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PII: S0008-6215(16)30282-8

DOI: 10.1016/j.carres.2016.08.003

Reference: CAR 7243

To appear in: *Carbohydrate Research*

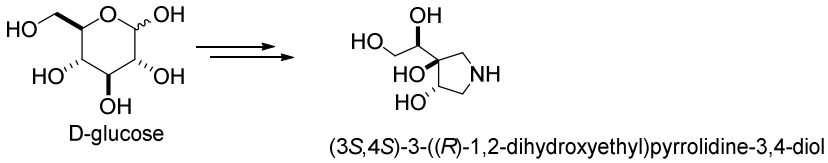
Received Date: 9 April 2016

Revised Date: 26 July 2016

Accepted Date: 2 August 2016

Please cite this article as: E. Zhang, P.-Y. Bai, W. Sun, S. Wang, M.-M. Wang, S.-M. Xu, H.-M. Liu, Synthesis and glycosidase inhibition evaluation of (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol, *Carbohydrate Research* (2016), doi: 10.1016/j.carres.2016.08.003.

Graphical abstract



A new azasugar isomer (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol was obtained from D-glucose in ten steps and 24.3% overall yield using one-pot reduction cyclization as the key step. Only three column chromatography purifications were needed in this synthesis. Biological activity evaluation as inhibitor against glycosidase were studied but the results were not ideal.

Synthesis and glycosidase inhibition evaluation of (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol

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Abstract

A new azasugar (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidine-3,4-diol (**1**) was obtained from commercially available D-glucose using one-pot reductive cyclization as a key step. The target product, i.e., the iminosugar isomer, was obtained in 10 steps and 24.3% overall yield. Only three column chromatography purifications were needed in this synthesis. The biological activity of the target molecule as glycosidase inhibitor was studied, but the inhibitory activity against four glycosidases was not good ($IC_{50} > 100$ μM).

Keywords*:* Azasugar, One-pot reaction, Reductive cyclization, Isomer

1. Introduction

Many sugars with the ring oxygen replaced by nitrogen, i.e., azasugars or iminosugars,[1] occur widely in plants and microorganisms.[2] Azasugars are carbohydrate analogs in which the anomeric hydroxyl group has been preserved or removed, and they include polyhydroxylated pyrrolidines and piperidines.[3]

Iminosugars are potent inhibitors of common carbohydrate-processing enzymes and have significant glycosidase and glycosyltransferase inhibitory activities.[4] Glycosidases and glycosyltransferases participate in sugar processing and synthesis. It is therefore important to study and develop compounds that inhibit glycosidases. Glycosidase inhibitors have attracted much attention because they are potentially antidiabetic,[5] antiviral,[6] and anticancer agents,[7] and they have potential in obesity therapy.[5] Recently, many novel glycosidase inhibitors used in herbal medicine, including polysaccharides, alkaloids, glycosides and polypeptides, have been screened.[8] Because of their important biological activities and potential applications, the study of azasugars and their derivatives has become an important research topic in organic and pharmaceutical chemistry.[9] Recent studies have shown that azasugars can be used to treat a wide range of conditions, including diabetes, viral infections, tumor metastasis, lysosomal storage disorders and cystic fibrosis.[10, 11]

As a result from their potent inhibitory activities, a large number of natural and non-natural structural analogs have been prepared and tested as therapeutically potent inhibitors. Chiral carbohydrate or non-sugar compounds are useful for studying

azasugar synthesis.[12]

Some azasugars are used as drugs, e.g., *N*-hydroxyethyl **DNJ** (miglitol, Fig. 1)[13] and **NB-DNJ** (miglustat, Fig. 1)[14] are widely used in clinical practice for the treatment of type-II diabetes and Gaucher's disease (a severe genetic disease caused lysosomal storage disorder), respectively. The galactofuranose pyrrolidine analog **2**, which is an inhibitor of UDP-Gal mutase and intervenes in the biosynthesis of mycobacterial galactan, has been obtained.[15] The synthesis and biological evaluation of new inhibitors (**3** and **4**, Fig. 1) of UDP-Galf transferase, which is a significant enzyme in *Mycobacterium tuberculosis* cell wall biosynthesis, have been reported;[16] ring-closing metathesis reactions were the key step in generating novel compounds. A considerable number of nitrogen-containing azasugar isomers have attracted attention because of their importance as glycosidase inhibitors. Polyhydroxylated piperidines are excellent glycosidase inhibitors.[17] Azasugar isomers have the potential to be good glycosidase inhibitors.

In terms of diversity-oriented synthesis, it is important to develop new strategies for synthesizing novel azasugar isomers, especially with high stereoselectivity. During our investigations of α-glucosidase inhibitors[18] and their synthesis from sugars,[19] we developed an effective synthetic method for the preparation of new azasugars based on deprotection and reductive amination in one pot. The target compound (**1**) was obtained in 10 steps and 24.3% overall yield. Only three column chromatography purifications were needed in this synthesis. The biological activity of the target

molecule as a glycosidase inhibitor was studied but the inhibitory activity against four glycosidases was not good (IC_{50} > 100 μM).

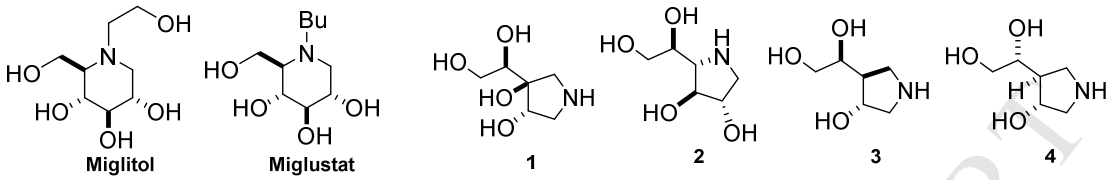


Fig. 1. Structures of some iminosugars.

2. Results and discussion

*2.1 Synthesis of a new azasugar isomer (3S,4S)-3-((R)-1,2-dihydroxyethyl) pyrrolidi-ne-3,4-diol (**1**)*

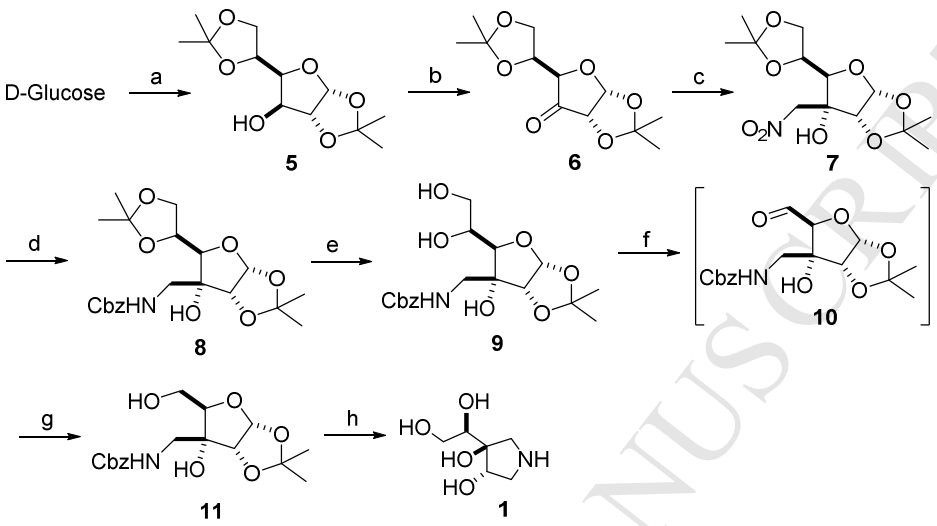
In this study, a new azasugar (**1**) was synthesized from D-glucose in 10 steps (Scheme 1). 1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranose (**5**) was obtained in 95% yield from commercially available D-glucose using a previously reported method.[20] Then, compound **5** was oxidized with pyridinium dichromate (PDC) to give the furan-3-ulose **6**. Compound **7** was obtained via the highly stereoselective Henry reaction,[20] treated with HCO_2NH_4 in the presence of Pd/C and then converted to the N-benzyloxycarbonyl (Cbz)-protected compound **8** in one pot.[21] The nitro group in compound **7** was hydrogenated using the method reported in the literature.[22, 23] However, we could not identify the main thin-layer chromatography spot. Based on a literature search,[21, 24, 25] we chose Pd/C as the catalyst and HCO_2NH_4 as the hydrogen source for nitro group reduction. The reduction product was used directly in the next step, without purification.

Selective deprotection of the 5,6-acetonide group in **8** using 75% acetic acid,[26] gave triol **9** in 79% yield. Treatment of **9** with sodium metaperiodate gave the *N*-protected aminoaldehyde **10** in good yield. A proton signal from the aldehyde group was not observed in the NMR spectrum. We deduced that **10** is unstable and the nitrogen atom may attack the aldehyde group to give a hemiacetal (Fig. 2). Compound **10** was reduced with sodium borohydride in one pot, without purification, to give the N-protected amino alcohol **11**. Removal of the 1,2-acetonide group of **11** with trifluoroacetic acid/water and subsequent reductive aminocyclization using ammonium formate and 5% Pd/C in methanol under reflux conditions afforded product **1** as a thick liquid. This one-pot three-step process involves hydrogenolysis of a N-Cbz group to give in situ formation of a primary amine, which concomitantly undergoes reductive aminocyclization with a C1 aldehyde to give the target molecule **1**.[27]

*2.2 Biological activity evaluation of the (3S,4S)-3-((R)-1,2-dihydroxyethyl)pyrrolidi-ne-3,4-diol (**1**)*

Biological studies showed that the glycosidase inhibitory activity of compound (**1**) was not good (IC_{50} > 100 μM). The inhibition percentage against four glycosidases for compound **1** at 100 μM concentration. The results are summarized in the Table 1. In the α-glucosidase inhibition activity testing, acarbose was taken as a positive control. The inhibition percentage of 1 mM acarbose was 56.5%. The results showed that compound **1** had an inhibition of 45.6% at 100 μM against α-glucosidase.

Compound **1** specific for β-glucosidase showed 34.7% inhibition activity at 100 μM, and the inhibition activity against α-mannosidase was 27.1%. It has little significant activity against α-galactosidase.



Scheme 1. Synthesis of (3S,4S)-3-((R)-1,2-dihydroxyethyl) pyrrolidine-3,4-diol (**1**)

Reagents and conditions: (a) $ZnCl_2$, phosphoric acid, acetone; (b) PDC, Ac_2O, CH_2Cl_2; (c) CH_3NO_2, KF, THF, rt.; (d) 1) 5% Pd/C, HCO_2NH_4, CH_3OH, reflux, 1 h and 2) CH_3OH/H_2O (5:1), $NaHCO_3$, CbzCl, 0 °C → room temperature, 2 h; (e) 75% CH_3CO_2H, 55 °C, 3 h; (f) $NaIO_4$, acetone/H_2O (9:1), 0 °C, 40 min; (g) $NaBH_4$, THF/H_2O (v/v = 4/1), 0 °C; (h) 1) TFA/H_2O (3:1), 0 °C and 2) 5% Pd/C, HCO_2NH_4, CH_3OH, reflux, 1 h.

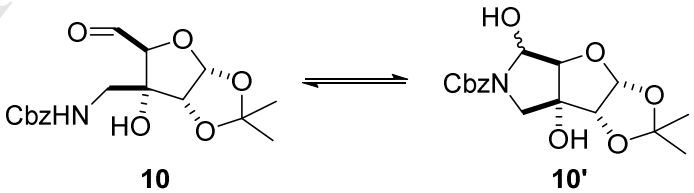


Fig. 2. Possible structure of aminoaldehyde **10**.

Table 1. Inhibitory potencies of compound **1**

Enzyme	% inhibition [a]
α-glucosidase (yeast)	45.6
β-glucosidase (almond)	34.7
α-mannosidase (jack bean)	27.1
α-galactosidase (almond)	13.4

[a] % inhibition determined at 100 μM concentration of compound.

3. Conclusion

In conclusion, azasugar **1** was synthesized in 10 steps from commercially available D-glucose in 24.3% overall yield. Only three column chromatography purifications were needed in the entire synthesis. The key step was hydrogenolysis of a N-Cbz group to give in situ formation of a primary amine with concomitant reductive aminocyclization to give the polyhydroxylated pyrrolidine in one pot. This method of synthesizing azasugars should be generally applicable.

4. Experimental sections

4.1 General

Melting points were measured on a WC-1 melting-point apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Bruker Vector-22 FTIR spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter using thin film on KBr plates. NMR spectra were recorded on a Bruker advance DPX-400 instrument and TMS as an internal standard reference. HRMS (high-resolution mass spectra) were taken with a Q-Tof Micromass spectrometer. Coupling constants (J) are given in Hertz (Hz). Thin-layer chromatography (TLC)

was performed on glass plates precoated with silica gel (5–40 μm, Qingdao Marine Chemical Factory (China)) to monitor the reactions, and 5% Pd/C was purchased from Shanghai Chemical Factory (China). For enzyme inhibition studies substrates were from a commercial source. α-glucosidase and α-mannosidase were purchased from Sigma Chemicals Co. USA, and α-galactosidase and β-glucosidase were purchased from a native reagent company (China). The substrates were purchased from Sigma Chemicals Co. USA., namely p-nitrophenyl-α-D-glucopyranoside, p-nitrophenyl-β-D-glucopyranoside, p-nitrophenyl-α-D-galactopyranoside and p-nitrophenyl-α-D-mannopyranoside.

*4.2 1,2;5,6-Di-O-isopropylidene-3-C-nitromethyl-α-D-allofuranose (**7**)*

Compound **7** was synthesized according to the reference literature.[20] White crystal, yield: 7.8 g (63.4% from **5**). m.p.: 110-112°C, $[\alpha]_D^{20}$ = +95 (c, 1.0, CH_3OH), IR(KBr) cm^{-1}: 3362, 2988, 1560, 1377, 1080, 874. ^1H NMR (400 MHz, $CDCl_3$): δ 5.87 (d, J = 3.9 Hz, 1H), 4.99 (d, J = 12.2 Hz, 1H), 4.90 (d, J = 3.9 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.14 (dd, J = 8.5, 5.9 Hz, 1H), 4.09–3.99 (m, 1H), 3.96 (dd, J = 8.5, 4.8 Hz, 1H), 3.90 (d, J = 8.6 Hz, 1H), 3.31 (s, 1H), 1.62 (s, 3H), 1.49 (s, 3H), 1.39 (d, J=11.3 Hz 6H); ^{13}C NMR (100MHz, $CDCl_3$): δ 113.3, 110.4, 103.7, 81.6, 79.8, 78.5, 77.0, 72.9, 67.9, 26.6, 26.5, 26.4, 25.0. HRMS: calcd for $[M+Na]^+$: m/z 342.1163, found: m/z 342.1165.

*4.3 1,2;5,6-Di-O-isopropylidene-3-C-[[[(phenylmethoxy)carbonyl]amino] methyl]-α-D-allofuranose (**8**)*

To a solution of solid **7** (2.0 g, 6.3 mmol) and ammonium formate (2.0 g, 31.7 mmol) in methanol 30 mL, 5% Pd/C (0.8 g) was added and reacted at reflux

temperature for 1 h. The catalyst was filtered through Celite and washed with CH_3OH (2 × 10 mL). H_2O (10 mL) was added to the filtrate. $NaHCO_3$ (1.58 g, 18.8 mmol) and benzyloxy carbonyl chloride (1.56 g, 9.1 mmol) were added at 0°C. Then, the system was stirred at r.t. for 2 h. CH_3OH was removed under reduced pressure and the residue was extracted with EtOAc (3 × 40 mL). The combined extract was washed with brine, dried with $MgSO_4$ and concentrated to afford a residue that was purified by column chromatography (petroleum ether : EtOAc = 5 : 2) to give **8** as a white solid. 1.39 g, Yield: 76.8%. m.p.: 115-116 °C, $[\alpha]_D^{28}$ = +49 (c = 0.1, $CHCl_3$), IR (KBr) cm^{-1}: 3446, 2990, 1728, 1545, 1244, 1010, 858. ^1H NMR (400 MHz, $CDCl_3$): δ: 7.39 (d, *J* = 4.4 Hz, 5H), 5.80 (d, *J* = 3.8 Hz, 1H), 5.36 (d, *J* = 5.8 Hz, 1H) 5.21 - 5.08 (m, 2H) 4.35 (d, *J* = 3.8 Hz, 1H) 4.13 (dd, *J* = 6.5, 3.8 Hz, 2H) 3.93 (d, *J* = 2.7 Hz, 1H) 3.80 (d, *J* = 8.1 Hz, 1H) 3.55 (dd, *J* = 13.9, 8.8 Hz, 1H) 3.46 (dd, *J* = 13.9, 3.3 Hz, 1H) 2.93 (s, 1H) 1.60 (s, 3H) 1.47 (s, 3H) 1.37 (s, 6H); ^{13}C NMR (100MHz, $CDCl_3$): *δ* 156.9, 136.3, 128.6, 128.2, 128.1, 112.7, 109.9, 103.7, 81.4, 80.3, 79.4, 73.0, 68.1, 67.0, 42.0, 26.7, 26.6, 26.5, 25.2. HRMS: calcd for $[M+Na]^+$: m/z 446.1790, found: m/z 446.1791.

*4.4 1,2-O-isopropylidene-3-C-[[[(phenylmethoxy)carbonyl]amino] methyl]-α-D-allofuranose (**9**)*

Compound **8** (2.0 g, 4.7 mmol) was added to a solution of 75% acetate acid (20 mL) and stirred for 2 h at 55°C. The reaction mixture was evaporated under reduced pressure to obtain a syrup and purified by column chromatography (petroleum ether : acetone = 3 : 2). White solid, 1.48 g, yield: 81.9%. m.p.: 106-107 ˚C, $[\alpha]_D^{28}$ = +56 (c = 0.1, $CHCl_3$), IR (KBr) cm^{-1}: 3515, 3340, 1713, 1533, 1238, 872, 700. ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.41 - 7.25 (m, 5H), 5.86 - 5.61 (m, 2H), 5.18 - 4.95 (m, 2H), 4.31 (d,

J = 3.5 Hz, 1H), 3.79 (d, *J* = 15.8 Hz, 3H), 3.64 (s, 1H), 3.56 - 3.34 (m, 5H), 1.53 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 136.3, 128.6, 128.2, 128.1, 112.6, 103.4, 80.2, 79.8, 79.0, 69.9, 67.1, 64.3, 42.0, 26.4, 26.3. HRMS: calcd for $[M+Na]^+$: m/z 406.1480, found: m/z 406.1478.

*4.5 1,2-O-isopropylidene-3-C-[[[(phenylmethoxy)carbonyl]amino] methyl]-α-D-ribofuranose (**11**)*

To a solution of compound **9** (1.5 g, 3.9 mmol) in acetone/H_2O (9:1, 15 mL), sodium periodate (1.26 g, 5.9 mmol) was added and stirred for 40 min at 0 ˚C. Ethylene glycol (1 mL) was added, and the acetone was removed under reduced pressure. The residue was extracted with EtOAc (3× 30 mL). The combined extract was washed with brine, dried with $MgSO_4$ and concentrated to afford a syrup. To an ice-cooled solution of the syrup in THF/H_2O (v/v = 4/1, 15 mL), sodium borohydride (0.18 g, 4.7 mmol) was added in two portions. The reaction mixture was stirred for 1.5 h, and then some NH_4Cl (s) was added to terminate the reaction. THF was evaporated under reduced pressure, extracted with EtOAc and concentrated. Purification by column chromatography (petroleum ether : acetone = 2 : 1) to give **11** as white solid. 1.28 g, yield: 85.3%. m.p.: 114-115 ˚C, $[\alpha]_D^{28}$ = +51 (c = 0.1, $CHCl_3$), IR(KBr) cm^{-1}: 3455, 3343, 1716, 1547, 1243, 1003, 700. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 - 7.31 (m, 5H), 5.81 (d, *J* = 3.6 Hz, 1H), 5.43 (d, *J* = 3.6 Hz,1H), 5.11 (q, *J* = 12.2 Hz, 2H), 4.31 (d, *J* = 3.4 Hz, 1H), 3.88 (d, *J* = 7.3 Hz, 2H), 3.83 - 3.72 (m, 1H), 3.48 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.27 (dd, *J* = 14.4, 4.1 Hz, 1H), 3.02 (s, 1H) 2.20 (s, 1H) 1.56 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 157.1, 136.3, 128.6, 128.3, 128.2, 112.7, 103.6, 81.5, 80.1, 79.2, 67.1, 59.3, 41.9, 26.5, 26.4. HRMS: calcd for $[M+Na]^+$: m/z 376.1371, found: m/z 376.1372.

*4.6 (3S,4S)-3-((R)-1,2-Dihydroxyethyl)pyrrolidine-3,4-diol (**1**)*

A solution of **11** (0.5 g, 1.42 mmol) in TFA/water (10 mL, 3 : 1) was stirred for 3 h at 0 °C. TFA was co-evaporated with toluene at reduced pressure to furnish a hemiacetal as a liquid. To a solution of hemiacetal (0.45 g, 1.44 mmol) in methanol (10 mL), 5% Pd/C (0.25 g) and ammonium formate (0.45 g, 7.14 mmol) were added, and the reaction mixture was refluxed for 1 h. After cooling, the reaction mixture was filtered through celite, washed with methanol, and the solvent was evaporated at reduced pressure. Purification by column chromatography (methanol) to give **1** as an oil. 0.16 mg, yield: 71.3%. $[\alpha]_D^{28}$ = +9.6 (c = 0.4), IR (KBr) cm^{-1}: 3405, 3146, 1685, 1401, 1208, 1139, 725. ^{1}H NMR (400 MHz, MeOD) δ 4.20 (d, *J* = 3.6 Hz, 1H), 4.03 (dd, *J* = 6.4, 4.2 Hz, 1H), 3.83 (dd, *J* = 11.3, 4.2 Hz, 1H), 3.77 – 3.72 (m, 1H), 3.72 – 3.68 (m, 1H), 3.65 (dd, *J* = 14.9, 5.4 Hz, 1H), 3.53 (d, *J* = 12.1 Hz, 1H), 3.37 (d, *J* = 12.1 Hz, 1H), 3.33 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.29 (d, *J* = 12.1 Hz, 1H).^{13}C NMR (100MHz, MeOD) *δ* 82.8, 74.4, 71.7, 62.2, 52.9, 52.7. HRMS: calcd for $[M+H]^+$: m/z 164.0919, found: m/z 164.0923.

4.7 General procedure for α-glucosidase inhibition assay.

Inhibition rate was determined at 37 ˚C in 0.067 M K_2HPO_4/KH_2PO_4 buffer (pH 6.8). The reaction mixture contained 40 μL of enzyme solution, 40 μL of inhibitor and 20 μL of substrate. The enzymatic reaction was started after incubation of the enzyme (0.04 U/mL) for 30 min in the presence of the inhibitor (0.1 mM) by the addition of substrate (0.5 mM). The mixture was incubated at 37 ˚C for 5 min, and the reaction was quenched by the addition of 0.1 M Na_2CO_3 (pH 9.8). The absorption at 405 nm was measured immediately and taken as the relative rate for the hydrolysis of

substrate. All experiments were carried out in triplicate. The IC_{50} value is the concentration of inhibitor at 50% of enzyme activity[18].

4.8 General procedure for β-glucosidase inhibition assay

Inhibition rate was determined at 37 ˚C in 0.08 M citric acid/Na_2HPO_4 buffer (pH 4.2). The enzymatic reaction was started after incubation of the enzyme (0.02 U/mL) for 30 min in the presence of the inhibitor (0.1 mM) by the addition of substrate (5 mM). The mixture was incubated at 37 ˚C for 5 min, and the reaction was quenched by the addition of 0.25 M borate buffer (pH 9.8). The absorption at 405 nm was measured immediately and taken as the relative rate for the hydrolysis of substrate[18].

4.9 General procedure for α-galactosidase and α-mannosidase inhibition assay

The substrates p-nitrophenyl-α-D-galactopyranoside, of 2 mM concentration were prepared in 0.025 M citrate buffer with pH 6.0. P-nitrophenyl-α-D-mannopyranoside of 2 mM was prepared in 0.025 M citrate buffer with pH 4.0. The test compound was preincubated with the respective enzyme buffered at their optimal pH for 1 h at 25 ˚C. The enzyme reaction was initiated by the addition of 100 µL substrate. Controls were run simultaneously in the absence of test compound. The reaction was terminated at the end of 10 min by the addition of 0.05 M borate buffer (pH 9.8) and absorbance of the liberated p-nitrophenol was measured at 405 nm. One unit of glycosidase activity is defined as the amount of enzyme that hydrolyzed 1 µmol of p-nitrophenyl pyranoside per minute at 25 ˚C.[28]

Acknowledgment

We are grateful for the financial support from the National Natural Science Foundation of China (U1204206, 81430085, 21372206).

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version.

References

1. Van den Broek L, Vermaas D, Heskamp B, Van Boeckel C, Tan M, Bolscher J, Ploegh H, Van Kemenade F, De Goede R, Miedema F. *Recl Trav Chim Pays-Bas* 1993;**112**:82-94.

2. Naoki A. *Curr Top Med Chem* 2003;**3**:471-84.

3. Pearson MSM, Mathé-Allainmat M, Fargeas V, Lebreton J. *Eur J Org Chem* 2005;**2005**:2159-91.

4. Cren S, Gurcha SS, Blake AJ, Besra GS, Thomas NR. *Org Biomol Chem* 2004;**2**:2418-20.

5. Scheen A. *Diabetes Metab* 1998;**24**:311-20.

6. Asano N. *Glycobiology* 2003;**13**:93R-104R.

7. Humphries MJ, Matsumoto K, White SL, Olden K. *Cancer Res* 1986;**46**:5215-22.

8. Niwa T, Inouye S, Tsuruoka T, Koaze Y, Niida T. *Agric Biol Chem* 1970;**34**:966-68.

9. Fuentes J, Illangua JM, Sayago FJ, Angulo M, Gasch C, Pradera MÁ. *Tetrahedron-asymmetr* 2004;**15**:3783-89.

10. Best D, Jenkinson SF, Saville AW, Alonzi DS, Wormald MR, Butters TD, Norez C, Becq F, Blériot Y, Adachi I, Kato A, Fleet GWJ. *Tetrahedron Lett* 2010;**51**:4170-74.

11. Wang GN, Yang L, Zhang LH, Ye XS. *J Org Chem* 2011;**76**:2001-9.

12. Subramanian T, Lin C-C, Lin C-C. *Tetrahedron Lett* 2001;**42**:4079-82.

13. Aoki K, Nakamura A, Ito S, Nezu U, Iwasaki T, Takahashi M, Kimura M, Terauchi Y. *Diabetes Res Clin Pr* 2007;**78**:30-33.

14. Alfonso P, Pampín S, Estrada J, Rodríguez-Rey JC, Giraldo P, Sancho J, Pocoví M. *Blood Cell Mol Dis* 2005;**35**:268-76.

15. Lee RE, Smith MD, Nash RJ, Griffiths RC, McNeil M, Grewal RK, Yan W, Besra GS, Brennan PJ, Fleet GW. *Tetrahedron Lett* 1997;**38**:6733-36.

16. Cren S, Wilson C, Thomas NR. *Org Lett* 2005;**7**:3521-23.

17. Stütz AE, Iminosugars as glycosidase inhibitors, Wiley-VCH, 1999.

18. Dai G-F, Xu H-W, Wang J-F, Liu F-W, Liu H-M. *Bioorg Med Chem Lett* 2006;**16**:2710-13.

19. Zhao ML, Zhang E, Gao J, Zhang Z, Zhao YT, Qu W, Liu HM. *Carbohyd Res* 2012;**351**:126-9.

20. Saito Y, Zevaco TA, Agrofoglio LA. *Tetrahedron* 2002;**58**:9593-603.

21. Markad SD, Karanjule NS, Sharma T, Sabharwal SG, Puranik VG, Dhavale DD. *Org Biomol Chem* 2006;**4**:2549-55.

22. Yoshimura J, Kobayashi K, Sato K-i, Funabashi M. *B Chem Soc Jpn* 1972;**45**:1806-12.

23. Sato K-i, Yoshimura J, Shin C-g. *B Chem Soc Jpn* 1977;**50**:1191-94.

24. Rosenthal A, Khong-Seng O. *Tetrahedron Lett* 1969;**10**:3981–83.

25. Chakraborty C, Dhavale DD. *Carbohyd Res* 2006;**341**:912-7.

26. Yadav JS, Satyanarayana M, Raghavendra S, Balanarsaiah E. *Tetrahedron Lett* 2005;**46**:8745-48.

27. Mane RS, Kumar KA, Dhavale DD. *J Org Chem* 2008;**73**:3284-87.

28. Dhavale DD, Kumar KA, Chaudhari VD, Sharma T, Sabharwal SG, PrakashaReddy J. *Org Biomol Chem* 2005;**3**:3720-26.

1) A new azasugar was synthesized using one-pot reaction as a key step.
2) Our method plays an important role in the research of new azasugars.
3) The glycosidase inhibitory activity of the target molecule were not ideal.