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RESEARCH ARTICLE

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A practical and efficient synthesis of five-membered azasugar derivatives

Abstract A practical and efficient synthesis of 1,4-dideoxy-1,4-imino-D-arabinol and its partially protected derivatives has been described via the key intermediate with a norbornane-like structure using D-glucose as a starting material.

Keywords D-glucose, norbornane-like structure, five membered azasugar

1 Introduction

Azasugars (also called iminosugars) are classes of carbohydrate derivatives in which the ring oxygen has been replaced by nitrogen and exhibit remarkable inhibitory activity against glycosidases. Because the glycosidases can adjust the biosynthesis and hydrolysis of the glucoproteins which play important roles in biological recognition and structure modulation of enzymes, such kind of enzyme inhibitors are potential therapeutic reagents for the treatment of diseases caused by disorders of carbohydrate metabolism such as those used for anti-diabetic, antiviral (including AIDS), antibiotics and anticancer agents [1–7]. The important biological activity of azasugars and their excellent potentia, on pharmaceutical applications has attracted great attention for the research on their synthesis, biological activipy and application, which has got remarkable progress [4–19].

2 Experimental

2.1 General methods

^{1}H NMR, ^{13}C NMR and 2D-COSY spectra were measured on a FT-NMR Bruker AVANCE 400 (400 MHz) NMR spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Mass spectra (MS) were carried out on a VG-7070E mass spectrometer with FAB (Fast Atomic Bombardment) using 3-nitrobenzyl alcohol (NBA) as the matrix. Thin-layer chromatography (TLC) was performed on pre-coated plates (Qingdao GF_{254}), detected by UV light or with phosphormolybdic acid in $EtOH/H_2O$ followed by heating. Column chromatography was performed using SiO_2 (Qingdao 200∼300 mesh).

2.2 Synthesis of five-membered azasugars derivative

2.2.1 Synthesis of compound **6**

NaH (60% in oil (3.077 g, 77 mmol) was washed with petroleum ether, dried under reduced pressure, then 10 mL of dry DMF was added under N_2 atmosphere, and a solution of compound **5** (10.0 g, 38.5 mmol) in 10 mL of DMF was added drop-wise. The mixture was stirred at room temperature for 1 h, at the end of which 8.0 mL (67.3 mmol) of newly distilled BnBr was added drop-wise. The reaction mixture was stirred at room temperature for 12 h, at the end of which time 5 mL of MeOH was added slowly. Then, the mixture was diluted with 50 mL of water, and extracted with 300 mL of ethyl acetate. The organic phase was washed successively with 150 mL of water (two times) and 150 mL of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in 20 mL of 60% AcOH, the mixture was stirred at 40–50°C for 8 h, then extracted with CH_2Cl_2 (80 mL × 2). The organic phase was washed with 100 mL of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to produce **6** as a yellow syrup.

2.2.2 Synthesis of compound **7**

The crude **6** was dissolved in 30 mL of THF and 8 mL of aqueous solution of $NaIO_4$ (8.2 g) was added and the reaction mixture was stirred at room temperature for

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10 h. After filtration to remove the solid, the mother liquor was extracted with 100 mL of CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 20 mL of MeOH, cooled to 0°C, and then the aqueous solution of $NaBH_4$ (2.2 g, 57.8 mmol) in 30 mL of water was added dropwise, The mixture was stirred at room temperature and then concentrated to remove MeOH under reduced pressure. To the residue was added 200 mL of water. Then, the mixture was extracted with 100 mL of EtOAc. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the residue was dried *in vacuum* to produce a slightly yellow syrup. Further purification of 100 mg of this crude product by silica gel column chromatography (petroleum ether: ethyl acetate *V*/*V* 3:1) gave compound **7** (81.1 mg). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.82–3.85 (m, 2H, CH_2OH), 4.03 (d, $J = 3.6$ Hz, 1H, H-2), 4.28–4.31 (m, 1H, H-4), 4.60–4.63 (m, 2H, CH_2Ph), 4.65 (d, $J = 3.6$ Hz, 1H, H-3), 6.00 (d, $J = 3.6$ Hz, 1H, H-1), 7.32–7.39 (m, 5H, ArH).

2.2.3 Synthesis of compound 8

The crude compound **7** was dissolved in 35 mL of dry pyridine and cooled to 0°C. 8.8 g (46 mmol) of TsCl was added in portions to the solution and the reaction mixture was stirred at room temperature under a N_2 atmosphere for 8 h and then diluted with 20 mL of water, extracted with 100 mL of EtOAc. The organic layer was washed successively with 100 mL of water, 50 mL of diluted hydrochloric acid, 100 mL × 2 of water, and 100 mL of brine, and dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was co-distilled with toluene and dried under reduced pressure to produce a tosylated intermediate syrup.

The crude tosylated intermediate was dissolved in 20 mL of dry DMF. Then, 3.0 g (46, 2 mmol) of NaN_3 was added, and the reaction mixture was heated at 100°C for 10 h and diluted with 50 mL of water, extracted with 100 mL of EtOAc. The organic layer was washed successively with 100 mL of brine, water (100 mL × 3), 100 mL of brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate *V*/*V* 6:1) to produce compound **8** (6.99 g, yield 59.5% based on **6**). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H, CH_3), 1, 53 (s, 3H, CH_3), 3.56–3.58 (m, 2H, CH_2N_3), 3.98 (d, $J = 2.6$ Hz, 1H, H-2), 4.33–3.35 (m, 1H, H-4), 4.62–4.64 (m, 2H, CH_2Ph), 4.66 (d, $J = 3.4$ Hz, 1H, H-3), 5.96 (d, $J = 3.4$ Hz, 1H, H-1), 7.35–7.39 (m, 5H, ArH).

2.2.4 Synthesis of compound 11

Compound **8** (8.1g, 26.6 mmol) was dissolved in 20 mL of MeOH-2% HCl. The solution was heated at 45°C for 4 h, neutralized by adding solid sodium carbonate and filtrated to remove the solid. The filtrate was concentrated under reduced pressure to produce syrup **9**. The crude product **9** was dissolved in 20 mL of CH_2Cl_2, cooled to 0°C in an ice-salt bath and 4.3 mL (53.1 mmol) of dry pyridine was added under a N_2 atmosphere. To the solution, 4.5 mL of triflic anhydride was added dropwise. The reaction mixture was stirred at room temperature for 5 h and concentrated under reduced pressure. The residue was extracted with diethyl ether and the organic layer was washed successively with 50 mL of diluted hydrochloric acid, 100 mL of water, 100 mL of brine, dried over anhydrous magnesium sulfate and then concentrated *in vacuum* to give a syrup. The obtained syrup was dissolved in 30 mL of ethanol, and 1 g of 10% Pd/C catalyst was added. The mixture was vigorously stirred for 3 h under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a syrupy product **10**. The crude product **10** was dissolved in 80 mL ethyl acetate and saturated sodium carbonate solution 40 mL was added. The mixture was cooled to 0°C. Benzoxycarbonyl chloride 4.56 mL (31.9 mmol) was added and the reaction mixture was stirred vigorously for 5 h. The organic phase was separated, and washed with brine, dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate *V*/*V* 6:1) to give compound **11a** (α-configuration, 0.56 g), compound **11b** (β-configuration, 0.39 g), and a mixture of **11a** and **11b** (6.45 g, total 7.39 g, yield 75.2%).

11a (including rotamer): ^1H NMR ($CDCl_3$) δ: 3.37, 3.40 (s, 3H, OCH_3), 3.46–3.49 (m, 2H, H-5), 4.27–4.30 (m, 1H, H-3), 4.35–4.44 (m, 1H, H-4), 4.57 (d, $J = 11.6$ Hz, 1H, H-2) 4.57–4.59 (m, 2H, CH_2Ph), 4.78 (d, $J = 38.0$ Hz, 1H, H-1), 5.19–5.22 (m, 2H, $CbzCH_2$), 7.28–7.37 (m, 10 H, ArH); ^{13}C NMR ($CDCl_3$) δ: 51.19 (OCH_3), 55.58, 55.74 (C-5), 60.10, 60.64 (C-3), 67.35, 67.48 (C-6), 72.68, 72.75 (C-7), 75.50, 75.89 (O-CH_2), 78.35, 78.88 ($COOCH_2$), 106.00, 106.23 (C-2), 128.05, 128.13, 128.26, 128.55, 128.69, 128.87, 136.95, 137.03, 137.70, 137.72 (Ar), 155.83, 155.97 (COO).

11b (including rotamer): ^1H NMR ($CDCl_3$) δ: 3.38, 3.43 (s, 3H, OCH_3), 3.58–3.61 (m, 2H, H-5), 4.05 (d, $J = 8.4$ Hz, 1H, H-3), 4.30–4.39 (m, 1H, H-4), 4.57 (d, $J = 7.2$ Hz, 1H, H-2), 4.56–4.59 (m, 2H, CH_2Ph), 5.04 (d, $J = 22.4$ Hz, 1H, H-1), 5.19–5.22 (m, 2H, $CbzCH_2$), 7.28–7.38 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$) δ: 51.46, 51.49 (OCH_3), 56.06, 56.24 (C-5), 59.93, 60.57 (C-3), 67.12, 67.14 (C-6), 72.35, 72.43 (C-7), 77.89, 78.43 (O-CH_2), 78.88, 79.53 ($COOCH_2$), 104.97, 105.37 (C-2), 127.48, 127.66, 127.87, 128.06, 128.13, 129.18, 137.37, 137.40, 137.49, 140.15 (Ar), 156.43, 156.60 (COO).

2.2.5 Synthesis of compound **12**

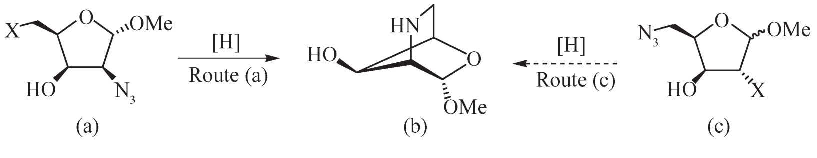
The mixture of **11a** and **11b** (6.45 g, 17.5 mmol) was dissolved in a 50 mL solution of triflic acid (TfOH): water = 4:1 (*V*:*V*). The reaction mixture was stirred at room temperature for 10 min and was then cooled to 0°C. 50 mL of water was added slowly. The mixture was extracted with 100 mL of CH_2Cl_2 thrice and the organic phase was washed successively with 100 mL of water, saturated sodium hydrogen carbonate solution (100 mL × 2), 100 mL of brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in 150 mL of ethanol and 10 mL of aqueous solution of $NaBH_4$ (0.5 g, 13.3 mmol) was added at 0°C. The reaction mixture was stirred for 20 min. 20 mL of saturated aqueous solution of ammonium chloride was then added at the same temperature. The mixture was concentrated to remove most of methanol under reduced pressure. To the residue, 100 mL of water was added. The mixture was extracted with EtOAc (100 mL × 2) and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain compound **12** (5.1 g, yield 81.6%) as colorless oil. ^{1}H NMR ($CDCl_3$) δ: 3.38 (d, $J = 11.7$ Hz, 1H), 3.53~3.61 (m, 1H), 3.67–3.88 (m, 4H), 4.15–4.26 (m, 3H), 5.01~5.12 (m, 2H), 7.12~7.28 (m, 10H); ^{13}C NMR ($CDCl_3$): δ: 48.81, 49.10, 56.72, 56.89, 58.19, 58.32, 66.90, 67.02, 73.54, 73.78, 74.29, 78.71, 127.22, 127.53, 127.58, 127.72, 128.03, 128.42, 129.12, 129.23, 137.28, 137.52, 139.20, 157.04, 157.33; MS (FAB) *m*/*z*: 358 $(M+H)^+$.

3 Results and discussion

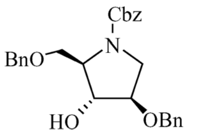
The synthesis of azasugar derivatives was readily achieved through a suitable cyclization reaction, usually using the compound containing chiral carbon, such as sugar, aminosugar ornon-sugar compounds with amino acid as the starting material and according to its structure. The conventional methods for constructing an azasugar ring includes: intramolecular substituted amination-cyclizatioN [14–19], intramolecular amination-cyclization of aminosugar derivatives [20,21], reductive amination-cyclization of dicarbonyl compounds [22,23], metathesis [24,25], cycloaddition [26,27] and so on. The key step to construct the azasugar ring is the stereospecific cyclization [8–21]. In addition, Fleet and coworkers [28,29] reported a synthesis of 5-membered azasugars via the key intermediate of norbonyl like bicyclic acetal, (Scheme 1, route (a)). In the synthesis, the configuration of the target azasugar depends on the configuration of the starting material. Thus, a variety of 5-membered azasugars could be synthesized by using a certain starting material, conveniently realizing the selective protection of the hydroxyl groups in the process.

With this synthetic strategy, the partially protected azasugar derivatives **1** and **2** and their fluorinated derivatives **3** and **4** (Fig. 1) were synthesized using D-xylose and D-glucose as the starting materials. The more complex azadisaccharide derivative [30] was also explored.

However, in the key step of synthesizing the intermediate **B**, only the α-isomer of **A** underwent the reaction of reductive amination-cyclization, the β-isomer could not, probably due to the spatial hindrance of the β-glycosidic bond. So the α-, β-isomers have to be separated during the process of synthesizing the intermediate **A**, resulting in the low utilization of the starting material, complicated separation steps and decreasing the yield and synthetic efficiency. However, the intermediate **B** can also be obtained via route (c) by reductive amination-cyclization of the intermediate **C** as shown in Scheme 1. Thus, the 5-azide in **C** could be firstly reduced to a 5-amino group which attacked by 2-C in a S_N2 reaction to form the intermediate **B**, which possesses the same configuration as from route (a). From the above point of view, synthesis of five-membered azasugar derivatives via intermediate **C**



Scheme 1.
The formation of norbornane like intermediate in the synthesis of 5-membered azasugar



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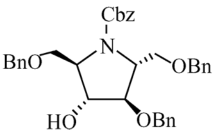

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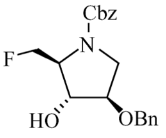

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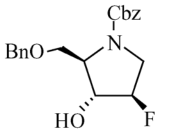

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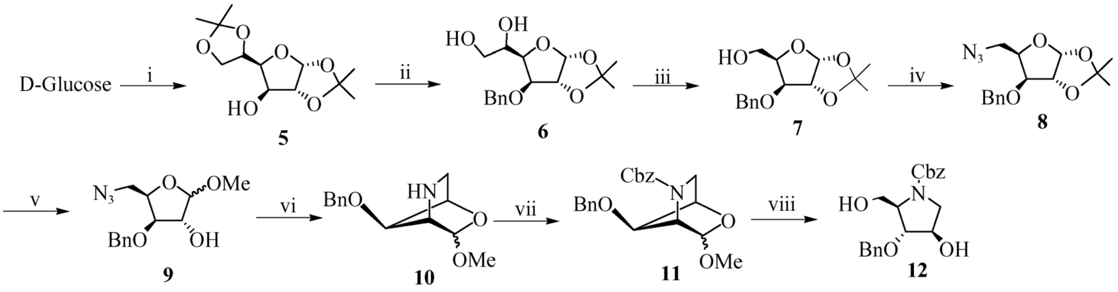
Fig. 1 Partially protected five-membered azasugar derivatives

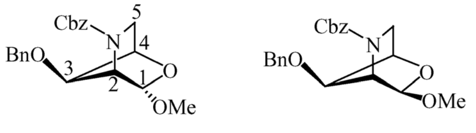


Scheme 2 i) ref. 31. ii) a) BnBr, NaH, TBAI, THF, r.t, 2 h; b) 80% AcOH, 50°C, 1 h. iii) a) $NaIO_4$, THF/H_2O, r.t., 0.5 h; b) $NaBH_4$, THF, r.t., 1 h. iv) a) TsCl, Py, r.t., 6 h, quant.; b) NaN_3, DMF, 90°C, 18 h. v) 2% HCl-MeOH, 50°C, 1.5 h. vi) a) Tf_2O, Py, CH_2Cl_2, 0°C; b) Pd/C, H_2, AcOEt, 3 h. vii) CbzCl, Et_3N, AcOEt, 0°C, 20 min. viii) a) CF_3COOH/H_2O (*V*/*V* = 4/1), r.t., 30 min; b) $NaBH_4$, EtOH, 0°C, 30 min.

was explored using glucose as the starting material as shown in Scheme 2, producing the azasugar derivative **12** which has the same configuration as compound **1**.

One of the key steps in the synthesis was the formation of intermediate **9** (the mixture of α, β isomers of **A**), as shown in Scheme 2. We utilized 1,2:5,6-di-*O*-isopropylidene-D-glucose (**5**) as the starting material. The next steps are 3-*O*-Benzylation of **5**, selective deprotection of the 5,6-isopropylidene group, followed by C(5)-C(6) bond cleavage by sodium periodate oxidation and reduction producing a D-xylose derivative (**7**). Compound **7** underwent tosylation of 5-OH, azidation, hydrolysis and methyl glycosylation to give the key intermediate methyl 5-deoxy-5-azido-3-*O*-benzyl-D-xyloside (α- and β-isomers) (**9**). Triflation of the α, β-mixture of **9** and reductive cyclization-amination by palladium catalyzed hydrogenation gave the corresponding mixture of norbonyl-like bicyclic acetal (**10**). Then, amino group protection, acid hydrolysis of the acetal and reduction resulted in the partially protected azasugar derivative (**12**). In the synthesis, the α, β-mixture of **9** produced the corresponding mixture of two stereoisomers (**10**). Meanwhile, amino protection of **10** with benzoxycarbonyl chloride and isolation produced the corresponding two isomers of **11a** and **11b** (Scheme 2). Consequently, **11a** and **11b,** respectively, underwent acidic hydrolysis and reduction by $NaBH_4$ to provide the same azasugar product (**12**). As a result, both of the α, β-isomers of **9** were utilized in the synthesis. In the 12-step synthesis from the starting material **5** to the azasugar derivative (**12**), the overall yield was up to 36.3% with only two times of chromatographic purification for the intermediates **8** and **11**, respectively. Comparatively, the synthesis of **12** from D-xylose via the intermediate **A** (Scheme 1, Route a) needed ten steps and five times of chromatographic purification, and provided the total yield of 9.4% [28].

The structures of all the products and the intermediates were characterized by the analyses of ^1H NMR, ^{13}C NMR, 2D-COSY and MS (FAB) spectra. The ^1H NMR and ^{13}C NMR spectra of the isomers **11a**, **11b** and the product **12** show the existence of rotamers in a ratio of about 1:1, probably because the free rotation of the N-Cbz group and the lone-pair electron was limited, resulting in a geometry similar to isomers (rotamers) as shown in Scheme 2. This observation is consistent with that in literature [28].



11a (α-isomer) **11b** (β-isomer)

Fig. 2 The stereoisomers of intermediate **11**

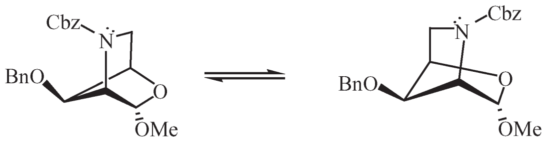


Fig. 3 The rotamers of the intermediate **11a**

In summary, we have developed a practical and efficient synthesis of five-membered azasugar derivatives via the key intermediate with a norbornane-like bicyclic acetal structure using D-glucose as the starting material. After modification of the reaction conditions, the overall yield of the 12-step synthesis was up to 36.3% with twice column chromatographic purification. The further study of synthesis and application of azasugar derivatives is under way in the laboratory.

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