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RESEARCH ARTICLE

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Stereoselective synthesis of partially protected azasugar derivatives

Abstract Five-membered azasugar derivatives with partially protected hydroxyl groups, and their fluorinated derivatives were synthesized via the key intermediates of norbornyl-like bicyclic acetals using D-xylose and D-glucose as starting materials. The glycosylation of the azasugar intermediate and 1-methylenesugar was also explored.

Keywords azasugar, partial protection, fluorinated azasugar, saccharide

1 Introduction

Azasugars (also called iminosugars) are a class of carbohydrate derivatives, in which the ring oxygen is replaced by nitrogen, and now believed to be widespread in plants and microorganisms. Structurally, azasugars mainly include multi-hydroxyl pyrrolidines, piperidines, azepines, and other condensed alkaloids. Because of their similar structures to sugars, azasugars exhibit remarkable biological activity to inhibit glycoside-processing enzymes and can adjust the biosynthesis and hydrolysis of the glucoproteins which play an important role in biological recognization and structure modulation of enzymes. Such kind of inhibitors is a potential therapeutic to treat the diseases caused by carbohydrate metabolic disorders, such as antidiabetic, antivirus infections (including AIDS), antibiotic, and anticancer agents [1−3]. Because of the important biological activity and excellent foreground on pharmaceutical application, the study on the synthesis, biological activity, and application of azasugar derivatives have attracted great attention, and made remarkable progress especially on monoazasugar [4−11]. For example, miglitol, one of the important six-membered azasugar derivatives, has been used in clinic as an antidiabetic based on its glycosidase inhibition activity [1,2,4−8], and recently some azasugars are also found to be antiviral (such as HIV) activity [4−8]. However, the study of synthesis and biological activity of various azasugars to find an effective glycosidase inhibitor or antiviral agent still remains a great challenge. We have synthesized ketosyl disaccharide, amino-C-disaccharide, and C-glycosyl amino acid derivatives from 1-methylenesugars in recent years [12−16]. In order to synthesize some new disaccharides containing azasugar moiety and to study their biological activities, it is necessary to synthesize the partially protected azasugar as the glycosyl acceptors in the disaccharides synthesis.

Different methods could be selected for the synthesis of azasugar derivatives according to its structure. Usually, the compounds containing a chiral carbon, such as sugar, aminosugar or nonsugar compounds (i.e. amino acids) are used as starting materials, and the key step of the synthesis is construction of the azasugar ring by stereospecific cyclization [4−11], conventionally including the reductive amination–cyclization of dicarbonyl compounds [17,18], substituted amination–cyclization [19−25], metathesis [26,27], cycloaddition [28,29], electrochemical oxidation [30] and so on. In addition, Fleet and coworkers [31,32] also reported the synthesis of five-membered azasugars via the key intermediates of norbornyl-like bicyclic acetals (Schemes 1 and 2). In the synthesis, the configurations of the target azasugars depend on the configurations of the starting materials and the cyclization stereoselectivity in the formation reaction of the intermediates. Thus, the synthesis of a variety of five-membered azasugars could be achieved by selecting the starting materials, and the selective protection of the hydroxyl groups could be conveniently realized in the process. With this synthetic strategy, the partially protected azasugar derivatives **5** and **11** (Scheme 1 and Scheme 2) and the fluorinated derivatives **14** and **17** (Scheme 3 and Scheme 4) were synthesized using D-xylose and D-glucose as the starting material, and the glycosylation of **5** with 1-methylenesugar **18** was also explored (Scheme 5).

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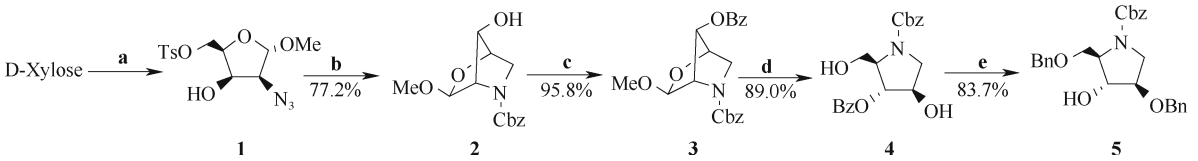


Scheme 1 a. ref. [31]. b. i) Pd/C, H_2, EtOH; ii) BnOCOCl, Na_2CO_3/H_2O. c. BzCl (99.6 mmol)/Py, CH_2Cl_2, 0°C. d. i) CF_3COOH/H_2O (1:4); ii) $NaBH_4$ (20.7 mmol), $EtOH/H_2O$, 0°C. e. i) $BnOC(NH)CCl_3$ (57.5 mmol), TfOH (1.7 mmol), CH_2Cl_2/cyclohexane, r.t.; ii) $K_2CO_3/MeOH/H_2O$

2 Experimental

2.1 General methods

^{1}H-NMR, ^{13}C-NMR, and 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 precoated plates (Qingdao GF_{254}) with detection by UV light or with phosphomolybdic acid in $EtOH/H_2O$ followed by heating. Column chromatography was performed using SiO_2 (Qingdao 200–300 mesh).

2.2 Synthesis of (2*R*,3*R*,4*R*)-*N*-benzyloxylcarbonyl-2-benzyloxymethyl-4-benzyloxy- pyrrolidine (**5**)

Compound **2** [31] (13.9 g, 49.8 mmol) was dissolved in 200 mL of dry dichloromethane and 20 mL (249.0 mmol) of dry pyridine. To this solution, 11.6 mL (99.6 mmol) of benzoyl chloride was added under N_2 atmosphere. The reaction mixture was stirred at room temperature for 2 h, and then cooled down to 0°C, slowly added 200 mL of diluted hydrogen chloride (1 mol/L), and extracted with dichloromethane (100 mL). The organic phase was washed successively with saturated sodium hydrogen carbonate (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V*/*V* 6:1−4:1) to afford the intermediate **3** (18.29 g, yield 95.8%). Intermediate **3** was dissolved in a solution (160 mL) of trifloroacetic acid and water (4:1). The solution was stirred at room temperature for 15 min., and was cooled to 0°C. The reaction mixture was added with 200 mL of water, and the mixture was extracted with dichloromethane (300 mL). The organic phase was work up as the previous procedure. The residue was dissolved in 150 mL of ethanol, and 0.78 g (20.7 mmol) of sodium borohydride in 15 mL of water was added at 0°C. The mixture was stirred at 0°C for 20 min, and saturated ammonium chloride (20 mL) was added at the same temperature. The ethanol was removed in vacuum, 100 mL of water was added, and extracted with 100 mL of ethyl acetate. The organic phase was washed, dried, and concentrated similar to the previous procedure. The residue was applied on a silica gel column chromatography (petroleum ether: ethyl acetate *V*/*V* 1:1) to afford a colorless syrup **4** (15.69 g, yield 89.0%).

To a solution of **4** (4.26 g 11.5 mmol) in 180 mL of dichloromethane and cyclohexane (*V*/*V* 1:2), 10.6 mL (57.5 mmol) of benzyl 2,2,2-trichloroacetimidate was added, and then 0.15 mL (1.7 mmol) of trifloromethanesulfonic acid slowly, the mixture was stirred at room temperature for 3 h. The reaction mixture was cooled to 0°C, and 10 mL of saturated sodium hydrogen carbonate and 200 mL of ethyl acetate were added. The organic phase was successively washed, dried, and concentrated as similar to the previous procedure. The residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V*/*V* 10:1−5:1) to afford 7.85 g of pale yellow syrup. The syrup was dissolved in 100 mL of methanol, and 4 mL of 1 mol/L aq. solution of potassium carbonate was added. The reaction mixture was stirred at room temperature for 5 h and concentrated to remove methanol in vacuum, then 100 mL of water was added and extracted with 100 mL of AcOEt. The organic phase was washed, dried, and concentrated, and the residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V*/*V* 2:1) to afford colorless solid of **5** (4.30 g, yield 83.7%). ^{1}H-NMR ($CDCl_3$), δ: 3.35 (1H, dd, J = 11.7, 3.7 Hz), 3.51−3.72 (1H, m), 3.66–3.89 (4H, m), 4.37–4.52 (5H, m), 4.98–5.07 (2H, m), 7.09−7.26 (15H, m); ^{13}C-NMR ($CDCl_3$: δ: 46.6, 56.3, 66.5, 67.6, 71.8, 74.8, 75.1, 76.7, 127.0, 127.4, 127.5, 127.6, 127.7, 127.9, 128.6, 128.7, 128.8, 129.1, 129.2, 129.9, 137.3, 137.5, 139.2, 157.7; MS (FAB), *m/z*: 448 $(M+H)^+$.

2.3 Synthesis of (2*R*,3*R*,4*R*,5*R*)-*N*-benzyloxylcarbonyl-3-hydroxyl-2,5-dibenzyloxymethyl-4-benzyloxy-pyrrolidine (**11**)

To a solution of compound **7** [32] (1.12 g, 4.22 mmol) in 25 mL of methanol, 300 mg of $Pd(OH)_2/C$ (20%) catalyst was added, the reaction mixture was vigorously stirred for 6 h under hydrogen atmosphere. The reaction mixture was filtered to remove the catalyst and concentrated under reduced pressure. Twenty-five milliliters of AcOEt and saturated sodium carbonate solution (2:1), and 0.9 mL (6.33 mmol) of benzyl chloroformate were added to the residue at 0°C. The reaction mixture was stirred at 0°C for 2 h, then 25 mL of water was added and extracted with AcOEt. The organic phase was washed, dried, and concentrated following the previous procedure, and the residue was applied on a silica

gel column chromatography (petroleum ether: ethyl acetate *V/V* 3:1−1:1) to afford colorless solid of **8** (940 mg, yield 72.0%).

To the solution of **8** (350 mg, 1.13 mmol) in 10 mL of dry pyridine, *tert*-butyl-dimethylsilyl chloride (TBDMSCl) (190 mg, 1.25 mmol) was added, the mixture was stirred at 0°C for 3 h. After the reaction was complete (detected by TLC), 200 μL (1.72 mmol) of benzoyl chloride was added, and stirred at 0°C for 1 h, then 40 mL of water was added at the same temperature. The mixture was extracted with ethyl acetate. The organic phase was washed, dried, and concentrated in vacuum, and the residue was submitted on a silica gel column chromatography using petroleum ether : ethyl acetate V/V 10:1 as the eleunt to afford a colorless syrupy product **9** (506 mg, yield 84.9%).

The solution of the intermediate **9** (1.0 g, 1.90 mmol) in 12 mL of trifluoroacetic acid and water (4:1) was stirred at room temperature for 15 min., then was cooled to 0°C. The reaction mixture was added with 20 mL of water, and the mixture was extracted with dichloromethane (20 mL). The organic phase was work up as usual and concentrated in vacuum. The residue was dissolved in 15 mL of ethanol, and 35.7 mg (0.10 mmol) of sodium borohydride in 1.5 mL of water was added at 0°C. The mixture was stirred at 0°C for 20 min, and saturated ammonium chloride (2 mL) was added at the same temperature. The ethanol was removed in vacuum, 15 mL of water was added, and extracted with 15 mL of ethyl acetate. The organic phase was washed, dried, and concentrated as usual. The residue was applied on a silica gel column chromatography (petroleum ether: ethyl acetate *V/V* 2:1) to afford a colorless syrup **10** (667 mg, 87.5%).

10 (643 mg, 1.60 mmol) was dissolved in 18 mL of dichloromethane/cyclohexane (1:2), benzyl trichloroacetimidate (2.7 mL, 14.4 mmol) and triflic acid (29 μL, 0.32 mmol) were added to the solution in turn. The reaction mixture was stirred at room temperature for 2 h, then saturated sodium hydrogen carbonate solution (5 mL) was added, and diluted with ethyl acetate (200 mL). The organic solution was washed, dried, and concentrated using the described procedure. The residue was submitted on a silica gel column chromatography using petroleum ether:ethyl acetate *V/V* 20:1−10:1 as the eleunt to afford colorless syrup (1.08 g). The syrup was dissolved in 25 mL of methanol/tetrahedrofuran (4:1), 44 mg (0.32 mmol) of powdered potassium carbonate was added to the solution, then stirred at room temperature for 2.5 h. The solvent was removed under reduced pressure, 15 mL of water and 15 mL of ethyl acetate were added for extraction. The organic phase was separated, washed, dried, and concentrated in vacuum. The residue was applied on a silica gel column chromatography using petroleum ether: ethyl acetate *V/V* 4:1 as the eleunt to afford a colorless syrup **11** (36 mg, 81.0%). ^{1}H-NMR ($CDCl_3$), δ: 3.40–3.49 (2H, m), 3.62 (1H, dd, $J = 4.4$, 8.8 Hz), 3.79–4.12 (4H, m), 4.19 (1H, dd, $J = 3.7$, 10.3 Hz), 4.26–4.61 (6H, m), 5.01 (1H, d, $J = 16.8$ Hz), 5.03 (1H, d, $J = 16.8$ Hz), 5.51 (1H, m), 7.15−7.38 (20H, m); ^{13}C-NMR ($CDCl_3$), δ: 52.2, 55.3, 66.1, 67.6, 67.9, 72.8, 73.3, 75.1, 75.8, 82.6, 127.1, 127.5, 127.6, 127.9, 128.5, 128.6, 128.6, 128.7, 129.1, 129.2, 137.3, 137.5, 140.0, 156.8; MS (FAB), *m/z* : 568 $(M+H)^+$.

2.4 Synthesis of (2*R*,3*R*,4*R*)-*N*-benzyloxylcarbonyl-4-benzyloxy-2-fluoromethyl-3-hydroxyl- pyrrolidine (**14**)

Intermediate **4** (257 mg, 0.69 mmol) was dissolved in 5 mL of 1,2-dichloroethane, (diethylamino)sulfur trifluoride (DAST) (0.11 mL, 0.83 mmol) was added to the solution at −20°C. The reaction temperature went up gradually to 60°C. The reaction mixture was stirred at the same temperature for 1 h, then was cooled to 0°C, and neutralized by slowly adding saturated sodium hydrogen carbonate at 0°C. The mixture was extracted with ethyl acetate (15 mL), and the organic phase was washed, dried, and concentrated. The residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 3:1) to afford colorless syrup of **12** (135 mg, 52.4%).

To the solution of **12** (344 mg, 0.92 mmol) in 10 mL of dichloromethane/cyclohexane (1:2), benzyl trichloroacetimidate (0.68 mL, 3.68 mmol) and triflic acid (16 μL, 0.18 mmol) were added slowly. The reaction mixture was stirred at room temperature for 4 h, and then cooled to 0°C. Saturated sodium hydrogen carbonate (1 mL) and ethyl acetate (20 mL) were added to the reaction mixture for extraction. The organic phase was washed, dried, and concentrated as usual, and the residue was applied on a silica gel column chromatography (petroleum ether: ethyl acetate *V/V* 8:1−5:1 as eluent) to afford colorless syrup of **13** (317 mg, 74.2%).

The intermediate **13** (317 mg, 0.68 mmol) was dissolved in 6 mL of methanol, powdered potassium carbonate (27 mg, 0.20 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h, then concentrated under reduced pressure. The residue was dissolved in 15 mL of water and 15 mL of ethyl acetate, after extraction the organic phase was washed, dried, and concentrated as usual. The residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 3:1 as eluent) to afford colorless syrup of **14** (187 mg, 76.5%). ^{1}H-NMR ($CDCl_3$), δ: 3.35–4.80 (7H, m), 5.50–5.75 (4H, m), 7.20–7.50 (10H, m); ^{13}C-NMR ($CDCl_3$), *δ:* 48.4, 54.6, 66.1, 72.5, 74.6, 75.3, 78.1, 127.1, 127.4, 127.5, 128.6, 128.7, 129.2, 135.4, 138.4, 157.6; MS (FAB), *m/z*: 360 $(M+H)^+$.

2.5 Synthesis of (2*R*,3*R*,4*R*)-*N*-benzyloxylcarbonyl-2-benzyloxymethyl-4-fluoro-3-hydroxyl-pyrrolidine (**17**)

To the solution of **4** (3.37 g, 9.07 mmol) in 189 mL of dichloromethane/cyclohexane (1:2), benzyl trichloroacetimidate (2.0 mL, 10.88 mmol) and then triflic acid (2.57 mL, 15.3 mmol) were added slowly. The reaction mixture was stirred at room temperature for 1 h, and then cooled to 0°C. Saturated sodium hydrogen carbonate (20 mL) and ethyl acetate (200 mL) were added to the mixture for extraction. The organic phase was washed, dried and concentrated as usual, and the residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 5:1–2:1 as eluent) to afford straw yellow syrup of **15** (4.17 g, 99.5%).

The intermediate **15** (1.85 mg, 4.0 mmol) was dissolved in 40 mL of dichloromethane, pyridine (1.0 mL, 12.0 mmol) and triflic anhydride (1.0 mL, 6.0 mmol) were added to the solution in turn. The reaction mixture was stirred at 0°C for 20 min, then 100 mL of water was added at 0°C, and extracted with dichloromethane. The organic phase was washed, dried, and concentrated as usual, and the residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 2:1 as eluent) to afford straw yellow syrup of **16** (1.22 g, 65.9%).

To the solution of **16** (980 mg, 2.12 mmol) in 20 mL of 1,2-dichloroethane, were added 0.84 mL (6.36 mmol) of DAST at −20°C. The reaction mixture was gradually warmed up to 60°C, stirred at the same temperature for 1 h, then cooled to 0°C, neutralized by slowly adding saturated sodium hydrogen carbonate at 0°C, and extracted with ethyl acetate. The organic phase was washed, dried, and concentrated as usual, and the residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 4:1 as eluent) to afford pale yellow syrup. The syrup was dissolved in 10 mL of methanol, and followed by the addition of 50 mg of powdered potassium carbonate. The mixture was stirred at room temperature for 20 h and concentrated under reduced pressure. The residue was added with 20 mL of water, and extracted with ethyl acetate. The organic phase was washed, dried, and concentrated as usual, and the residue was applied on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 2:1 as eluent) to afford colorless syrup of **17** (351 mg, 46.1%). ^{1}H-NMR ($CDCl_3$), δ: 3.10–4.20 (4H, m), 4.25–4.75 (3H, m), 4.80–5.20 (5H, m), 7.30–7.45 (10H, m); ^{13}C-NMR ($CDCl_3$), δ: 43.8, 56.3, 66.1, 66.4, 69.6, 75.4, 91.4, 127.1, 127.3, 127.6, 127.8, 128.2, 128.7, 129.1, 129.4, 137.4, 140.1, 156.7; MS (FAB), *m/z*: 360 $(M+H)^+$.

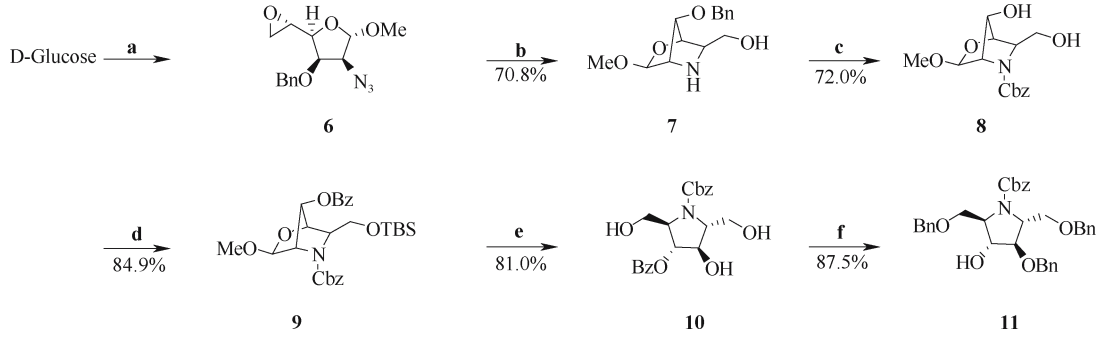
2.6 Synthesis of the disaccharide derivative (**19**)

A solution was prepared by dissolving 53.6 mg (0.1 mmol) of **18** and 50.0 mg (0.11 mmol) of **5** in 3 mL of dry CH_2Cl_2, and then 100 mg of anhydrous $MgSO_4$ was added to the solution. The mixture was stirred at room temperature for 15 min under nitrogen atmosphere, and then 0.9 μL (0.01 mmol) of triflic acid (TfOH) was added at –78°C with stirring. The reaction mixture was stirred at –78°C for 1 h, and then gradually warmed up to 0°C, one drop of triethylamine was added to quench the reaction. After removing the solvent under reduced pressure, the residue was submitted on a silica gel column chromatography (petroleum ether : ethyl acetate *V/V* 4:1 as eluent) to afford colorless syrup of **19** (87.5 mg, 88.9%). ^{1}H-NMR ($CDCl_3$), δ: 1.32 (s, 3H, CH_3), 3.25 (d, 1H, $J = 9.45$ Hz), 3.43 (t, 1H, $J = 9.22$ Hz), 3.49–3.78 (m, 4H), 3.83–3.94 (m, 4H), 4.19 (t, 1H, $J = 9.46$ Hz), 4.36–4.55 (m, 8H), 4.64 (d, 1H, $J = 12.20$ Hz), 4.72−4.85 (m, 4H), 4.88−5.05 (2H, m), 5.28 (d, 1H, $J = 11.60$ Hz), 7.09−7.36 (33H, m), 7.44 (2H, d, $J = 7.53$ Hz); ^{13}C-NMR ($CDCl_3$), δ: 21.4 (CH_3), 45.5, 55.2, 65.0, 66.3, 67.4, 68.3, 69.4, 71.3, 73.3, 73.5, 73.6, 74.2, 75.6, 75.7, 75.8, 78.1, 82.4, 83.7, 102.2, 126.8, 127.2, 127.3, 127.4, 127.5, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 129.0, 137.9, 138.0, 138.2, 138.3, 138.6, 140.1, 159.2; MS (FAB), *m/z*: 985 $(M+H)^+$.

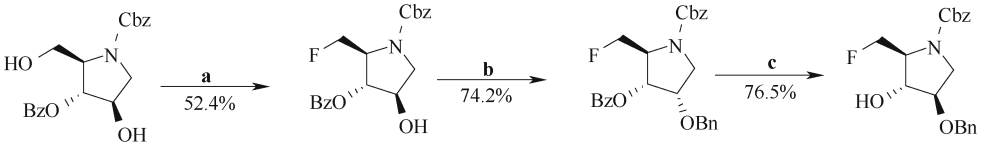
3 Results and discussion

Hydroxyl protection is one of the most important jobs in carbohydrate chemistry, in order to get the given hydroxyl protected intermediates it is necessary to select different methods to introduce certain protecting groups in suitable steps [33]. Thus, in order to get compound **5** with 3-hydroxyl free as shown in Scheme 1, the 7-hydroxyl in the intermediate **2** was firstly benzoylated before the cycloacetal ring of **3** was opened by acidic hydrolysis, providing an opportunity to the selective protection of 3,4-hydroxyl groups in the following steps. The intermediate **4** was carried out the acidic benzylation in 4-hydroxyl and 1-methylhydroxyl, and basic hydrolysis to remove 3-benzoyl group, to afford the selectively protected product **5**. It should be mentioned that in the key step of reductive cyclization from **1** to **2** (Scheme 1, step b), only *α*-isomer of **1** underwent the reaction, the *β*-isomer could not, probably due to the spatial hindrance of the β-glycosidic bond.

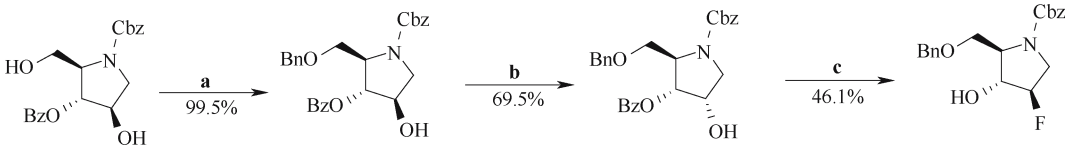
With the same method, the azasugar derivative **11** was synthesized from D-glucose via intermediate **7** [32] as shown in Scheme 2. One of the most important steps in the synthesis



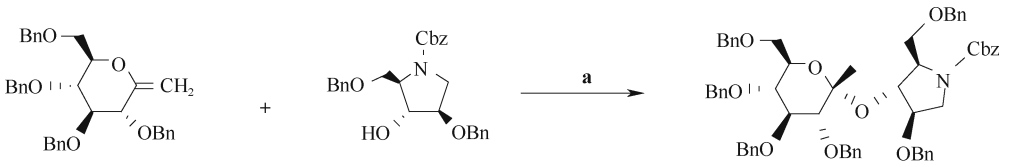
Scheme 2 a. ref. [32]. b. Lindlar cat./H_2, EtOH, r.t. c. i) $Pd(OH)_2/C$, H_2, MeOH; ii) BnOCOCl (6.33 mmol), aq.Na_2CO_3/ CH_2Cl_2, r.t. d. i) TBDMSCl (1.25 mmol)/Py, 0°C; ii) PhCOCl (1.72 mmol)/Py, 0°C. e. i) CF_3COOH/H_2O (4:1), r.t.; ii) $NaBH_4$ (0.10 mmol)/EtOH/H_2O, 0°C f. i) $CCl_3C(NH)OBn$ (14.4 mmol), CH_2Cl_2, r.t.; ii) K_2CO_3/MeOH, r.t



Scheme 3 a. DAST(0.83 mmol)/CH_2Cl_2, −20°C, then 60°C; b. $CCl_3C(NH)OBn$ (3.68 mmol), TfOH (0.18 mmol), CH_2Cl_2/cyclo-C_6H_{12}, r.t.; c. K_2CO_3/MeOH,r.t



Scheme 4 a. $CCl_3C(NH)OBn$ (10.88 mmol), TfOH(15.3 mmol), CH_2Cl_2/ cyclohexane, 0°C; b. Tf_2O (6.0 mmol)/Py(12.0 mmol)/CH_2Cl_2, 0°C; c. i) DAST(6.36 mmol), CH_2Cl_2, −20°C, then 60°C; ii) K_2CO_3/MeOH,r.t



Scheme 5 a. TfOH (0.01 mmol), CH_2Cl_2, −78°C~0°C

is the selective protection of the primary hydroxyl in **8** utilizing the reactive difference of *tert*-butyldimethylsilyl chloride (TBDMSCl) to the primary and secondary hydroxyl groups.

Organofluorine compounds commonly exhibit some special properties due to the high electronegativity and lower atom radius of fluorine, and have been widely used in material and pharmaceutical sciences. For instance, in designing a chemical drug, certain hydrogen atom(s) in lead compound were sometimes replaced by fluorine to improve the biological activity. Moreover, fluorinated glycosides have been found to be of interesting in anticancer and antiviral potentials [34]. From this point of view, the fluorinated azasugar derivatives **14** and **17** were also synthesized based on the synthesis of azasugar intermediate **4**. Thus, the substitution of primary hydroxyl of **4** by direct fluorination with DAST, and followed by benzylation and debenzoylation, produced the fluorinated derivative **14** (Scheme 3). As for the synthesis of derivative **17**, the primary hydroxyl group in **4** should be firstly protected with benzyl group, the configuration of 4-C in **4** was reversed by triflate esterification and hydrolysis to afford intermediate **16**. Followed by fluorination with DAST on 4-C and debenzoylation the target compound **17** was obtained (Scheme 4).

With the partially protected azasugars in hand, we explored the glycosylation of **5** and benzylated 1-methylenesugar **18** [35] and obtained the disaccharide **19** containing azasugar moiety (Scheme 5). Similar to the previous observation [12], the reaction could take place smoothly with catalytic amount of Lewis acid TfOH at low temperature to afford α-disaccharide **19** exclusively.

The structures of all the intermediates and target compounds were characterized based on the analyses of ^{1}H-NMR, ^{13}C-NMR, 2D-COSY and MS (FABMS) spectra.

In conclusion, four azasugar derivatives **5**, **11**, **14** and **17** possessing the same configuration on 4-C and 3-OH free were prepared using D-xylose and D-glucose as the starting materials, and the glycosylation of the derivative **5** with benzylated 1-methylenesugar was approached in obtaining a novel disaccharide **19** containing azasugar moiety.

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