000, NB-DNJ, known as an inhibitorof α-glucosidase I, II and ER-localized enzymes [5,6], was approved for the treatment of type I GD ascribed to the inhibition on the glucosylceramide synthaseand reducing GC biosynthesis [7]. After then, NB-DNJ has been used for the therapy of GC in Israel, USA and Europe [8].

Recently, pharmacological chaperones therapy (PCT) has attracted much attention for the therapeutic of GD. It is assumed that a small molecular can selectively bind to mutant enzyme in ER, and induce the correct folding of it, then promotethe lysosome-target translocation. Iminosugars are the first class of compounds exploited as pharmacological chaperones (PC)for the treatment of GD. *N*-nonyl-DNJ (NN-DNJ, **4**), one of the site-directed GCase inhibitors, which can lead to a 2-fold increase in the cellular activity of N370S GCase mutant at sub-inhibitory concentration. Modifications with a variety of functional groups at the endocyclic nitrogen of DNJ including the incorporation of amido or/and a sulfur atom (**5**, **6**), and the popular copper-catalyzed azide-alkyne cycloaddition (CuAAC)(**7**)in the alkyl chain [9,10], a vast series of derivatives have been screened as potential therapeutics for GD. As a part of our continuous efforts in the pharmacological chaperones for the treatment of GD, we have developed a series of excellent PCs such as C2-subsituted 3,3-dimethyl-*N*-phenyl-4-amide-1-butyl glucoimidazole [11] and *O*-(D-glucopyranosylidene) amino-*Z*-*N*-dodecylcarbamate [12], which gave 2.1-fold and 1.9-fold increase in N370S GCase mutant cell line, respectively (Figure 1).

Various synthetic methods have been developed to obtain 1-deoxynojirimycin **1** and its derivatives, some of which are starting with natural materials such as nojirimycin, L-sorbofurnose, aldohexoses and ketohexoses [13-17]. In addition, many biochemistry, microbiology and immunochemistry have been also employed to explore new synthetic methodology [18]. One of the most classic methods was reported by Carlos R. R. Matos and co-workers, they utilized 2,3,4,6-tetra-O-benzyl-α-glucopyranose as the starting material which was firstly reduced the hemik group with lithium aluminum hydride in THF, then Pftizner-Moffat oxidation of 1,5-diol to afford unstable 1,5-dicarbonyl which was cyclized in the presence of ammonium formate and sodium cyanoborohydride; Cleavage of protected group by treating with lithium/ammonia to furnish the desired compounds. While the above multistep chemical procedure was adequate for the laboratory limited by the unstable 1,5-dicarbonyl intermediate and the deprotected conditions. In 2011, Zhang reported a practical and facile method of double inversion mechanism for securing the stereochemistry at C5 position to synthesis of **2** [19]. Recently, another novel approach was explored to synthesize *N*-butyl-1-deoxynojirmycin **2**, 2,3,4,6-tetra-O-benzyl-D-glucono-δ-lactam was obtained from 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose by four-step reactions, followed by introduction of butyl group using *N*-alkylation reaction with n-butyl bromide in the presence of bases, however, both of the efficiency of introduction of n-butyl are not high [20,21]. Here we report an efficient and improved synthetic pathway to generate *N*-butyl-1-deoxynojirimycin.

Experimental

All reagents were purchased from commercially sources and were used without further purification. Reactions were monitored by Thin Layer Chromatography (TLC), which were visualized under 254 nm UV light and/or stained the TLC plate with a solution of 10% phosphomolybdic acid in ethanol. Flash columns chromatographies were performed by silica gel (100-200 mesh) with petroleum ether and ethyl acetate or dichloromethane and methanol as eluent. ^{1}HNMR and

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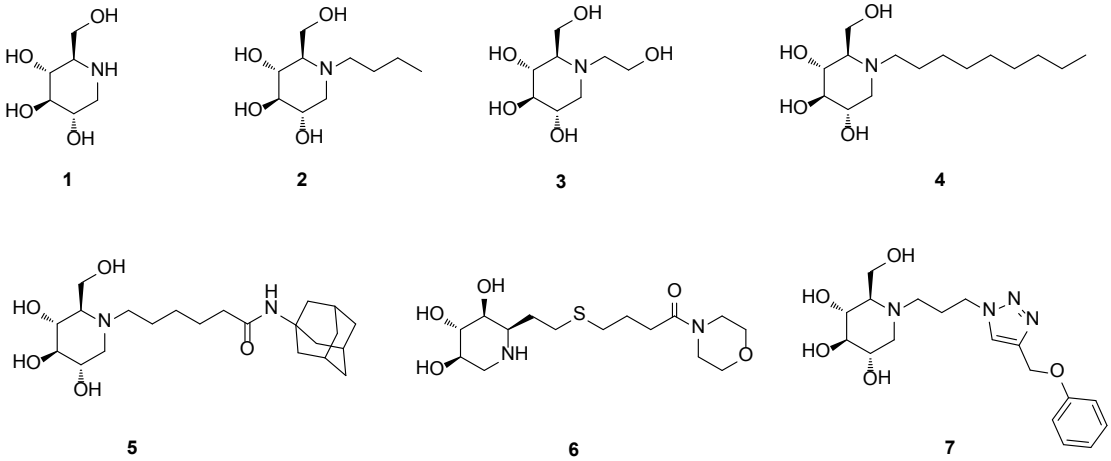
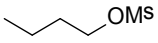


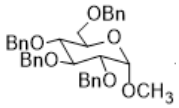
Figure 1: Structure of DNJ and representative derivatives.

^{13}C NMR experiments were recorded with Bruker AV 400 spectrometer at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR) using $CDCl_3$ or D_2O as solvents. The chemical shifts were recorded in part per million (ppm) relative to TMS and the coupling constants *J* were reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained on a Varian QFT-ESI mass spectrometer.



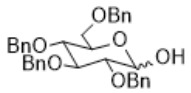
Butyl methanesulfonate(9)

To a solution of butanol (500 mg, 6.7 mmol) in dry CH_2Cl_2 (10 mL) pyridine (0.82 mL, 10.1 mmol) and MsCl (0.78 mL, 10.1 mmol) were added in sequence. The reaction was stirredat 0°C and allowed to warm to temperature. After 6 h, the mixture was quenched with MeOH and concentrated, then diluted with ethyl acetate (50 mL), washed with 1M HCl (10 mL), saturated $NaHCO_3$ (10 mL) and saturated brine (10 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by silica gel column chromatography to afford compound **2** as colorless oil (0.94 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (t, *J* = 13.2, 6.4 Hz, 2H), 3.01 (s, 3H), 1.76 – 1.72 (m, 2H), 1.48 – 1.42 (m, 2H), 0.96 (t, *J* = 12.8, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.99, 37.30, 31.05, 18.67, 13.48. HRMS (ESI) calcd for $[C_5H_{12}SO_3 + Na]^+$175.0405, found 175.0401.



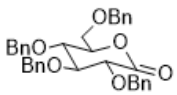
Methyl 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranoside (11)

To a solution of methyl α-D-glucopyranoside **10** (10.0 g, 51.5 mmol) in anhydrous DMF (30 mL) and the reaction mixture wascooled to 0 °C, then sodium hydride (12.4 g, 0.31 mol) and benzyl bromide (36.7 mL, 0.31 mol) were added successively. The mixture was then allowed to warm to room temperature. After 8h, the reaction was analyzed by TLC (petroleum ether/ethyl acetate = 5:1) whichindicating that the starting material was consumed and conversed to a major product. The reaction mixture was quenched with methanol, diluted with ethyl acetate (350 mL), the organic layer washed with water (100 mL), $NaHCO_3$ (100 mL) and saturated brine (100 mL) in sequence, then collected the organic layer and dried over anhydrous Na_2SO_4, the solvent was removed in vacuo and the residue was purified by flash column chromatography to give **11** (23.2 g, 81.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.18 (m, 18H), 7.14 -7.12 (m, 2H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.84 – 4.77 (m, 3H), 4.67 – 4.58 (m, 3H), 4.47 (d, *J* = 11.6 Hz, 2H), 3.98 (t, *J* = 9.2 Hz, 1H), 3.75 – 3.69 (m, 2H), 3.63 (d, *J* = 9.2 Hz, 2H), 3.56 (dd, *J* = 9.6, 3.6 Hz, 2H), 3.37 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 138.86, 138.32, 138.22, 137.98, 128.48, 128.39, 128.17, 128.00, 127.93, 127.87, 127.71, 127.61, 98.25, 82.17, 79.91, 77.73, 75.78, 75.05, 73.52, 73.42, 70.11, 68.55, 55.20. HRMS (ESI) calcd for $[C_{35}H_{38}O_6 + Na]^+$ 577.2566, found 577.2563.



2,3,4,6-Tetra-O-benzyl-D-glucopyranoside (12)

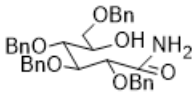
Methyl 2,3,4,6-tetra-O-benzyl-a-D-glucopyranoside **11**(15.2 g, 27.4 mmol) was dissolved in 80% AcOH (300 mL) and H_2SO_4 (75 mL), the solution was refluxed overnight and cooled to the warm temperature. The white solid was filtered and washed with 3×100 mL water, the white slide was dried by oil pump and afford the pure **12** as white solid (7.1 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 18H), 7.13 (m, 2H), 5.21 (d, *J* = 3.6 Hz, 1H), 4.93 (t, *J* = 11.2 Hz, 1H), 4.84 – 4.81 (m, 2H), 4.76 – 4.65 (m, 2H), 4.59 – 4.44 (m, 3H), 3.99 (t, *J* = 9.2 Hz, 1H), 3.69 – 3.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ138.74, 138.23, 137.94, 137.85, 128.56, 128.48, 128.45, 128.12, 128.05, 128.02, 127.95, 127.78, 127.70, 91.31, 81.81, 80.00, 77.80, 75.80, 75.09, 73.51, 73.24, 70.24, 68.63. HRMS (ESI) calcd for $[C_{34}H_{36}O_6 + Na]^+$ 563.2410, found 563.2412.



2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone (13)

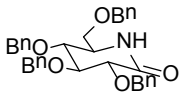
To a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranoside **12** (7.1 g, 13.1 mmol) in anhydrous DMSO was dropwise added acetic anhydride (26.8 mL, 0.26 mol), the mixture was stirred at room temperature overnight. The reaction was analyzed and showed the starting material was completely converted to a major product. The

mixture was diluted with diethyl ether (300 mL) and washed with water (8 × 100 mL), saturated brine (100 mL). The organic layer was collected and dried over anhydrous Na_2SO_4, after removing solvent, the crude product was purified by silica gel column chromatography and get 2,3,4,6-Tetra-*O*-benzyl-D-gluconolactone **13** as colorless oil (6.4 g, 92%). ^{1}H NMR (400 MHz, DMSO)δ7.36 - 7.22 (m, 20H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.72 – 4.60 (m, 5H), 4.56 – 4.44 (dd, *J* = 20.8, 11.6 Hz, 3H), 4.37 (d, *J* = 6.4 Hz, 1H), 4.02 (t, *J* = 11.6, 5.6 Hz, 1H), 3.89 (t, *J* = 13.2, 6.6 Hz, 1H), 3.73 – 3.67 (m, 2H); ^{13}C NMR (100 MHz, DMSO)δ 169.08, 137.86, 137.82, 137.61, 137.50, 128.25, 127.87, 127.80, 127.75, 127.72, 127.67, 127.58, 79.61, 77.58, 77.39, 75.30, 72.74, 72.38, 72.30, 68.30. HRMS (ESI) calcd for $[C_{34}H_{34}O_6 + Na]^+$ 561.2253, found 561.2254.



2,3,4,6-Tetra-*O*-benzyl-D-gluconamide (14)

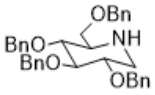
2,3,4,6-tetra-O-benzyl-D-gluconolactone **13**(6.4 g, 10 mmol) was dissolved in saturated methanolic ammonia and the reaction was stirred at 0 °C for 3 h. TLC analysis indicated that the starting material was completely consumed. The solvent was removed in vacuo and the crude product was purified by column chromatography (petroleum ether/ ethyl acetate = 5:1), affording 2,3,4,6-Tetra-O-benzyl-D-gluconamide **14** as colorless oil (6.4 g, 96%). ^{1}H NMR (400 MHz, DMSO) δ 7.50 (d, *J* = 7.0 Hz, 2H), 7.41 (d, *J* = 6.7 Hz, 2H), 7.37 – 7.19 (m, 16H), 5.09 (d, *J* = 5.6 Hz, 1H), 4.72-4.64 (m, 4H), 4.50 – 4.45 (m, 4H), 4.09-4.05 (m, 2H), 3.70 - 3.63 (m, 2H), 3.53 (dd, *J* = 10.0, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 172.56, 138.91, 138.88, 138.48, 137.87, 128.22, 128.18, 128.06, 128.01, 127.83, 127.66, 127.60, 127.38, 127.31, 127.25, 81.83, 80.36, 79.66, 73.57, 72.40, 71.72, 69.84. HRMS (ESI) calcd for $[C_{34}H_{37}NO_6 + Na]^+$ 578.2519, found 578.2518.



2,3,4,6-Tetra-*O*-benzyl-D-gluconolactam (16)

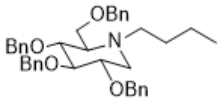
To the solution of Compound **14** (6.4 g, 11.5 mmol) in anhydrous DMSO was added acetic anhydride (21.7 mL, 0.23 mol), the solution was stirred at room temperature for 6h and analyzed by TLC which indicating that the starting material was completely consumed. The mixture was diluted with diethyl ether (300 mL) and washed with water (6 × 100 mL), saturated brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, the crude product **15** was directly used for next step without further purification.

A solution of compound **15** (11.5 mmol) and $NaCNBH_3$ (1.4 g, 23.0 mmol) in $CH_3CN$was dropwise added formic acid (25.8 mL, 0.68 mol), the reaction was refluxed for 3h and allowed to cool to room temperature. The reaction was quenched with 100 mL saturated $NaHCO_3$ and continuously stirred for 15 min. The aqueous was extracted with ethyl acetate (150 mL)and the organic layer was washed with saturated brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure. Purification by flash chromatography to afford compound **16** as white solid (2.96 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.35 – 7.24 (m, 16H), 7.18 (m, 2H), 5.97 (s, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 4.84 (dd, *J* = 11.2, 7.6 Hz, 1H), 4.75 (dd, *J* = 17.2, 11.2 Hz, 1H), 4.52 – 4.33 (m, 3H), 4.00 (d, *J* = 8.0 Hz, 1H), 3.91 (t, *J* = 8.0 Hz, 1H), 3.55 (m, 3H), 3.26 (t, *J* =16.8, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.61, 138.13, 137.95, 137.67, 137.37, 128.68, 128.60, 128.54, 128.50, 128.27, 128.14, 128.01, 127.93, 82.45, 78.93, 77.22, 74.88, 74.76, 73.46, 70.15, 53.89. HRMS (ESI) calcd for $[C_{34}H_{35}NO_5 + Na]^+$ 560.2413, found 560.2406.



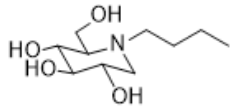
2,3,4,6-Tetra-O-benzyl-1-deoxynojirimycin (17)

To a solution of **16** (2.96 g, 5.5 mmol) in 100 mL anhydrous THF was slowly added $LiAlH_4$ (314 mg, 8.2 mmol) and the mixture was refluxed for 3 h. TLC analysis showed that starting material was consumed completely (Petroleum ether/ ethyl acetate = 5:1, Rf = 0.30), after cooling to room temperature, the mixture was poured into diethyl ether/ water (V/V = 1/1, 500 mL) and continuously stirred for 15 min. The aqueous was filtered and extracted with diethyl ether 300 mL, the organic layer was washed with water (100 mL) and saturated brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated, the resulting residue was purified by silica gel column chromatography to afford **17** as white solid (2.2 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 18H), 7.19 (m, 2H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.85 (t, *J* = 10.4 Hz, 2H), 4.68 (dd, *J* = 16.0, 11.6 Hz, 1H), 4.51 – 4.40 (m, 3H), 3.66 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.59 – 3.45 (m, 3H), 3.35 (t, *J* = 9.2 Hz, 1H), 3.24 (dd, *J* = 12.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.94, 138.53, 138.42, 138.02, 128.48, 128.45, 128.09, 128.02, 127.93, 127.85, 127.82, 127.74, 127.60, 87.39, 80.71, 80.14, 75.75, 75.26, 73.44, 72.84, 70.33, 59.78, 48.19. HRMS (ESI) calcd for $[C_{34}H_{37}NO_4 + Na]^+$ 546.2620, found 546.2621.



2,3,4,6-Tetra-O-benzyl-*N*-butyl-1-deoxynojirimycin (18)

To a solution of **17**(500 mg, 0.95 mmol) and 4-methylsulfonybutane **9** (218 mg, 1.43 mmol) in CH_3CN (5 mL) was added potassium carbonate (262.2 mg, 1.9 mmol). The reaction mixture was refluxed for 24 h under an argon atmosphere then cooled. Most of the solvent was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2(50 mL) and washed withwater (25 mL), saturated brine (25 mL) in sequence. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel to afford **18** as a white solid (506 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 18H), 7.06 – 7.04 (m, 2H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.77 (dd, *J* = 23.6, 10.8 Hz, 12H), 4.60 (d, *J* = 5.4 Hz, 2H), 4.40 (dd, *J* =15.2, 12.4 Hz, 2H), 4.33 (d, *J* = 10.8 Hz, 1H),3.62 – 3.42 (m, 1H), 3.38 (t, *J* = 9.1 Hz, 1H), 3.02 (m, 1H), 2.61 – 2.51 (m, 2H), 2.23 – 2.13 (m, 2H), 1.15 (m, 4H), 0.79 (t, *J* = 14.4, 7.2 Hz, 3H);^{13}C NMR (400 MHz, $CDCl_3$) δ 139.06, 138.59, 137.82, 128.50, 128.41, 128.36, 128.03, 127.90, 127.78, 127.67, 127.57, 127.47, 87.42, 78.61, 75.35, 75.23, 73.50, 72.79, 65.21, 63.69, 54.49, 52.13, 25.61, 20.70, 14.05. HRMS (ESI) calcd for $[C_{38}H_{45}NO_4 + H]^+$580.3427, found 580.3420.



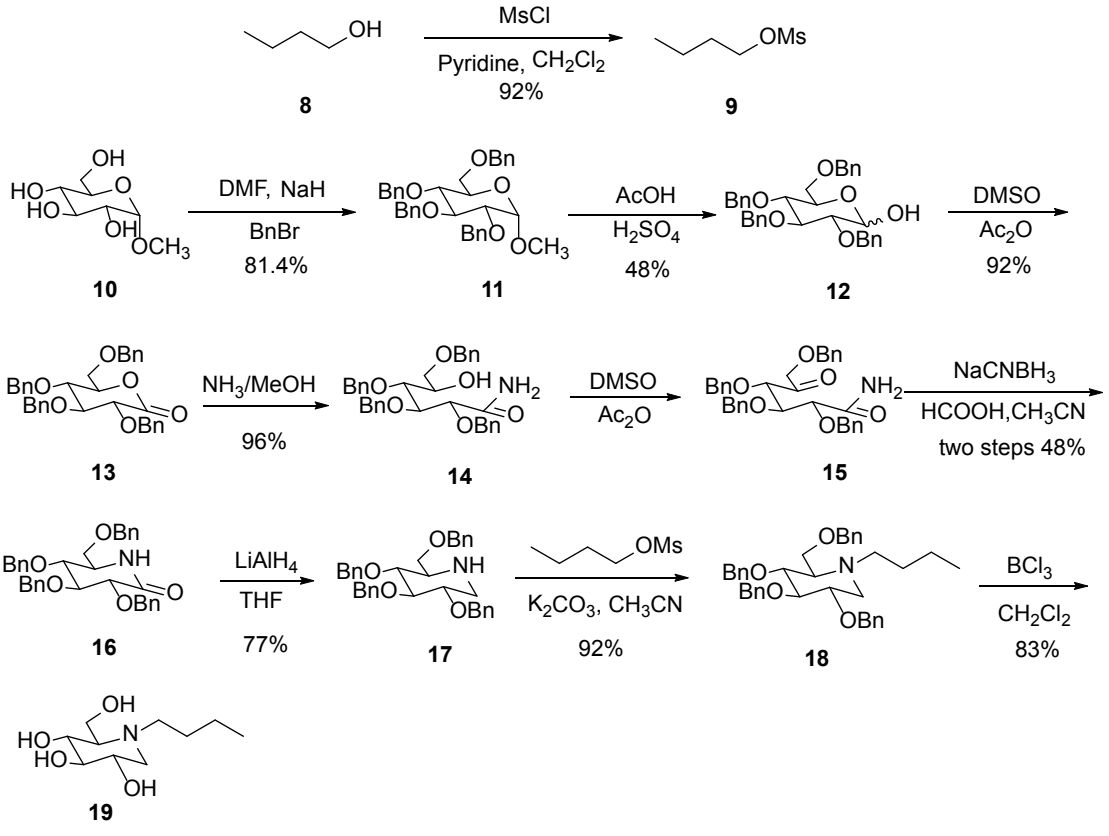
N-butyl-1-deoxynojirimycin (19)

A solution of BCl_3 (1 M in hexane) (5 mL) was added slowly to a stirred solution of **18** (200 mg, 0.34 mmol) in dry CH_2Cl_2(10 mL). The reaction was stirred at -78 °C overnight and then quenched by addition of MeOH (5 mL). The solvent was removed and the residue was purified by flash chromatography to afford the target compound *N*-butyl-1-deoxynojirimycin **19** as white solid (62.8 mg, 83%). ^{1}H NMR (400 MHz, D_2O) δ 4.05 (d, *J* = 13.2, 1H), 3.92 (t, *J* = 13.2, 2.8 Hz, 1H), 3.73 – 3.67 (m, 1H), 3.59 (t, *J* = 10.0 Hz, 1H), 3.53 (dd, *J* =12.4, 4.8 Hz, 1H), 3.44 (t, *J* = 9.2 Hz, 1H), 3.03 – 2.97 (m, 1H), 3.16 (dd, *J* =12.0, 5.6 Hz, 1H), 3.11 (dd, *J* =9.8, 2.4 Hz, 1H), 3.02 (t, *J* = 11.6 Hz, 1H), 1.65 - 1.63 (m, 1H), 1.32 - 1.29 (m, 1H), 0.82 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.82, 67.12, 66.13, 65.25, 53.07, 53.04, 24.29, 19.25, 12.75. HRMS (ESI) calcd for $[C_{10}H_{21}NO_4 + H]^+$ 220.1549, found 220.1544.

Results and Discussion

A successful and novel synthetic strategy of *N*-butyl-1-deoxynojirimycin was outlined in Scheme 1. Initially, *N*-butanol was modified with methylsulfonyl chloride to generate active *N*-butyl methanesulfonate **9**, which will be used follow-up; Commercially available methyl α-D-glucopyranoside **10** was first subjected to BnBr and NaH to form per-benzylation compound **11**, followed by hydrolysis of the glycosidic bond in the presence of $AcOH/H_2SO_4$, then the hydroxyl of **12** was oxidized through Swern oxidation. After ammonolyzation with methanolic ammonia, **14** was subjected to Swern oxidation again to generate the corresponding keto amide **15**, which was cyclization under the reduced conditions of formic acid and sodium cyanoborohydride to afford the intermediate lactam **16**. The carbonyl of lactam was reduced by treating with $LiAlH_4$ to yield the 2,3,4,6-tetra-O-benzyl-1-deoxynojirimycin **17**, and then the nitrogen of **17** attacked the secondary carbon linked with methanesulfonateof **9** in the presence of K_2CO_3 to afford the benzyl protected NB-DNJ **18** in high yield 92%. Cleavage the protected benzyl groupsunder the conditions of BCl_3 to provide the desired compound NB-DNJ **19** (Scheme 1).

The improvement of this synthetic method, herein, is similar to but different from the reported procedures [20,21]. During the step of introducing *N*-butyl, Zhang utilized *N*-butyl bromide to react with 2,3,4,6-tetra-O-benzyl-1-deoxynojirimycin, after the reduction of carbonyl, to afford the 2,3,4,6-tetra-*O*-benzyl-*N*-butyl-1-deoxynojirimycin in low yield 39%, the yields of this two steps was only 24.5% [20]. The reasons may be attributed to thatthe product as a tertiary amine has similar activities to the imine structure, which may further react to form quaternary ammonium salt. Moreover, Qin introduced the *N*-butyl to the iminosugar prior to the reduction of carbonyl, the yield of this key step can be increased to 53% after reduction with $LiAlH_4$, which was twice as much as the former [21]. Compared to the reported procedures, we improved the yield of *N*-butylationwith the high leaving activity of methylsulfonyl group after the carbonyl reduced, which can be effectively coupled with the iminosugar without any byproducts. This two steps yield was 70.8%, which was much higher than the other two. In addition, **16** was also attempted to react directly with *N*-butyl methanesulfonate **9**, leading to 2,3,4,6-tetra-O-benzyl-*N*-butyl-gluconolactamwith a low yield. It can beconcluded that the nucleophilicity of nitrogen was increased after the reduction of carbonyl.



Scheme 1: The improved synthetic route of *N*-butyl-1-deoxynojirimycin.

Conclusion

In conclusion, we have developed an efficient total-synthesis route for *N*-butyl-1-deoxynojirimycin, which is an effective therapeutic for a number of lysosomal storage diseases. This new method provides an alternative procedure for the synthesis of NB-DNJ, which can be applied to the generation of other *N*-alkyl chain DNJ analogues such as NN-DNJ from the easily available tetra-*O*-benzyl DNJ. Overall, the current work contributes tohigh yield and large scale library generation of *N*-alkyl substituted DNJ for biomedical field.

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