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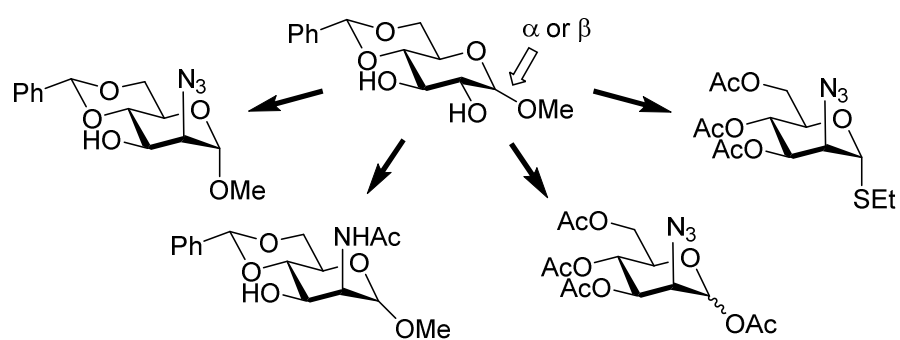
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Synthesis of 2-azido-2-deoxy- and 2-acetamido-2-deoxy-D-manno derivatives as versatile building blocks

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Supporting Information Placeholder

ABSTRACT: Reported herein is the synthesis of a number of building blocks of 2-amino-2-deoxy-D-mannose from common D-glucose precursors.

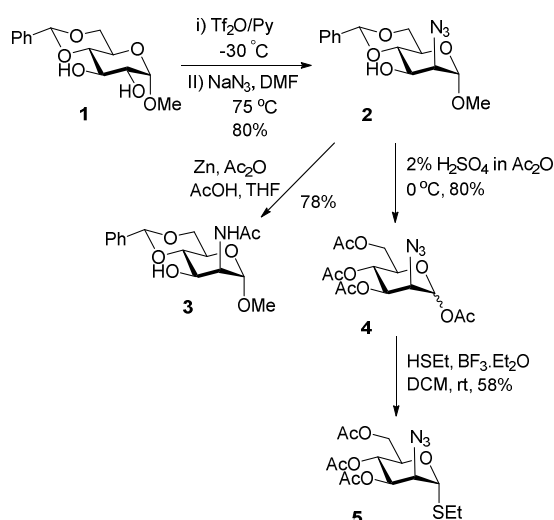
All oligosaccharides comprise an oligomeric sequence wherein monomers are linked via *O*-glycosidic linkages. This type of linkage is obtained by a glycosylation reaction, which, in spite of significant progress, remains challenging due to the requirement to achieve high stereocontrol^{1,2} and suppress side reactions.^{3,4} Due to significant advances, many glycans can now be obtained by using chemical methods and automated platforms in solution and on solid phases.⁵ However, poor accessibility to sugar building blocks hampers development of all synthetic approaches. Things are further complicated because “*unlike the synthesis of peptides and oligonucleotides, there are no universal building blocks or methods for the synthesis of all glycans.*”⁶ In spite of general improvements in application of protecting groups in the mainstream carbohydrate research,^{7–12} building blocks for the introduction of uncommon (rare) sugars remain largely underdeveloped or not available at all.¹³ Reported herein are reliable and scalable procedures for the synthesis of mannosamine building blocks.

N-Acetylmannosamine (ManNAc) is the biosynthetic precursor of *N*-acetylneuraminic acid^{14,15} and a constituent of many bacterial glycans.^{16–18} Hence, a considerable interest has been devoted to the synthesis of ManNAc and its derivatives. Nevertheless, mannosamine remains prohibitively expensive as the starting material both for the laboratory and industrial application. The total synthesis from D-arabinose reported by O'Neill¹⁹ and alkaline-mediated epimerization of C-2 in *N*-acetylglucosamine by Spivak and Roseman²⁰ are the classics of the synthesis of ManNAc. More recently, building blocks of ManNAc have been prepared via the inversion of configuration at C-2 of D-glucose with nitrogen nucleophiles.^{21–23}

Reported herein are two modes to obtain ManNAc derivatives from methyl 4,6-*O*-benzylidene- α and β -D-

glucopyranosides **1** and **6**.^{24,25} As previously shown by Knapp *et al*,²³ high regioselectivity of sulfonation of diol **1** with triflic anhydride in pyridine toward the C-2 position could be achieved at low temperature. The resulting 2-*O*-triflate was then subjected to the nucleophilic displacement with sodium azide in DMF to afford 2-azido-2-deoxy-D-mannopyranoside intermediate **2** (Scheme 1). This two-step protocol represent a common approach to obtain rare or inaccessible amino-sugars.²⁶ The latter can be used for a number of pathways that is showcased herein by two synthetic transformations. First, treatment of compound **2** with zinc in the presence of acetic anhydride provided direct transformation of the 2-azido into 2-acetamido group. As a result, ManNAc derivative **3** was obtained in 78% yield. It should be noted that derivatives **2** and **3** can be used as glycosyl acceptors or as intermediates to access other functionalized derivatives. In addition, while we were specifically targeting 2-azido and 2-acetamido derivatives, many other *N*-protecting groups can be introduced after the azide reduction step, if so desired.

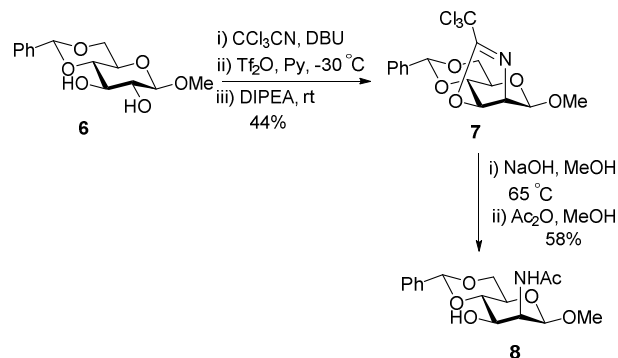
Scheme 1. The synthesis of D-mannosamine building blocks 2-5 from D-glucose derivative 1



We also performed acetolysis of intermediate **2** with acetic anhydride in the presence of H_2SO_4 . This reaction led to concomitant replacement of methyl glycoside and benzylidene acetal with acetyl groups. As a result, tetraacetate **4** was smoothly produced in 80% yield. The latter derivative can be used as a versatile intermediate for further functionalization. Herein, tetraacetate **4** was reacted with ethane thiol in the presence of BF_3 etherate. As a result, ethylthio glycoside **5** was produced in 58% yield. While thioglycosides can be used as versatile building blocks and as glycosyl donors, the synthesis of other types of glycosyl donors or building blocks can be readily achieved using similar synthetic routes.

The second approach to produce mannosamine derivatives described herein involves adaptation of the *O*-trichloroacetimidoyl protecting group migration approach developed by van der Marel and co-workers for the synthesis of other aminosugar targets.^{27,28} This was affected by regioselective *O*-imidoylation at the C-3 position of diol **6**. Preferential substitution at the C-3 position was achieved with trichloroacetonitrile in the presence of DBU at room temperature. Subsequent *in-situ* sulfonation with triflic anhydride in pyridine at C-2 followed by the treatment with DIPEA led to the formation of 2,3-*N,O*-oxazoline **7**, all in one pot. The intermediate **7** was isolated in 44% yield over three steps. The fair yield is due to marginal regioselectivity obtained during the first step and the necessity to separate product **7** from the resulting side products. The oxazoline ring in derivative **7** was hydrolyzed by reaction with sodium hydroxide. The amine group in the resulting partially protected derivative was then chemoselectively *N*-acetylated to afford ManNAc derivative **8**. While we were specifically interested in obtaining 2-acetamido derivatives, many other *N*-protecting groups can be introduced after the oxazoline ring removal, if so desired. The resulting 3-OH derivative **8** can be used as a glycosyl acceptor directly, or employed in further functionalization per specific synthetic targets.

Scheme 2. The synthesis of D-mannosamine building block 8



In summary, presented herein is an efficient synthesis of a variety of 2-amino-2-deoxy derivatives of D-mannose. We investigated gram-scale syntheses, and the developed protocols appear to be sufficiently straightforward and reliable to be attempted at a greater scale if needed. The utility of these building blocks has been demonstrated by the synthesis of glycosyl acceptors **2**, **3** and **8** as well as thioglycoside donor **5**. While we were specifically targeting 2-azido and 2-acetamido derivatives, many other *N*-protecting groups can be introduced, if necessary. Further application of these versatile building blocks, both as glycosyl donors and as glycosyl acceptors, are currently underway in our laboratories.

Experimental

General methods. Solvents were purified according to standard procedures.²⁹ Reactions were performed using commercial reagents (Millipore Sigma, Carbosynth, TCI, or Acros), and monitored by TLC on Kieselgel 60 F₂₅₄ (EM Science). Compounds were detected by UV light and by charring with 10% sulfuric acid in methanol. Solvents were removed under reduced pressure at <40 °C. Column chromatography was performed on silica gel 60 (70-230 mesh). Optical rotations were measured at 'Jasco P-2000' polarimeter at 22 °C. ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker Avance spectrometer. The chemical shifts are referenced to the signal of the residual CHCl_3 ($\delta_{\text{H}} = 7.27$ ppm, $\delta_{\text{C}} = 77.23$ ppm) for solutions in CDCl_3 . COSY and HMQC experiments were done to aid nuclei assignments. HRMS were recorded with a JEOL MStation (JMS-700) Mass Spectrometer. Melting points were measured at Digimelt MPA 160 melting point apparatus.

Methyl 2-azido-4,6-O-benzylidene-2-deoxy- α -D-mannopyranoside (2). Pyridine (14 mL, 173.8 mmol) and trifluoromethanesulfonic anhydride (Tf_2O , 0.65 mL, 3.87 mmol) were added at -30 °C under argon to a stirred solution of methyl 4,6-O-benzylidene- α -D-glucopyranoside (**1**, 0.99 g, 3.52 mmol) in CH_2Cl_2 (14 mL) and the resulting mixture was stirred at -30 °C for 3 h. The volatiles were removed under reduced pressure, and the residue was dried *in vacuo* for 2 h. Sodium azide (NaN_3 , 1.14 g, 17.6 mmol) was added to a solution of the residue in DMF (15 mL) and the resulting mixture was stirred at 75 °C for 12 h. After that, the reaction mixture was allowed to cool to rt, volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc-hexane gradient elution) to afford the title compound (0.874 g, 2.84 mmol) in 80% as a pale-yellow syrup. Analytical data for **2**: R_f 0.7 (EtOAc-hexanes, 2/3, v/v). $[\alpha]_{\text{D}}^{+70.8}$ (c 1.0, CHCl_3); ¹H NMR: δ , 2.60 (s, 1H, 3-OH), 3.39 (s, 3H, OCH_3), 3.72-3.87 (m, 2H, H-

5, 6a), 3.91 (dd, 1H, $J_{4,5}$ = 7.6 Hz, H-4), 3.99 (dd, 1H, $J_{2,3}$ = 3.9 Hz, H-2), 4.21-4.32 (m, 2H, $J_{3,4}$ = 7.6 Hz, H-3, 6b), 4.70 (d, 1H, $J_{1,2}$ = 1.1 Hz, H-1), 5.58 (s, 1H, CHPh), 7.34-7.44 (m, 3H, aromatic), 7.45-7.54 (m, 2H, aromatic) ppm; ^{13}C NMR: δ , 55.3 (OCH₃), 63.4 (C-5), 63.8 (C-2), 68.8 (C-6), 69.0 (C-3), 79.1 (C-4), 100.2 (C-1), 102.4 (CHPh), 126.4, 128.5, 129.4, 137.2 (6C, aromatic) ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}_5\text{Na}$, 330.1066; found, 330.1069. Partial characterization data $[\alpha]_{\text{D}}^{25}$ +69.5 (c 1.1, CHCl_3)³⁰ and ^{13}C NMR for **2** were reported previously.²²

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy- α -D-mannopyranoside (3). Acetic acid (2.0 mL, 30.7 mmol), acetic anhydride (Ac_2O , 2.0 mL, 18.6 mmol), and zinc dust (2.0 g, 26.9 mmol) were added to a solution of methyl 2-azido-4,6-O-benzylidene-2-deoxy- α -D-mannopyranoside (**2**, 0.83 g, 2.72 mmol) in THF (10 mL) and the resulting mixture was stirred under argon for 1 h at rt. The solids were filtered off through a pad of Celite, volatiles were removed under reduced pressure, and the residue was purified by column chromatography on silica gel (MeOH- CH_2Cl_2 gradient elution) to afford the title compound (0.68 g, 2.10 mmol) as white crystals in 78% yield. Analytical data for **3**: m.p. 227-228 °C (CH_2Cl_2 - hexanes); $[\alpha]_{\text{D}}^{25}$ +40.5 (c 1.0, CHCl_3); R_f 0.6 (MeOH/ CH_2Cl_2 , 1/9, v/v); ^1H NMR: δ , 2.07 (s, 3H, COCH₃), 3.38 (s, 3H, OCH₃), 3.66 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.75-3.92 (m, 2H, H-5, 6a), 4.25-4.34 (m, 2H, H-3, 6b), 4.45 (br ddd, 1H, H-2), 4.77 (d, 1H, $J_{1,2}$ = 0.8 Hz, H-1), 5.59 (s, 1H, CHPh), 5.85 (br d, 1H, $J_{2,\text{NH}}$ = 7.0 Hz, NH), 7.33-7.39 (m, 3H, aromatic), 7.45-7.51 (m, 2H, aromatic) ppm; ^{13}C NMR: δ , 23.5 (COCH₃), 53.6 (C-2), 55.4 (OCH₃), 62.8 (C-5), 67.2 (C-3), 68.9 (C-6), 79.7 (C-4), 100.8 (C-1), 102.5 (CHPh), 126.4, 128.5, 129.4, 137.1 (6C, aromatic), 171.8 (C=O) ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_6\text{Na}$, 346.1267; found, 346.1261.

1,3,4,6-Tetra-O-acetyl-2-azido-2-deoxy-D-mannopyranose (4). Sulfuric acid (0.2 mL, 3.73 mmol) was added dropwise to a solution of **2** (0.76 g, 2.47 mmol) in acetic anhydride (10.0 mL, 106.0 mmol) at 0 °C. The external cooling was removed, and the resulting mixture was stirred under argon for 4 h at rt. Sat. aq. NaHCO_3 was added carefully to the reaction mixture until gas evolution has ceased. EtOAc (30 mL) was added, and the resulting mixture was washed with sat. aq. NaHCO_3 . The organic layer was separated, dried over Na_2SO_4 , and filtered. Volatiles were removed under reduced pressure and the residue was co-evaporated with toluene. The resulting residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound (0.74 g, 1.97 mmol) as a pale-yellow amorphous solid in 80% yield (α/β = 7/1). Analytical data for **4**: R_f 0.5 (EtOAc/hexanes, 1/1, v/v); ^1H NMR: δ , 2.11, 2.15, 2.17, 2.22 (4 s, 12H, 4 x COCH₃), 4.04-4.20 (m, 3H, H-2, 5, 6a), 4.30 (dd, 1H, J = 4.5, 12.4 Hz, H-6a), 5.39-5.50 (m, 2H, H-3, 4), 6.17 (d, 1H, J = 1.9 Hz, H-1) ppm; ^{13}C NMR: δ , 20.6, 20.7, 20.8, 20.9, 60.5, 61.8, 65.3, 70.6, 70.7, 91.3, 168.3, 169.4, 170.1, 170.8 ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{N}_3\text{O}_9\text{Na}$, 396.1019; found, 396.1024.

Ethyl 3,4,6-tri-O-acetyl-2-azido-2-deoxy-1-thio- α -D-mannopyranoside (5). Boron trifluoride diethyl etherate (3.05 mL, 24.05 mmol) was added dropwise to a solution of **4** (2.24 g, 6.01 mmol) and ethane thiol (0.89 mL, 12.03 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The external cooling was then removed and the resulting mixture was stirred under argon for 16 h at rt. After that, the reaction mixture was diluted with

CH_2Cl_2 (~150 mL) and was washed with H_2O (50 mL), sat. aq. NaHCO_3 (50 mL), and H_2O (2 x 50 mL). The organic layer was separated, dried, and volatiles were removed under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate-hexanes gradient elution) to afford the title compound (1.31 g, 3.49 mmol) as a pale-yellow syrup in 58% yield. Analytical data for **5**: R_f 0.7 (EtOAc/hexanes, 1/1, v/v); $[\alpha]_{\text{D}}^{25}$ +26.6 (c 1.0, CHCl_3); ^1H NMR: δ , 1.35 (t, 3H, J = 7.4 Hz, SCH_2CH_3), 2.09, 2.13, 2.13 (3 s, 9H, COCH₃), 2.59-2.78 (m, 2H, SCH_2CH_3), 4.09-4.17 (m, 2H, H-2, 6a), 4.29-4.42 (m, 2H, H-5, 6b), 5.30-5.42 (m, 3H, H-1, 3, 4) ppm; ^{13}C NMR: δ , 14.7, 20.6, 20.7, 20.8, 25.5, 62.1, 62.8, 66.1, 68.8, 71.3, 82.3, 169.6, 170.0, 170.8 ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_7\text{SNa}$, 398.0998; found, 398.1003.

Methyl 4,6-O-benzylidene-2-deoxy-2N,3O-(2,2,2-trichloroethylidene)- β -D-mannopyranoside (7). Trichloroacetonitrile (CCl_3CN , 535 μL , 5.33 mmol) and activated molecular sieves (3 Å, 1.20 g) were added to a solution of **6** (1.25 g, 4.44 mmol) in CH_2Cl_2 (50 mL) and the resulting mixture was stirred under argon for 15 min at rt. After that, DBU (67 μL , 0.44 mmol) was added, and the reaction mixture was stirred for 5 h at rt. The mixture was then cooled to -30 °C, pyridine (1.79 mL, 22.2 mmol) and Ti_2O (897 μL , 5.33 mmol) were added, and the resulting mixture was stirred under argon for 2 h at -30 °C. The cooling was removed, *N,N*-diisopropylethylamine (DIPEA, 7.7 mL, 44.4 mmol) was added, and the bright-red colored mixture was stirred under argon for 12 h at rt. The volatiles were removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc-hexanes gradient elution) to afford the title compound (805 mg, 1.97 mmol) as colorless crystals in 44% yield. Analytical data for **7**: R_f 0.6 (EtOAc/hexanes, 2/3, v/v); m.p. 164-165 °C (from aq. MeOH); $[\alpha]_{\text{D}}^{25}$ -76.5 (c 1.0, CHCl_3); ^1H NMR: δ , 3.46 (s, 3H, OCH₃), 3.64 (m, 1H, $J_{5,6a}$ = 10.1 Hz, $J_{5,6b}$ = 4.4 Hz, H-5), 3.72 (dd, 1H, $J_{6a,6b}$ = 10.0 Hz, H-6a), 4.38 (dd, 1H, H-6b), 4.56-5.65 (m, 2H, H-2, 4), 4.92 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.02 (dd, 1H, $J_{2,3}$ = 7.4, $J_{3,4}$ = 9.8 Hz, H-3), 5.61 (s, 1H, CHPh), 7.34-7.42 (m, 3H, aromatic), 7.46-7.55 (m, 2H, aromatic) ppm; ^{13}C NMR: δ , 56.1 (OCH₃), 64.5 (C-5), 67.4 (C-2), 70.3 (C-6), 76.9 (C-4), 77.4 (CCl_3), 82.6 (C-3), 97.5 (C-1), 101.8 (CHPh), 126.4, 128.5, 129.5, 136.9 (6C, aromatic), 164.7 (C=N) ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{16}\text{Cl}_3\text{NO}_5\text{Na}$, 429.9992; found, 429.9980.

Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy- β -D-mannopyranoside (8). 1 M aq. NaOH (10 mL) was added dropwise to a solution of **7** (559 mg, 1.37 mmol) in MeOH (30 mL) and the resulting mixture was kept for 12 h at reflux (~65 °C). The reaction mixture was allowed to cool to rt, the volatiles were removed under reduced pressure, and the residue was dried in *vacuo* for 1 h. The crude residue was dissolved in MeOH (15 mL), Ac_2O (0.65 mL, 6.91 mmol) was added, and the resulting mixture was stirred under argon for 2 h at rt. After that, volatiles were removed, and the residue was purified by column chromatography on silica gel (MeOH- CH_2Cl_2 gradient elution) to afford the title compound (252 mg, 0.78 mmol) as a white amorphous solid in 58% yield. Analytical data for **8**: R_f 0.5 (MeOH/ CH_2Cl_2 , 1/9, v/v); m.p. 217-219 °C (from CH_2Cl_2 -hexane); $[\alpha]_{\text{D}}^{25}$ -42.0 (c 1.0, CHCl_3); ^1H NMR: δ , 2.11 (s, 3H, COCH₃), 3.46 (m, 1H, $J_{5,6a}$ = 10.2, $J_{5,6b}$ = 4.9 Hz, H-5), 3.52 (s, 3H, OCH₃), 3.70 (dd, 1H, $J_{4,5}$ = 9.4 Hz, H-4), 3.80 (dd, 1H, $J_{6a,6b}$ = 10.2 Hz, H-6a), 4.00 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 4.34 (dd, 1H, H-6b), 4.52 (br dd, 1H, $J_{2,3}$ = 4.0 Hz, H-2),

4.64 (d, 1H, $J_{1,2} = 1.7$ Hz, H-1), 5.57 (s, 1H, CHPh), 5.98 (br d, 1H, $J_{2,NH} = 6.0$ Hz, NH), 7.30-7.40 (m, 3H, aromatic), 7.44-7.53 (m, 2H, aromatic) ppm; ^{13}C NMR: δ , 23.3 (COCH₃), 54.9 (C-2), 57.3 (OCH₃), 67.4 (C-5), 68.6 (C-6), 71.6 (C-3), 79.7 (C-4), 100.6 (C-1), 102.3 (CHPh), 126.4, 128.4, 129.3, 137.1 (6C, aromatic), 173.8 (C=O) ppm; HR-FAB MS: $[\text{M}+\text{Na}]^+$ calcd for C₁₆H₂₁NO₆Na, 346.1267; found, 346.1254.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for all new compounds. This material is available free of charge via the Internet at

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Notes

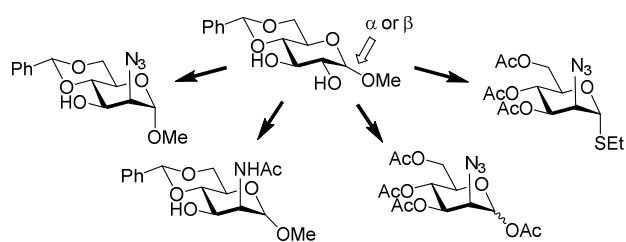
The authors declare no competing financial interests.

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- Chemical synthesis of a variety of derivatives of mannosamine has been completed using different approaches;
- The synthesized compounds can be used as glycosyl donors or glycosyl acceptors directly;
- Other modifications of protecting and/or leaving groups can be easily incorporated;
- The developed approaches are expected to expedite the synthesis of microbial glycans containing 2-acetamido-D-manno residues

The authors have no conflicts to declare

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