

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

An alternative route for the synthesis of *N*-substituted iminosugar derivative, miglitol

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Received 22 May 2012; Accepted 28 June 2012

Keywords: Methyl-D-glucose; iminosugar; antidiabetic; miglitol; synthesis

Abstract: An alternative synthesis of glucosylceramide synthase inhibitor miglitol, *N*-[2-hydroxyethyl]-1-deoxynojirimycin is described. Herein we report the development of new process for the synthesis of miglitol from dicarbonyl derivative **5**, which also includes improved process for the synthesis of dicarbonyl derivative **5** from methyl-D-glucose **1**. The described route enables the synthesis of miglitol with high purity (>99.97%).

Introduction

Coinciding with obesity, type 2 diabetes has reached epidemic proportions worldwide and Insulin resistance is one of the earliest detectable abnormalities during the development of type II diabetes. The precise cause for the rapidly increasing occurrence of insulin resistance has not been firmly established, but there is growing evidence that obesity and associated lipotoxicity play a crucial role.^[1,2] *N*-nonyl and *N*-hydroxyethyl (Miglitol, **7**) of nojirimycin have become pharmaceutical agents in the treatment of diabetes type II symptoms and

other metabolic disorders including Gaucher's disease.^[3] Miglitol (**7**) is used, alone or with other drugs, to treat type-2 diabetes in people whose diabetes cannot be controlled by diet alone. It slows down the breakdown and adsorption of table sugar and other oligosaccharides in the small intestine, therefore resulting in lowered blood sugar levels following meals. It acts as a competitive inhibitor of α -glucosidases, and in addition **7** suppresses the postprandial increase in interleukin-6 and increases active glucagon-like peptide 1 secretion.

Up to date, several methods designed pleasingly in literatures for the synthesis of iminosugars. For example, Ye and co-workers have recently described the synthesis of *N*-substituted δ -lactams using

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the glucosyl alkene as a key intermediate.^[4,5] In the meantime, Yu et al. have established the efficient assembly of the bicyclic iminosugar analogs *via* a common D-ribose-derived cyclic nitron intermediates.^[6] After Junge *et al.*^[7] have obtained **7** and disclosed its diabetes, hyperlipaemia or adiposity effects, it has been synthesized by a variety of methods. Kinast *et al.*^[8] obtained **7** from 6-hydroxyethylamino-L-sorbose hydrochloride through hydrogenation. Koebernick^[9] described a synthesis of **7** from 6-[(2-hydroxyethyl)-amino]-6-deoxy-L-sorbose hydrochloride with dimethylaminoborane in the presence of triethylamine and water. Schroder *et al.*^[10] described a process for the preparation of **7** which involves reacting *N*-formyl-*N*-hydroxyethyl-6-amino-6-deoxy-L-sorbose in water with NaOH in water and adding a solution of sodium boronate in water. Further, it also describes a process for the preparation of **7** which involves reacting *N*-dichloroacetyl-*N*-hydroxyethyl-6-amino-6-deoxy-L-sorbose in water with NaOH in water and adding a solution of sodium boronate in water. We herein report a new, facile route to **7** that enables its safe and rapid manufacture of **7**.

Results and Discussion

Schmidt *et al.*^[11] disclosed the preparation of a useful synthetic intermediate, 2, 3, 4, 6-tetra-*O*-benzyl- α -D-glucopyranose (**3**). The entire process of preparing **3** from methyl glucoside was significantly improved by us, in comparison with precedented approaches.^[12-16] In detail, the benzylation with NaH and BnCl in DMF was incomplete. We have successfully employed a modified version of this procedure for the synthesis of **3**. Intermediate **1** was benzylation quantitatively with BnCl in the presence of NaH in DMSO at 20-25 °C,

after the workup, crude **2** was demethylated using acetic acid and 2 N HCl. Solid was isolated by filtration to provide **3** as a white solid in 63% yield.

Matos and co-workers prepared **2**, **3**, **4**, 6-tetra-*O*-benzyl-1-deoxynojirimycin **6** from **3** in four steps^[13] in irreproducible and low yields. In our approach, intermediate **3** was reduced quantitatively with NaBH₄ in refluxing dichloromethane/methanol. Usual methods for the preparation of intermediate **6** from intermediate **4** are four steps process i.e. oxidation of diol **4** to dicarbonyl **5** followed by treating with corresponding carbonyl compound to provide imine and then reduction of imine to lead intermediate **6**. Based on the viewpoint to avoid these undesired processes in their syntheses, here we introduce a short and practicable synthetic pathway of intermediate **6** from diol **4**. Miglitol obtained from this intermediate **6** was characterized and found to be identical with the reference sample.^[17]

In another embodiment, we have also synthesized following related substances, (2*S*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-piperidine-3,4,5-triol (L-taro miglitol, **10**) and (2*R*,3*S*, 4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl)-piperidine-3,4,5-triol (*galacto* miglitol, **18**). Related substance **10** was prepared starting from benzyl protected diol **4**. Diol **4** was first converted into its dimesylate **8** and subsequently it was treated with aminoethanol to get benzyl protected miglitol **9**. Two nucleophilic substitutions are required to convert **8** into **9** and nucleophilic substitution at C-2 would follow an SN² mechanism which would lead to inversion of the stereochemistry (Scheme-2). A related substance **18** was prepared following miglitol synthetic pathway starting with *galactose* **11**. Structure of **11** is similar to D-glucose except stereochemistry at C-6 (Scheme-3).

Conclusion

N-substituted iminosugar derivative **7** was synthesized by facile and new route, and drug obtained by this process is substantially free from impurities (>99.97%). Similar synthetic pathway was also applied to prepare *L-taro* miglitol, **10** and *galacto* miglitol, **18**.

Experimental Section

General Methods

All solvents and reagents were obtained commercially and used as received unless stated otherwise. The reactions were monitored with analytical TLC on Silica Gel 60-F254-precoated aluminum plated and visualized under UV (254 nm) and/or by staining with KMnO₄ solution. NMR spectra were recorded on a Varian Gemini FT NMR (400 MHz) spectrometer. The mass analyses were performed on AB-4000 Q-trap LC-MS/MS mass spectrometer. Optical rotations were measured with a JASCO P-1030 digital polarimeter at 25 °C. Miglitol and its impurities were analyzed (Waters with empower software Binary pump, waters 2489 variable wavelength detector, Germany) with a waters spherisorb amino column, 150 mm × 4.6 mm, 3 μm (GL Sciences Inc., Japan), with mobile phase consisting of 0.02 M NH₄H₂PO₄ and acetonitrile in the ratio of 25:75 with a flow rate of 1.0 mL/min, and UV detection at 220 nm was used with a timed isocratic program.

2, 3, 4, 6-tetra-*O*-benzyl-*D*-glucose (**3**)

To a suspension of NaH (50 g, 2.08 mol) in Me₂SO (350 mL) was added a solution of methyl-*D*-glucose (**1**, 50 g, 0.257 mol) and BnCl (128.6 mL, 1.16 mol) in Me₂SO (250 mL) over a period of 2 h at 25-30 °C. The

resulting suspension was stirred at 20-25 °C and the progress of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was quenched by careful addition of MeOH (100 mL) followed by 0.75 N HOAc (500 mL). After the addition, the mixture was vigorously stirred for 30 min, whilst evacuating the remaining hydrogen gas with a nitrogen flow. Aq. layer was extracted with the solvent EtOAc and resultant organic layer was washed with 10% NaCl (500 mL) solution. Organic layer was concentrated under reduced pressure to produce **2** as colorless oil in quantitative yield. A solution of 2 N HCl (375 mL) was slowly added to a heated (80-85 °C) solution of **2** in acetic acid (2250 mL). The resulting mixture was stirred for 60-90 min at 80-85 °C, whereupon a solution of 2N HCl (375 mL) was slowly added. The suspension was stirred for 60-90 min at 80-85 °C and another an hour whilst cooling at 0-10 °C. The product was isolated by filtration, washed with water (100 mL) and dried under vacuum at 60-65 °C to afford **3** as an off-white solid (88.2 g, 63%).

Mp 149-149.5 °C; [α]_D²⁰ +48 (*c* = 1 in dioxane); FT IR (KBr) 3395, 3029, 1742, 1087, 1073 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.13 (m, 20H), 5.23-5.22 (s, 1H), 4.96-4.46 (m, 8H), 4.07-3.99 (m, 2H), 3.72-3.53 (m, 5H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 29.6, 68.6, 68.9, 70.3, 73.2, 73.5, 74.7, 74.8, 74.9, 75.6, 76.6, 77.0, 77.3, 77.7, 77.8, 80.0, 81.7, 83.1, 84.5, 91.3, 97.5, 127.5, 127.6, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 137.8, 137.9, 138.2, 138.3, 138.5, 138.7; MS (ESI, +ve) 563.2 (M⁺+Na); Purity by HPLC 98%.

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

To a suspension of **5** (50 g, 0.09 mol) in CH₂Cl₂ (500 mL) was added NaBH₄ (8.55 g, 0.23 mol) at 25-35 °C and the resulting suspension was heated to reflux (36-40 °C),

and then MeOH (150 mL) was added carefully. The reaction mixture was stirred for 2-3 h at reflux. Reaction mass was cooled to 25-35 °C and rest of the hydrogen gas was evacuated with a nitrogen flow. The reaction was quenched by careful addition of 2N HCl (100 mL) under vigorous stirring over a period of 2 h. After the addition, the mixture was vigorously stirred for 30 min, whilst evacuating the remaining H₂ gas with a nitrogen flow. The organic phase was separated and concentrated at 30 °C under reduced pressure to produce **4** (50 g, 99%) as a colorless oil in quantitative yield.

FT IR (KBr) 3449, 3030, 1453, 1090, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.19 (m, 20H), 4.71 (d, *J* = 11.3 Hz, 1H), 4.68–4.47 (m, 7H), 4.07–3.99 (m, 1H), 3.89 (dd, *J* = 3.7, 6.4 Hz, 1H), 3.82–3.68 (m, 3H), 3.68–3.60 (m, 2H), 3.60–3.52 (m, 1H), 2.98 (d, *J* = 4.9 Hz, 1H), 2.17 (s, 1H); MS (ESI, positive) 565.2 (M⁺+Na); Purity by HPLC 97%.

2, 3, 4, 6-Tetra-*O*-benzyl-*N*-[2-hydroxyethyl]-1-deoxynojirimycin (**6**)^[17]

A solution (water content by KF < 0.05%) of Me₂SO (76 mL, 0.97 mol) in CH₂Cl₂ (250 mL) was slowly added to a cooled (-75 °C) solution of oxalylchloride (72 mL, 0.79 mol) in CH₂Cl₂ (250 mL; water content by KF < 0.03%) so the internal temperature of the reaction mixture did not exceed -65 °C. The resulting mixture was stirred for 30 min at -75 °C, whereupon a solution of **4** (100 g, 0.18 mol) in CH₂Cl₂ (250 mL) was slowly added so the internal temperature of the reaction mixture did not exceed -65 °C (**4** was dried by azeotropic distillation with CH₂Cl₂ until water content <0.03%). After addition of **4**, the reaction mixture was stirred for 2 h at -75 °C after which Et₃N (270 mL, 1.97 mol) was slowly added so the

internal temperature of the reaction mixture did not exceed -65 °C. The resulting suspension was stirred for 4 h at -75 °C and then transferred to a cooled (0-5 °C) mixture of ethanolamine (113.4 mL, 1.85 mol), Na₂SO₄ (110 g, 0.77 mol) and NaBH₃CN (46 g, 0.74 mol) in methanol (1000 L). The reaction mixture was stirred for 18 h at 25-30 °C and allowed to warm to 20-25 °C. The reaction mixture was cooled to 5–10 °C water (400 mL) was added slowly over a period of 30 min, so the internal temperature of the mixture did not exceed 35 °C. An aqueous NaOH (147.5 mL, 50 wt %) solution was added to the mixture followed by addition of water (375 mL) over a 1 h period (*T* < 35 °C). The two-phase mixture was stirred for 1 h at 18–25 °C after which the organic phase was isolated. The aqueous phase was back-extracted once with CH₂Cl₂ (625 mL). The combined organic phases were cooled to 5–10 °C, and under vigorous stirring an aqueous NaOCl solution (1048 mL, 12 wt %) was added over a 1 h period (*T* < 35 °C). The two-phase reaction mixture was vigorously stirred for 1 h at 18-25 °C and then the organic phase was separated and concentrated to dryness. Water (400 mL) was added to the residue, and the mixture was vigorously stirred (*T* < 35 °C) for 1 h at ambient temperature. The product was isolated by filtration, washed with water (100 mL) and dried under vacuum at 35–40 °C to afford **6** (73.2 g, 70%) as an off-white solid.

FT IR (KBr) 3448, 3030, 2913, 2871, 1454, 1095, 1071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.9 (br s, 1H), 9.2 (br s, 1H), 7.40–7.28 (m, 18H), 7.15–7.13 (m, 2H) 4.86 (d, *J* = 11.2 Hz, 1H) 4.76–4.44 (m, 7H), 3.88–3.593 (m, 5H), 2.9 (t, *J* = 11.6 Hz, 1H); MS (ESI, positive) 524.4 (M⁺+1); Purity by HPLC 97%.

N-[2-hydroxyethyl]-1-deoxynojirimycin (7)

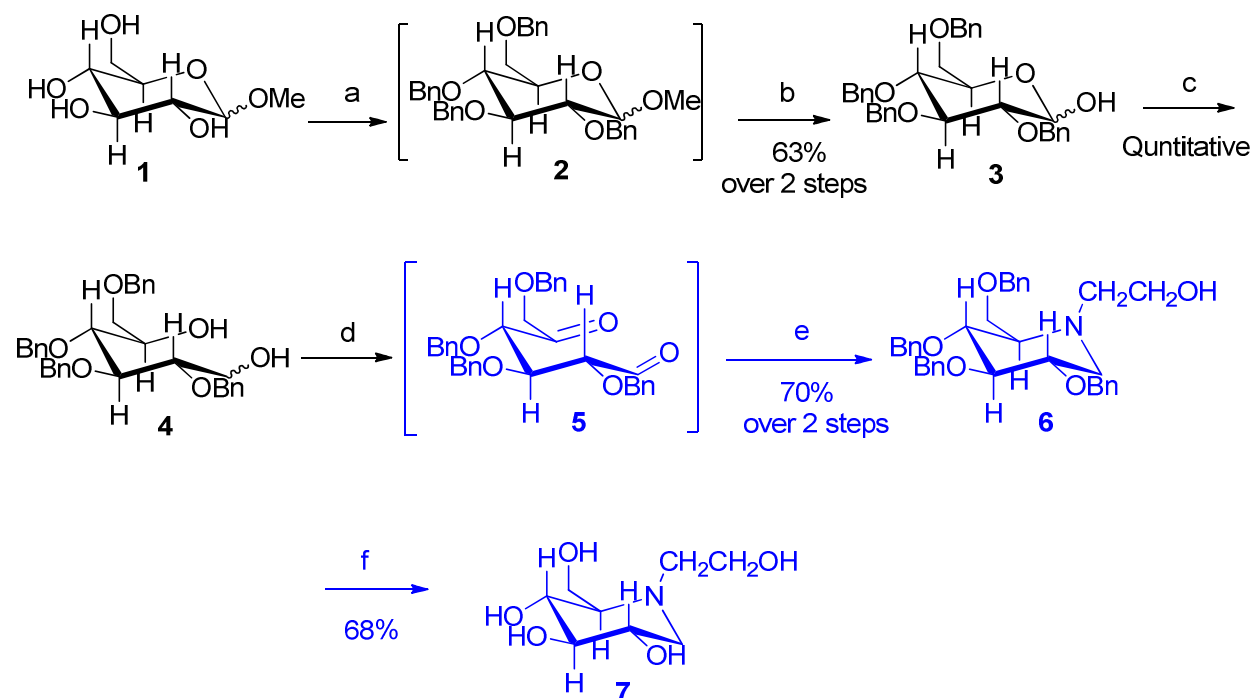
To a solution of **6** (150 g, 0.26 mol) in EtOH(1800 mL) was added 6 M HCl (70 mL) at 5-10 °C to produce a clear solution. Palladium on charcoal (30 g, 10% Pd-C 50 % wet) was added to the solution and the resulting suspension was hydrogenated in autoclave at 5 kg/cm² pressure for about 20-24 h. The progress of the reaction mass was determined by HPLC analysis. After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure and chased with the mixture of MeOH (75 ml) and acetone (750 mL). The brown oily residue obtained was purified by T-57 resin. The product was eluted with 6.2% liquid NH₃ and then ammonia solution was evaporated to get **7** as a residue. A mixture of **7** and methanol (750 mL) was heated to 60-65 °C and then was cooled to 5-10 °C. Product was separated by filtration

at 5-10 °C and dried at 60 °C to yield pure **7** (37.2 g, 68%).

Mp (DSC) 144.5 °C; $[\alpha]_{\text{D}}^{20} = -7.4$ ($c = 2.4$ in H₂O) (lit.:^[17] $[\alpha]_{\text{D}}^{22} = -7.7$ ($c = 0.26$ in H₂O)); FT IR (KBr) 3365, 3279, 1454, 1075, 1034 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 4.74-4.67 (m, 3H), 4.54-4.52 (m, 1H), 4.22-4.19 (m, 1H), 3.75-3.71 (m, 2H), 3.59-3.53 (m, 1H), 3.46-3.38 (m, 1H), 3.07-3.01 (m, 1H), 2.94-2.81 (m, 3H), 2.51-2.34 (m, 1H), 2.07-1.97 (m, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 79.21, 70.55, 69.27, 66.85, 58.71, 58.55, 57.81, 53.79; MS (ESI, positive) 208 (M⁺+1). Purity by HPLC 99.99%.

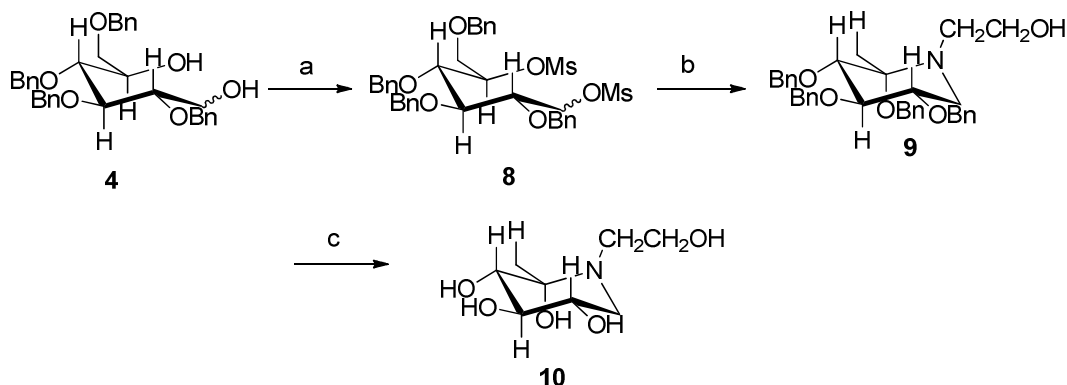
Acknowledgements

The authors are grateful to the colleagues of analytical research department of IPDO, discovery research and the management of Dr. Reddy's Laboratories Ltd. for providing necessary support.



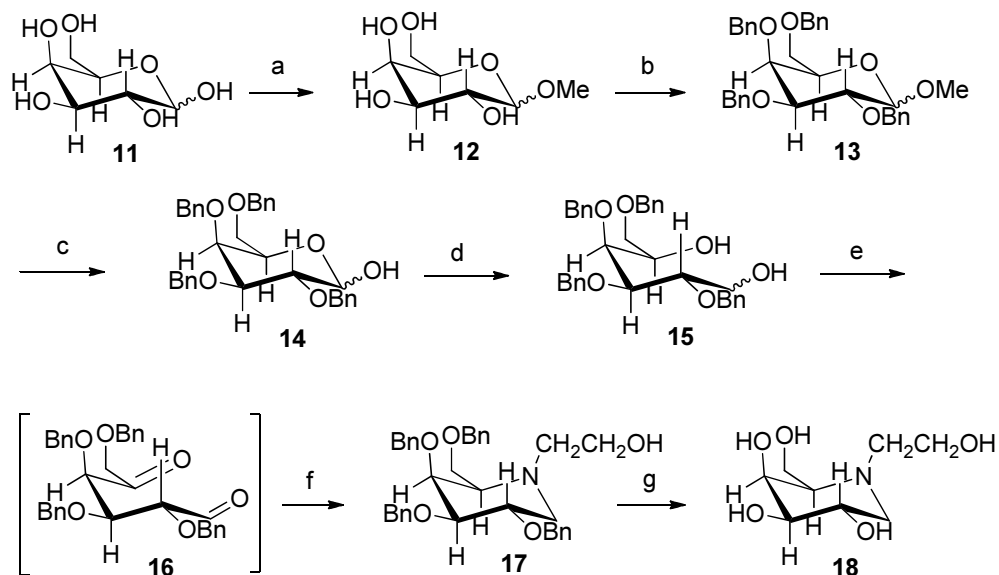
Scheme 1. Synthesis of Miglitol

Reagents and conditions: (a) BnCl, NaH, DMSO, 25 °C; (b) HCl, AcOH, 85 °C; (c) NaBH₄, MeOH:DCM, 40 °C; (d) DMSO, (COCl)₂, Et₃N, -78 °C; (e) NaBH₃CN, NH₂CH₂CH₂OH, MeOH, 0 °C to rt; (f) Pd-C, H₂, EtOH, T-57 Resin, MeOH, NH₄OH.



Scheme 2. Synthetic scheme for the synthesis of L-taro miglitol

Reagents and conditions: (a) MsCl, Et₃N, DCM, 25 °C, 94%; (b) NH₂CH₂CH₂OH, 45 °C, 78%; (c) Pd-C, H₂, EtOH, T-57 Resin, MeOH, NH₄OH.



Scheme 3. Synthesis of galacto miglitol

Reagents and conditions: (a) 11% HCl in MeOH, 65 °C, 14 h, Quantitative; (b) BnCl, NaH, DMSO, 25 °C, 95%; (c) 2N HCl, AcOH, 85 °C, 35%; (d) NaBH₄, MeOH:DCM, 40 °C, 96%; (e) DMSO, (COCl)₂, Et₃N, -78 °C; (f) BrCH₂CH₂OH, Et₃N, DCM, 50 °C DCM, 55%; (g) Pd-C, H₂, EtOH, T-57 Resin, MeOH, NH₄OH.

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