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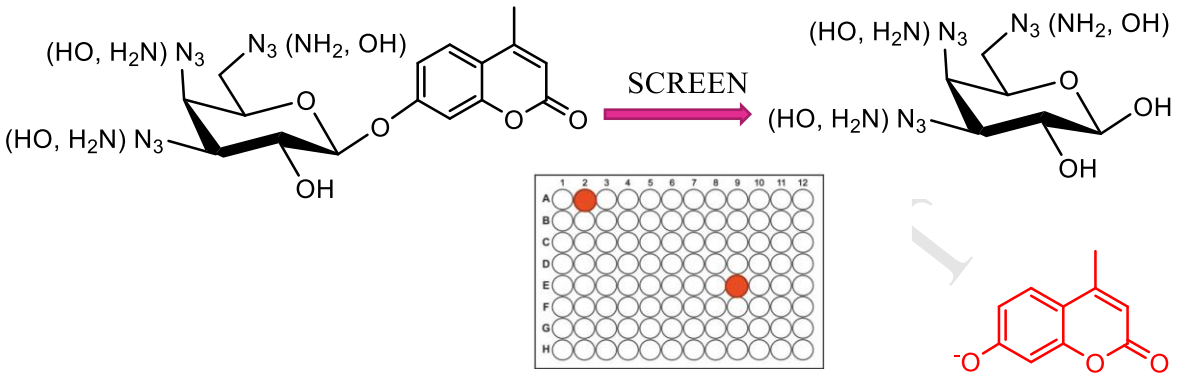

Synthesis of azido-deoxy and amino-deoxy glycosides and glycosyl fluorides for screening of glycosidase libraries and assembly of substituted glycosides.

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Abstract

Azide- and amine- substituted sugars can be useful tools in the probing of biological systems as well as in the assembly of libraries of derivatives using click chemistry or simple amine coupling approaches. A collection of methylumbelliferyl glycosides of

various azido- and amino-deoxy sugar derivatives of glucose, galactose and xylose was synthesised via azide displacement of the corresponding triflate derivatives and subsequent modification. These compounds will be used as substrates in a high-throughput screen to identify glycosidases that can process such modified sugars. The α-glycosyl fluoride derivatives of each modified sugar were also synthesised to serve as substrates for glycosynthases derived from the enzymes identified in the screen.

1. Introduction

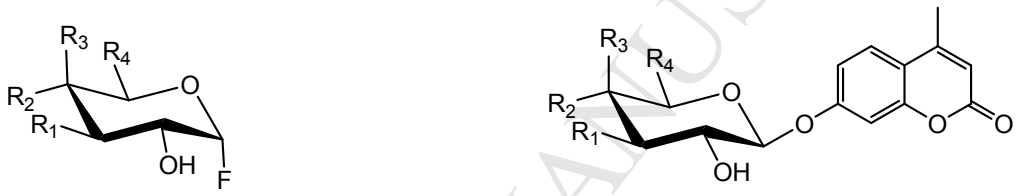
Azido-sugars have enjoyed substantial usage as reagents for probing cellular glycosylation events since, in many cases, they can be incorporated onto cell surfaces using the organism's own biosynthetic pathways. Once incorporated their locations can be determined through bio-orthogonal ligation reactions, primarily through click chemistry with alkyne-containing reagents. Most such studies have been performed with azide-modified sialic acids or fucose derivatives since these are common terminal sugars on cell surfaces [1-5].

Applications of azido-sugars are not, however, limited to cell surface labelling. They have been used in a number of areas, including the assembly of glycopolymers and dendrimers, in the generation of small molecule libraries and in protein surface modifications [6]. In a related manner, amino-deoxy sugars are also of interest, both as naturally occurring entities, such as components of antibiotics or glycosaminoglycans and themselves as modified, and modifiable sugars (though not bio-orthogonal).

As part of a program to explore the capacity of glycoside hydrolases to accommodate azido-deoxy and amino-deoxy sugars as substrates we needed access to a range of fluorogenic glycoside substrates bearing azide substituents at discrete locations around the ring. These can be used as sensitive potential substrates to screen libraries of glycosidases for their ability to process such modified sugars [7]. Our hope then is to generate glycosynthase variants of successful candidate β-glycosidases wherein the catalytic nucleophile has been replaced by a non-nucleophilic residue. When incubated with an α-glycosyl fluoride substrate such glycosynthase mutants typically perform essentially stoichiometric transfer of the glycosyl moiety to a cognate glycosyl acceptor

[8, 9]. Glycosynthase variants of our target enzymes should then accept their cognate azido- or amino-deoxy glycosyl fluoride donor sugar and transfer this to suitable acceptors to assemble azido-sugars containing conjugates under very mild conditions.

In this study, we describe the synthesis of a series of methylumbelliferyl glycosides bearing azide and amine substituents around the ring. Using common key intermediates, we further describe the synthesis of a corresponding series of α-glycosyl fluoride derivatives that will be used as donor sugars for glycosynthases derived from the candidate glycosidases.



4. R_1=OH, R_2=N_3, R_3=H, R_4=CH_2OH
5. R_1=OH, R_2=NH_2, R_3=H, R_4=CH_2OH
12. R_1=OH, R_2=OH, R_3=H, R_4=CH_2N_3
13. R_1=OH, R_2=OH, R_3=H, R_4=CH_2NH_2
21. R_1=N_3, R_2=OH, R_3=H, R_4=CH_2OH
22. R_1=NH_2, R_2=OH, R_3=H, R_4=CH_2OH
29. R_1=OH, R_2=H, R_3=N_3, R_4=CH_2OH
30. R_1=OH, R_2=H, R_3=NH_2, R_4=CH_2OH
38. R_1=OH, R_2=H, R_3=OH, R_4=CH_2N_3
39. R_1=OH, R_2=H, R_3=OH, R_4=CH_2NH_2
46. R_1=OH, R_2=N_3, R_3=H, R_4=H
47. R_1=OH, R_2=NH_2, R_3=H, R_4=H

7. R_1=OH, R_2=N_3, R_3=H, R_4=CH_2OH
8. R_1=OH, R_2=NH_2, R_3=H, R_4=CH_2OH
15. R_1=OH, R_2=OH, R_3=H, R_4=CH_2N_3
16. R_1=OH, R_2=OH, R_3=H, R_4=CH_2NH_2
24. R_1=N_3, R_2=OH, R_3=H, R_4=CH_2OH
25. R_1=NH_2, R_2=OH, R_3=H, R_4=CH_2OH
32. R_1=OH, R_2=H, R_3=N_3, R_4=CH_2OH
33. R_1=OH, R_2=H, R_3=NH_2, R_4=CH_2OH
41. R_1=OH, R_2=H, R_3=OH, R_4=CH_2N_3
42. R_1=OH, R_2=H, R_3=OH, R_4=CH_2NH_2
49. R_1=OH, R_2=N_3, R_3=H, R_4=H
50. R_1=OH, R_2=NH_2, R_3=H, R_4=H

Figure 1. α-D-Glycopyranosyl fluorides and 4-methylumbelliferyl β-D-glycopyranosides

2. Results and Discussion

Introduction of amine and azide substituents into sugar rings typically requires suitably protection strategy in which the site of substitution is unprotected and of opposite stereochemistry to the desired product. After activation of the hydroxy to introduce a

leaving group, substitution by azide is performed followed by introduction of the desired anomeric substituent. After deprotection, the resulting azido-sugar can be reduced to the corresponding amine as needed.

After screening a variety of strategies for the synthesis of the azido-deoxy and amino-deoxy sugar intermediates required we settled on a common approach involving reaction of the partially protected sugar with triflic anhydride to generate the corresponding triflate. After a simple work-up, the reactive intermediate was immediately subjected to azide displacement to generate the azido-deoxy sugar of inverted configuration at that centre (if stereogenic), typically in net yields of 70-90%. This protected azide was then converted to its per-*O*-acetate as necessary to generate the common intermediate for the two classes of substrate. Subsequent introduction of the methylumbelliferyl group at the anomeric centre was generally achieved via the anomeric trichloroacetimidate while the glycosyl fluorides were synthesised from the per-*O*-acetate using HF/pyridine. Reduction of the deprotected azido-glycosyl fluorides was achieved via catalytic hydrogenation, while reduction of the deprotected methylumbelliferyl azido-sugars required use of triphenylphosphine to avoid partial reduction of the methyumbelliferyl group.

4-Azido-4-deoxy and 4-amino-4-deoxy glucose derivatives were synthesised from the readily available 1,2,3,6-tetra-*O*-benzoyl-D-galactose as shown in Scheme 1. Conversion to the 4-azido-glucose derivative proceeded well via the triflate, with silica gel clean-up prior to Zemplen deprotection and per-*O*-acetylation in a total yield (over 4 steps) of 52%.

6-Azido-6-deoxy and 6-amino-deoxy glucose derivatives were generated by selective triflation of the 6-hydroxyl of 1,2,3-tri-*O*-acetyl-D-glucopyranose at low temperature, followed by azide displacement and then acetylation of the 4-hydroxyl using acetic anhydride in pyridine (Scheme 2). This yielded the per-*O*-acetate directly in a combined yield of 57%.

3-Azido-3-deoxy and 3-amino-deoxy glucose derivatives were generated from 1,2:5,6-di-*O*-cyclohexylidene-D-allofuranose [10, 11] by sequential triflation and azide

displacement (Scheme 3). Deprotection using aqueous trifluoroacetic acid (TFA) followed by acetylation using acetic anhydride and pyridine yielded the per-*O*-acetate of the 3-azido-sugar in a combined yield of 75%.

4-Azido-4-deoxy and 4-amino-deoxy galactose derivatives were synthesised from 1,2,3-tri-*O*-acetyl-D-glucopyranose by selective acetylation of the 6-hydroxyl using 1-(acetoxy)-benzotriazole followed by triflation of the free 4-hydroxyl and displacement with azide (Scheme 4). This yielded the per-*O*-acetate of 4-azido-4-deoxy-D-galactose directly in a combined yield of 72%.

6-Azido-6-deoxy and 6-amino-deoxy galactose derivatives were generated from 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose by triflation of the 6 hydroxyl at 0 °C followed by azide displacement in dry DMF (Scheme 5). Deprotection with aqueous TFA followed by acetylation with acetic anhydride and pyridine yielded the per-*O*-acetate of 6-azido-6-deoxy-D-galactose in a total yield of 69%.

4-Azido-4-deoxy and 4-amino-deoxy xylose derivatives were synthesised from L-arabinose by an initial selective benzoylation of the 1,2 and 3-hydroxyls using benzoyl chloride in pyridine at 0 °C, followed by triflation of the axial 4 hydroxyl and sodium azide displacement (Scheme 6). Deprotection under Zemplen conditions was followed by acetylation with acetic anhydride and pyridine to yield the per-*O*-acetate of 4-azido-4-deoxy-D-xylose in a total yield of 33% from L-arabinose.

3. Experimental

General Information

All chemicals were of analytical grade purchased from the Sigma-Aldrich company, unless otherwise stated. All solvents were BOC standard grade and distilled before use. Dichloromethane and pyridine were distilled from calcium hydride. Methanol was distilled from magnesium. THF was distilled from sodium. DMF was dried and stored over 4 Å molecular sieves. Analytical thin-layer chromatography (TLC) was performed on aluminium-backed sheets of Silica Gel $60F_{254}$ (E. Merck) of thickness 0.2 mm. The

plates were visualised using UV light (254 nm) and/or by exposure to 10% ammonium molybdate (2 M in H_2SO_4) followed by charring. Flash column chromatography was carried out using Silicycle silica gel (230-400 mesh). Proton and carbon NMR spectra were recorded on Bruker Advance 400inv, 400dir and 300 Fourier Transform spectrometer fitted with 5 mm BBI-Z probe. All spectra were recorded using an internal deuterium lock and are referenced internally using the residual solvent peak. Carbon and proton chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane, fluorine chemical shifts are quoted downfield of trifluoroacetic acid (TFA). Coupling constants (*J*) are given in Hertz (Hz). Carbon NMR spectra were performed with broadband proton decoupling and were recorded with DEPT. Mass spectra were recorded on a Waters/Micromass LCT using electrospray ionisation (ESI) and recorded using Time-Of-Flight (TOF) method using methanol as solvent.

General Procedures

A. Fluorination [12]

A solution of acetylated azido-sugar (5 mmol) in dry CH_2Cl_2 (10 mL) was transferred to a 100 mL plastic bottle, cooled to 0 °C, then HF/pyridine (15 mL, 70% HF) was added. The plastic bottle was capped and stirred overnight at 0 °C. The reaction mixture was slowly poured into a plastic beaker with ice, saturated $NaHCO_3$ and solid $NaHCO_3$ cooled with an ice bath with stirring. The crude product was extracted with EtOAc (2 x 100 mL), washed with saturated $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (4:1, petroleum ether-EtOAc).

B. Deacetylation with NH_3 [12]

To a solution of acetylated azido-glycosyl fluoride (2 mmol) in dry methanol (50 mL) was slowly bubbled ammonia for 5 minutes at 0 °C, and the reaction mixture was stirred at 0 °C until completion. The solvent was evaporated, and the resulting residue was purified by flash column chromatography (9:1, CH_2Cl_2-MeOH).

C. Reduction of azide with Pd/C [12]

A mixture of azido-glycosyl fluoride (3 mmol), Pd/C (10% on activated charcoal, 200 mg) and methanol (50 mL) was evacuated and refilled with H_2 three times, and stirred overnight at room temperature under an atmosphere of hydrogen. The reaction mixture was filtered through a short pad of Celite and washed with methanol, and then the solvent was evaporated. The resulting residue was purified by flash column chromatography (10:2:1, EtOAc-MeOH-1 M NH_4OH or 5:1, CH_2Cl_2-MeOH with 1% Et_3N).

D. Anomeric deacetylation [13, 14]

A solution of azido-D-glucose peracetate (3.0 mmol) and hydrazine acetate (360 mg, 3.9 mmol, 1.3 equiv) in DMF (11 mL) was stirred for 3 h at room temperature, diluted with EtOAc (100 mL), washed with H_2O (2 x 50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash column chromatography.

E. Glycosylation [15, 16]

To a solution of acetylated azido-sugar hemiacetal (2 mmol) and trichloroacetonitrile (TCA, 2 mL) in dry CH_2Cl_2 (20 mL) was added 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU, 20 μL) at -20 °C with stirring under N_2, and the mixture was gradually warmed to 0 °C. When TLC showed the reaction was complete, the solvent was evaporated under reduced pressure. The resulting residue was purified by passage through a silica gel plug (3:1, petroleum ether-EtOAc) to afford a colorless syrup. To the syrup were added dry CH_2Cl_2 (25 mL), 4-methyl-7-hydroxylcoumarin (Mu, 2 equiv) and 4 Å molecular sieves, and the mixture was stirred for 10 minutes at room temperature under N_2. The mixture was then cooled to -40 °C, $BF_3{\cdot}Et_2O$ (20 μL) was added dropwise and the reaction mixture was stirred for 5 h under the same conditions until completion. After quenching by addition of Et_3N, the mixture was filtered through a short pad of Celite and washed with CH_2Cl_2. The filtrate was washed with 1 M NaOH (3 x 50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The

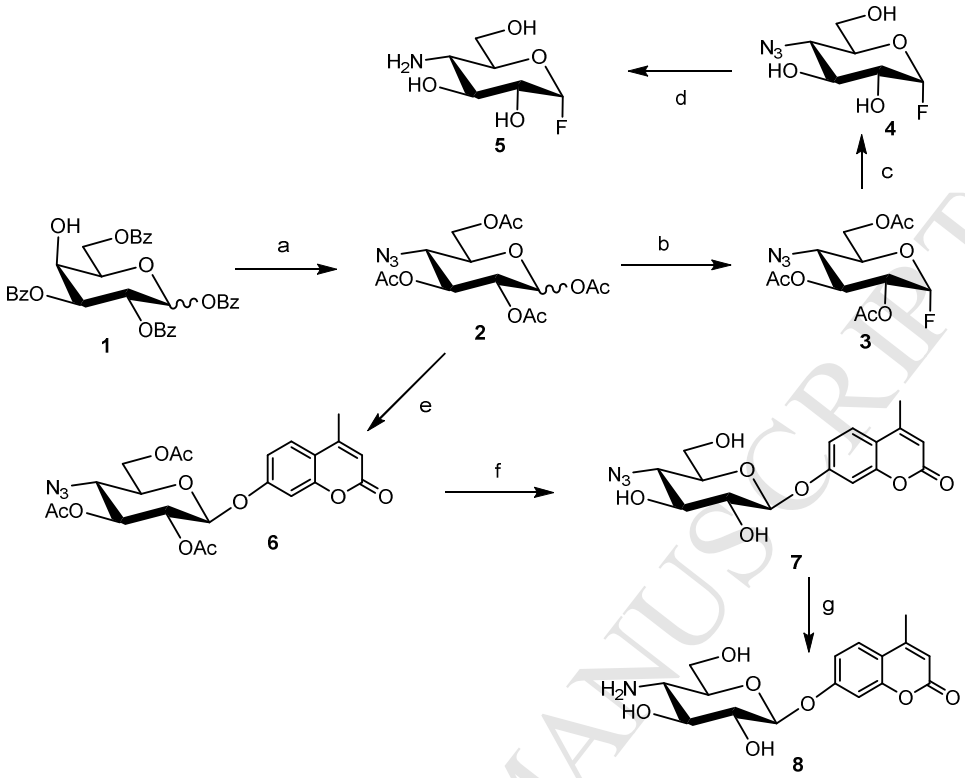
product was purified by flash column chromatography (2:1, petroleum ether-EtOAc) to afford a white solid.

F. Deacetylation with sodium [17, 18]

A solution of acetylated 4-methylumbelliferyl azido-glycoside (1 mmol) in dry methanol (60 mL) was treated with a catalytic amount of sodium under N_2 at room temperature. The white precipitate was filtered and washed with methanol. The mother liquor was neutralized with Amberlite 120 H, filtered and concentrated. The product was precipitated out with methanol and diethyl ether. The combined white solid was dried under vacuum.

G. Reduction of azide with triphenylphosphine [19, 20]

A mixture of acetylated 4-methylumbelliferyl azido-glycoside (0.3 mmol), Ph_3P (110 mg, 0.4 mmol, 1.4 equiv), silica gel (230~400 mesh, 300 mg) and THF/H_2O (4/1, 14 mL) was stirred overnight at 50 °C. After completion, the solvents were removed under reduced pressure. The product was purified by flash column chromatography (17:2:1 and 10:2:1, EtOAc/MeOH/1 M NH_4OH).



Scheme 1. Reagents and conditions: a) CH_2Cl_2, pyridine, Tf_2O, 0 °C; DMF, NaN_3, rt; MeOH, NaOMe, rt; pyridine, Ac_2O, rt; 52% (four steps). b) CH_2Cl_2, HF/pyridine, 0 °C, 73%. c) MeOH, NH_3 (g), 0 °C, 95%. d) MeOH, Pd/C, H_2, rt, 98%. e) DMF, hydrazine acetate, rt; CH_2Cl_2, TCA, DBU, -20~0 °C; CH_2Cl_2, 4 Å molecular sieves, Mu, $BF_3{\cdot}Et_2O$, -40~-30 °C; 52%. f) MeOH, Na, rt, 91%. g) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 98%.

4-Azido-4-deoxy-1,2,3,6-tetra-*O*-acetyl-D-glucopyranose (**2**): To a solution of **1** [21, 22] (16 g, 26.9 mmol) in dry CH_2Cl_2 (160 mL) and dry pyridine (20 mL), stirred at 0 °C under N_2, was added dropwise triflic anhydride (Tf_2O, 9.6 mL, 57.1 mmol, 2.1 equiv) [23]. After addition, the reaction mixture was stirred for 1.5 h under the same conditions, diluted with CH_2Cl_2 (150 mL), washed with cold 1 M HCl (3 x 100 mL), cold saturated $NaHCO_3$ (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated to afford a yellow foam. To the yellow foam were added dry DMF (100 mL) and NaN_3 (15 g, 230.8 mmol, 8.6 equiv) at room temperature under N_2, and the suspension was stirred vigorously for 4 h at the same condition. The reaction mixture was diluted with EtOAc (600 mL), washed with water (2 x 300 mL) and brine (300 mL), dried over

$MgSO_4$, filtered and concentrated. The resulting residue was purified over a silica gel plug (4:1 petroleum ether-EtOAc) to afford **4-azido-4-deoxy-1,2,3,6-tetra-*O*-benzoyl-D-glucose** [24] as a white foam. To a solution of the white foam in dry methanol (360 mL) was added sodium methylate solution in MeOH (3 mL, 5.4 M), and the reaction mixture was stirred overnight at room temperature, neutralized with Amberlite 120 H, filtered, washed with methanol and concentrated to give crude **4-azido-4-deoxy-D-glucose**. This material was acetylated with pyridine (75 mL) and acetic anhydride (50 mL) at room temperature overnight. After evaporation under reduced pressure, water (50 mL) was added to the residue, and the mixture was stirred for 0.5 h at room temperature, extracted with EtOAc (2 x 200 mL). The organic phase was washed with 1 M HCl (2 x 200 mL), saturated $NaHCO_3$ (3 x 200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash column chromatography (3:1 petroleum ether-EtOAc) to afford **2** as a colorless syrup (5.21 g, 52% overall yield). ^{1}H NMR showed the ratio of α/β is about 1/1. ESI-MS: Calcd for $[C_{14}H_{19}N_3O_9 + Na]^+$: 396.1; Found m/z: 396.3.

4-Azido-4-deoxy-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl fluoride (**3**) [12]: See general procedure A, **3** was obtained as a colorless syrup in 79% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.75 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 52.4 Hz, H-1), 5.54 (t, 1 H, H-3), 4.96 (dddd, 1 H, $J_{2,3}$ 10.0 Hz, $J_{H,F}$ 23.7 Hz, H-2), 4.47 (dd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.34 (dd, 1 H, $J_{5,6b}$ 4.0 Hz, H-6b), 4.00 (m, 1 H, H-5), 3.74 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.4 Hz, H-4), 2.18 (s, 3 H, CH_3CO), 2.17 (s, 3 H, CH_3CO), 2.15 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 170.3, 169.7, 104.1 (d, $J_{C,F}$ 228.4 Hz), 70.33 (d, $J_{C,F}$ 24.3 Hz), 70.31 (d, $J_{C,F}$ 3.8 Hz), 70.1, 62.2, 59.5, 20.9, 20.8, 20.7. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -149.4. ESI-HRMS: Calcd for $[C_{12}H_{16}N_3FO_7 + Na]^+$: 356.0870; Found m/z: 356.0861.

4-Azido-4-deoxy-α-D-glucopyranosyl fluoride (**4**): See general procedure B, the mixture was stirred for 2 days at 0 °C. The resulting residue was purified by flash column chromatography to afford **4** as a colorless syrup in 94% yield. ^{1}H NMR (CD_3OD, 400 MHz): δ 5.58 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.6 Hz, H-1), 3.80~3.49 (m, 5 H, H-3, 4, 5 & 6), 3.50 (dddd, 1 H, $J_{2,3}$ 10.0 Hz, $J_{H,F}$ 28.8 Hz, H-2). ^{13}C NMR (CD_3OD, 100 MHz): δ 107.7 (d, $J_{C,F}$ 223.0 Hz), 73.1 (d, $J_{C,F}$ 3.0 Hz), 72.3, 71.8 (d, $J_{C,F}$ 24.0 Hz), 61.3, 60.6.

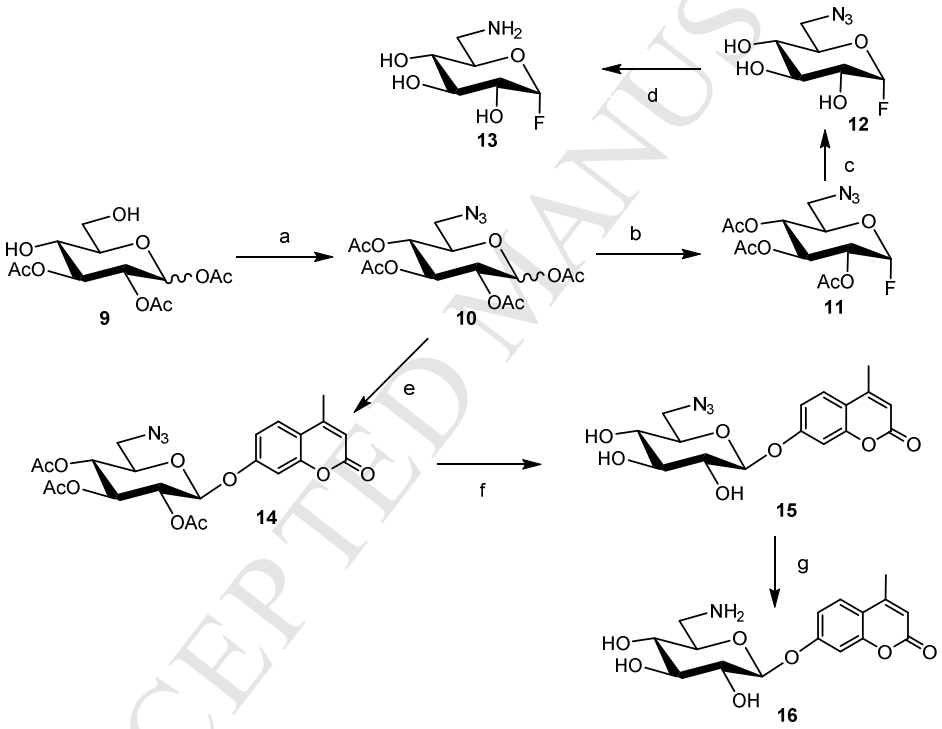
^{19}F-NMR (CD_3OD, 282 MHz): δ -152.1. ESI-HRMS: Calcd for $[C_6H_{10}N_3FO_4 - H]^-$: 206.0577; Found m/z: 206.0580.

4-Amino-4-deoxy-α-D-glucopyranosyl fluoride (**5**): See general procedure C, **5** was obtained as a white foam in 98% yield. ^{1}H NMR (CD_3OD, 400 MHz): δ 5.61 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 53.2 Hz, H-1), 3.52 (m, 1 H, H-5), 3.38 (m, 3 H, H-3 & H-6), 3.11 (dddd, 1 H, $J_{2,3}$ 9.2 Hz, $J_{H,F}$ 26.0 Hz, H-2), 2.71 (t, $J_{3,4}$ = $J_{4,5}$ 10.0 Hz, H-4). ^{13}C NMR (CD_3OD, 100 MHz): δ 109.8 (d, $J_{C,F}$ 224.0 Hz), 74.0 (d, $J_{C,F}$ 24.0 Hz), 73.8 (d, $J_{C,F}$ 4.0 Hz), 71.8, 63.0, 54.8. ^{19}F-NMR (CD_3OD, 282 MHz): δ -151.9. ESI-HRMS: Calcd for $[C_6H_{12}NFO_4 + H]^+$: 182.0829; Found m/z: 182.0826.

4-Methylumbelliferyl 4-azido-4-deoxy-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (**6**): See general procedure D, eluent (3:1 & 2:1 petroleum ether-ethyl acetate), **4-azido-4-deoxy-2,3,6-tri-*O*-acetyl-D-glucopyranose** was obtained as a colorless syrup in 74% yield. See general procedure E, eluent (2:1 petroleum ether-EtOAc), **6** was obtained as a white solid in 70% yield (overall yield: 52%). ^{1}H NMR (d_6-acetone, 400 MHz): δ 7.71 (d, 1 H, J 8.4 Hz, Ar-H), 7.01 (m, 2 H, Ar-H), 6.19 (d, 1 H, J 1.2 Hz, Ar-H), 5.59 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.42 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ 9.6 Hz, H-3), 5.19 (dd, 1 H, H-2), 4.48 (dd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.36 (dd, 1 H, $J_{5,6b}$ 5.6 Hz, H-6b), 4.14 (dddd, 1 H, H-5), 3.99 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 2.44 (d, J 1.2 Hz, 3 H, Ar-CH_3), 2.10 (s, 3 H, CH_3CO), 2.09 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO). ^{13}C NMR (d_6-acetone, 100 MHz): δ 170.0, 169.5, 169.2, 159.8, 159.6, 155.1, 152.7, 126.5, 115.4, 113.5, 112.7, 103.7, 97.8, 73.3, 72.4, 71.2, 62.6, 60.0, 19.9, 19.88, 19.8, 17.8. ESI-HRMS: Calcd for $[C_{22}H_{23}N_3O_{10} + Na]^+$: 512.1281; Found m/z: 512.1277.

4-Methylumbelliferyl 4-azido-4-deoxy-β-D-glucopyranoside (**7**): See general procedure F, **7** was obtained as a white solid in 91% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.72 (d, 1 H, J 9.6 Hz, Ar-H), 7.04 (m, 2 H, Ar-H), 6.26 (d, 1 H, J 1.2 Hz, Ar-H), 5.13 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.64~3.42 (m, 5 H, H-2, 3, 5 & 6), 3.35 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 8.4 Hz, H-4), 2.41 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.7, 160.5, 155.0, 153.9, 127.1, 114.8, 113.9, 112.4, 103.7, 100.0, 75.8, 75.0, 73.8, 62.1, 61.0, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{17}N_3O_7 + Na]^+$: 386.0964; Found m/z: 386.0956.

4-Methylumbelliferyl 4-amino-4-deoxy-β-D-glucopyranoside (**8**) [25]: See general procedure G, **8** was obtained as a white solid in 98% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.68 (d, 1 H, *J* 8.4 Hz, Ar-H), 7.03 (m, 2 H, Ar-H), 6.21 (s, 1 H, Ar-H), 5.00 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 3.67 (dd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{6a,6b}$ 12.0 Hz, H-6a), 3.50 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 3.40 (m, 1 H, H-5), 3.29 (t, 1 H, H-2), 3.21 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ 9.2 Hz, H-3), 2.54 (t, 1 H, $J_{4,5}$ 9.6 Hz, H-4), 2.38 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.7, 154.9, 154.1, 127.0, 114.7, 114.0, 112.2, 103.7, 100.7, 77.8, 76.6, 73.7, 61.6, 53.8, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{19}NO_7 + H]^+$: 338.1240; Found m/z: 338.1234.



Scheme 2. Reagents and conditions: a) CH_2Cl_2, pyridine, Tf_2O, -78~-30 °C; DMF, NaN_3, rt; pyridine, Ac_2O, rt;.57%. b) CH_2Cl_2, HF/pyridine, 0 °C, 75%. c) MeOH, NH_3 (g), 0 °C, 95%. d) MeOH, Pd/C, H_2, rt, 98%. e) DMF, hydrazine acetate, rt; CH_2Cl_2, TCA, DBU, -20~0 °C; DCM, 4 Å molecular sieves, Mu, $BF_3{\cdot}Et_2O$, -40~-30 °C; 51%. f) MeOH, Na, rt, 96%. g) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 93%.

6-Azido-6-deoxy-1,2,3,4-tetra-*O*-acetyl-D-glucopyranose (**10**): To a solution of **1,2,3-tri-*O*-acetyl-D-glucopyranose** [26, 27] (**9**, 0.58 g, 1.9 mmol) in dry CH_2Cl_2 (36 mL) and dry pyridine (2 mL), stirred at -78 °C under N_2, was added triflic anhydride (0.5 mL, 3.0 mmol, 1.6 equiv) dropwise. After addition, the dry-ice cooling bath was gradually warmed up to -30 °C, and TLC showed completion of reaction. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with cold 1 M HCl (30 mL), cold saturated $NaHCO_3$ (30 mL) and cold brine (30 mL), dried over $MgSO_4$, filtered and evaporated, dried under vacuum to afford a brownish foam. To the brownish foam were added dry DMF (10 mL) and NaN_3 (1.24 g, 19.1 mmol, 10 equiv), and the mixture was stirred vigorously overnight at room temperature under N_2. The reaction mixture was diluted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and evaporated to afford crude **6-Azido-6-deoxy-1,2,3-tri-*O*-acetyl-D-glucopyranose.** To the residue were added pyridine (5 mL) and acetic anhydride (2.5 mL), and the mixture was stirred overnight at room temperature. After evaporation under reduced pressure, the residue was dissolved in EtOAc (60 mL), washed with 1 M HCl (30 mL), saturated $NaHCO_3$ (2 x 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (2:1 petroleum ether-EtOAc) to afford **10** [28] as a colorless syrup (57%; α/β = 1/1.4). ^{1}H NMR ($CDCl_3$, 400 MHz, α-anomer): δ 6.38 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 5.49 (t, 1 H, H-3), 5.13 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 9.8 Hz, H-4), 5.12 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-2), 4.11 (dddd, 1 H, H-5), 3.43 (dd, 1 H, $J_{5,6a}$ 2.8 Hz, $J_{6a,6b}$ 13.6 Hz, H-6a), 3.33 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 2.22 (s, 3 H, CH_3CO), 2.09 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO). ESI-MS: Calcd for $[C_{14}H_{19}N_3O_9 + Na]^+$: 396.1; Found m/z: 396.5.

6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl fluoride (**11**): See general procedure A, **11** was obtained as a white solid in 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.78 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 52.8 Hz, H-1), 5.49 (t, 1 H, H-3), 5.14 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 9.8 Hz, H-4), 4.95 (dddd, 1 H, $J_{2,3}$ 10.4 Hz, $J_{H,F}$ 24.0 Hz, H-2), 4.15 (dddd, 1 H, H-5), 3.46 (dd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{6a,6b}$ 13.6 Hz, H-6a), 3.33 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 2.11 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 170.06, 170.5, 103.7 (d, $J_{C,F}$ 228.0 Hz), 70.9 (d, $J_{C,F}$ 4.0 Hz), 70.3 (d, $J_{C,F}$ 24.0

Hz), 69.3, 68.5, 50.7, 20.73, 20.69, 20.65. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -149.5. ESI-HRMS: Calcd for $[C_{12}H_{16}FN_3O_7 + Na]^+$: 356.0870; Found m/z: 356.0865.

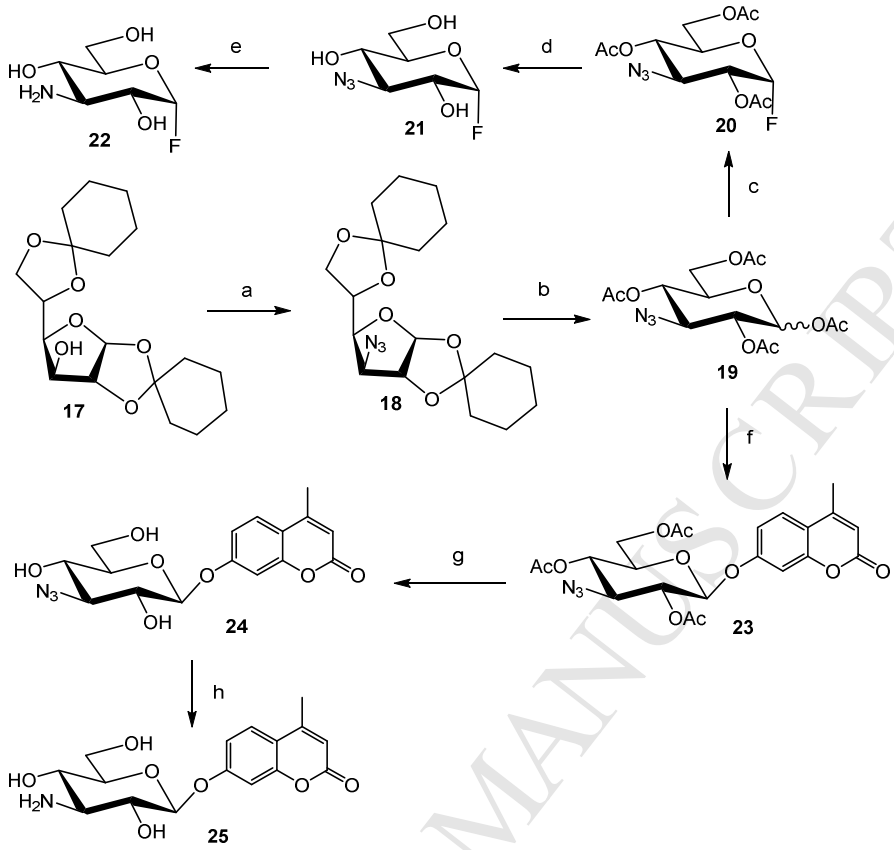
6-Azido-6-deoxy-α-D-glucopyranosyl fluoride (**12**): See general procedure B, **12** was obtained as a white solid in 95% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.60 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.2 Hz, H-1), 3.86 (dddd, 1 H, $J_{4,5}$ 9.6 Hz, $J_{5,6a}$ 2.4 Hz, $J_{5,6b}$ 5.2 Hz, H-5), 3.70 ~ 3.42 (m, 5 H, H-2, 3, 5 & 6). ^{13}C NMR (D_2O, 100 MHz): δ 107.3 (d, $J_{C,F}$ 222.0 Hz), 73.0 (d, $J_{C,F}$ 3.0 Hz), 72.3, 71.0 (d, $J_{C,F}$ 25.0 Hz), 69.4, 50.7. ^{19}F-NMR (D_2O, 282 MHz): δ -150.4. ESI-HRMS: Calcd for $[C_6H_{10}N_3FO_4 - H]^-$: 206.0577; Found m/z: 206.0585.

6-Amino-6-deoxy-α-D-glucopyranosyl fluoride (**13**): See general procedure C, **13** was obtained as a white solid in 98% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.59 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.2 Hz, H-1), 3.72 (m, 1 H, H-5), 3.62 (t, 1 H, H-3), 3.52 (dddd, 1 H, $J_{2,3}$ 9.6 Hz, $J_{H,F}$ 26.0 Hz, H-2), 3.32 (t, 1 H, $J_{3,4} = J_{4,5}$ 9.6 Hz, H-4), 3.00 (dd, 1 H, $J_{5,6a}$ 2.6 Hz, H-6a), 2.78 (dd, 1 H, $J_{5,6b}$ 7.2 Hz, $J_{6a,6b}$ 13.6 Hz, H-6b). ^{13}C NMR (D_2O, 100 MHz): δ 107.3 (d, $J_{C,F}$ 221.0 Hz), 73.6 (d, $J_{C,F}$ 3.0 Hz), 72.4, 71.2 (d, $J_{C,F}$ 25.0 Hz), 70.2, 41.0. ^{19}F-NMR (D_2O, 282 MHz): δ -150.0. ESI-HRMS: Calcd for $[C_6H_{12}NFO_4 + H]^+$: 182.0829; Found m/z: 182.0824.

4-Methylumbelliferyl 6-azido-6-deoxy-2,3,4-tri-*O*-acetyl-β-D-glucopyranoside (**14**): See general procedure D, eluent (3:1 & 2:1 petroleum ether-EtOAc), **6-azido-6-deoxy-2,3,4-tri-*O*-acetyl-D-glucopyranose** was obtained as a colorless syrup in 85% yield. See general procedure E, eluent (2:1 & 3:2 petroleum ether-EtOAc), **14** was obtained as a white solid in 60% yield (overall yield: 51%). ^{1}H NMR (d_6-acetone, 400 MHz): δ 7.73 (d, 1 H, J 9.2 Hz, Ar-H), 7.05 (m, 2 H, Ar-H), 6.20 (d, 1 H, J 1.2 Hz, Ar-H), 5.67 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 5.42 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 5.26 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 5.13 (t, 1 H, $J_{4,5}$ 10.0 Hz, H-4), 4.29 (dddd, 1 H, H-5), 3.62 (dd, 1 H, $J_{5,6a}$ 2.8 Hz, $J_{6a,6b}$ 13.6 Hz, H-6a), 3.53 (dd, 1 H, $J_{5,6b}$ 6.8 Hz, H-6b), 2.45 (d, J 1.2 Hz, 3 H, Ar-CH_3), 2.04 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO). ^{13}C NMR (d_6-acetone, 100 MHz): δ 169.6, 169.3, 169.0, 159.8, 159.6, 155.1, 152.7, 126.6, 115.5, 113.5, 112.8, 103.7, 97.9, 73.3, 72.4, 70.9, 69.2, 51.0, 19.9, 19.8 (2 C), 17.8. ESI-HRMS: Calcd for $[C_{22}H_{23}N_3O_{10} + Na]^+$: 512.1281; Found m/z: 512.1288.

4-Methylumbelliferyl 6-azido-6-deoxy-β-D-glucopyranoside (**15**): See general procedure F, **15** was obtained as a white solid in 96% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.70 (d, 1 H, *J* 8.8 Hz, Ar-H), 7.05 (m, 2 H, Ar-H), 6.24 (d, 1 H, *J* 0.8 Hz, Ar-H), 5.16 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 3.72 (m, 1 H, H-5), 3.50~3.40 (m, 2 H, H-6), 3.34~3.27 (m, 2 H, H-2 & H-3), 3.14 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 9.0 Hz, H-4), 2.40 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.4, 155.0, 154.0, 127.0, 114.8, 114.0, 112.3, 103.7, 100.1, 76.3, 75.8, 73.5, 71.0, 51.9, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{17}N_3O_7 + Na]^+$: 386.0964; Found m/z: 386.0953.

4-Methylumbelliferyl 6-amino-6-deoxy-β-D-glucopyranoside (**16**): See general procedure G, **16** was obtained as a white solid in 93% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.69 (d, 1 H, *J* 8.8 Hz, Ar-H), 7.03 (m, 2 H, Ar-H), 6.23(d, 1 H, *J* 0.8 Hz, Ar-H), 5.04 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 3.42 (m, 1 H, H-5), 3.29 (m, 2 H, H-2 & H-3), 3.12 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 9.2Hz, H-4), 2.91 (dd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 2.64 (dd, 1 H, $J_{5,6b}$ 7.2 Hz, H-6b), 2.39 (d, 3 H, *J* 1.4 Hz, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.7, 160.6, 155.0, 153.9, 127.1, 114.7, 113.8, 112.3, 103.7, 100.5, 77.2, 76.9, 73.8, 71.8, 43.2, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{19}NO_7 + Na]^+$: 360.1059; Found m/z: 360.1050.



Scheme 3. Reagents and conditions: a) CH_2Cl_2, DMP, 0 °C~rt; EtOH, H_2O, $NaBH_4$, 0 °C~rt; CH_2Cl_2, pyridine, Tf_2O, 0 °C; DMF, NaN_3, rt, 96%. b) TFA, H_2O, rt; pyridine, Ac_2O, rt, 78%. c) CH_2Cl_2, Ac_2O, HF/pyridine, 0 °C, 76%. d) MeOH, NH_3, 0 °C, 97%. e) MeOH, Pd/C, H_2, rt, 96%. f) DMF, hydrazine acetate, rt; CH_2Cl_2, TCA, DBU, -20~0 °C; CH_2Cl_2, 4 Å molecular sieves, Mu, $BF_3{\cdot}Et_2O$, -40~-30 °C; 34%. g) MeOH, Na, rt, 97 %. h) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 99%.

3-Azido-3-deoxy-1,2:5,6-di-*O*-cyclohexylidene-D-glucofuranose (**18**): To a solution of **17** [10] (3 g, 8.8 mmol) in dry CH_2Cl_2 (15 mL), stirred at 0 °C under N_2, was added Dess-Martin Periodinane (DMP) (5.61 g, 13.2 mmol, 1.5 equiv) in one portion. After 5 minutes, the cooling bath was removed and the reaction mixture was stirred overnight at room temperature. After dilution with CH_2Cl_2 (100 mL) and saturated $NaHCO_3$ containing $Na_2S_2O_3$ (0.12 g/mL, 100 mL), the mixture was stirred vigorously until the two layers were clear. After separation of the two layers, the organic phase was washed with $NaHCO_3$ containing $Na_2S_2O_3$ (100 mL). The aqueous phase was extracted with

EtOAc (100 mL), the combined organic phase was dried over $MgSO_4$, filtered and concentrated to afford a colorless syrup. The syrup was re-dissolved in ethanol (60 mL), cooled to 0 °C and a solution of $NaBH_4$ (0.43 g, 11.3 mmol, 1.3 equiv) in EtOH/H_2O (1/1, 14 mL) was added dropwise over 35 minutes, and stirred under the same conditions for a further 30 minutes. The cooling bath was then removed and the reaction mixture was stirred for 1 h at room temperature, quenched with saturated NH_4Cl, and water was added until all solids were dissolved. The ethanol was then evaporated under vacuum. The product was extracted with EtOAc (3 x 100 mL), washed with brine (150 mL), dried over $MgSO_4$, filtered and evaporated to dryness, then dried overnight under vacuum to afford a white foam (2.91 g) of **1,2:5,6-di-*O*-cyclohexylidene-D-allofuranose** [11]. ^{1}H NMR (d_6-acetone, 400 MHz): δ 5.76 (d, 1 H, *J* 4.0 Hz, H-1), 4.58 (t, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 4.28 (dt, 1 H, $J_{5,6}$ 2.8 Hz, H-5), 4.00 (dd, 1 H, $J_{4,5}$, 6.8 Hz, $J_{3,4}$ 8.0 Hz, H-4), 3.93 (m, 3 H, H-3 & H-6), 2.84 (s, 1 H, OH), 1.80~1.30 (m, 20 H). ^{13}C NMR (d_6-acetone, 100 MHz): δ 112.5, 109.5, 103.7, 79.3, 79.1, 75.4, 72.5, 64.5, 36.2, 36.0, 35.8, 35.1, 25.2, 24.9, 23.9, 23.86, 23.8, 23.6. ESI-HRMS: Calcd for $[C_{18}H_{28}O_6 + Na]^+$: 363.1784; Found m/z: 363.1783. The white foam was dissolved in dry CH_2Cl_2 (85 mL) and dry pyridine (12 mL), stirred at 0 °C under N_2, the triflic anhydride (3.1 mL, 2.2 equiv) was added dropwise. The reaction mixture was stirred for 2 h under the same conditions, diluted with CH_2Cl_2 (100 mL), washed with cold 1 M HCl (100 mL), cold saturated $NaHCO_3$ (100 mL) and cold brine (100 mL), dried over $MgSO_4$, filtered and concentrated, dried under vacuum to afford a yellow foam. To the yellow foam were added dry DMF (30 mL) and NaN_3 (4.7 g), and the suspension was stirred vigorously overnight at room temperature under N_2. The reaction mixture was diluted with EtOAc (300 mL), washed with water (2 x 100 mL) and brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (15:1 petroleum ether-EtOAc) to afford **18** as a colorless syrup (3.09 g, 96%). ^{1}H NMR (d_6-acetone, 400 MHz): δ 5.86 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.68 (d, 1 H, H-2), 4.22 (m, 1 H, H-5), 4.19 (d, 1 H, $J_{3,4}$, 3.6 Hz, H-3), 4.11 (dd, 1 H, $J_{5,6a}$ 6.0 Hz, $J_{6a,6b}$ 8.4 Hz, H-6a), 4.10 (dd, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 3.87 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 1.70~1.30 (m, 20 H). ^{13}C NMR (d_6-acetone, 100 MHz): δ 112.4, 109.7, 104.9, 83.2, 80.7, 73.1, 67.1, 67.0, 36.6,

36.3, 35.5, 34.7, 25.1, 24.8, 24.0, 23.9, 23.7, 23.6. ESI-HRMS: Calcd for $[C_{18}H_{27}N_3O_5 + Na]^+$: 388.1848; Found m/z: 388.1855.

3-Azido-3-deoxy-1,2,4,6-tetra-*O*-acetyl-D-glucopyranose (**19**): To compound **18** (2.98 g, 8.2 mmol) were added TFA (20 mL) and water (20 mL), and the mixture was stirred for 2 days at room temperature. After evaporation and co-evaporation with toluene three times, the resulting syrup was dried for 2 h under vacuum. To the residue were added pyridine (50 mL) and acetic anhydride (25 mL), and the mixture was stirred overnight at room temperature. After evaporation, water was added to the resulting residue and the mixture was stirred for 0.5 h at room temperature and extracted with EtOAc (2 x 150 mL). The organic phase was washed with 1 M HCl (150 mL), saturated $NaHCO_3$ (2 x 150 mL) and brine (150 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (3:1 & 7:3 petroleum ether-EtOAc) to afford **19** as a colorless syrup (2.38 g, 78%; α/β = 1.2/1). ESI-MS: Calcd for $[C_{14}H_{19}N_3O_9 + Na]^+$: 396.1; Found m/z: 396.4.

3-Azido-3-deoxy-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl fluoride (**20**): See the general procedure A, the reaction mixture was stirred for 2 days at 0 °C, **20** was obtained as a colorless syrup in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.74 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.2 Hz, H-1), 5.04 (t, 1 H, $J_{3,4}$ = $J_{4,5}$ 10.2 Hz, H-4), 4.80 (dddd, 1 H, $J_{2,3}$ 10.8 Hz, $J_{H,F}$ 23.6 Hz, H-2), 4.24 (dd, 1 H, $J_{5,6a}$ 4.6 Hz, $J_{6a,6b}$ 12.6 Hz, H-6a), 4.13 (dd, 1 H, $J_{5,6b}$ 2.0 Hz, H-6b), 4.09 (m, 1 H, H-5), 3.99 (t, 1 H, H-3), 2.19 (s, 3 H, CH_3CO), 2.14 (s, 3 H, CH_3CO), 2.10 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 169.9, 169.2, 103.5 (d, $J_{C,F}$ 228.0 Hz), 71.0 (d, $J_{C,F}$ 24.0 Hz), 70.1 (d, $J_{C,F}$ 4.0 Hz), 67.3, 61.3, 60.6, 20.8, 20.72, 20.7. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -151.0. ESI-HRMS: Calcd for $[C_{12}H_{16}N_3FO_7 + Na]^+$: 356.0870; Found m/z: 356.0873.

3-Azido-3-deoxy-α-D-glucopyranosyl fluoride (**21**): See general procedure B, the mixture was stirred for 30 h at 0 °C. The resulting residue was purified by flash column chromatography to afford **21** as a colorless syrup in 97% yield. ^{1}H NMR (CD_3OD, 400 MHz): δ 5.46 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 53.6 Hz, H-1), 3.73 (m, 1 H, H-5), 3.63 (m, 2 H, H-6), 3.50 (t, 1 H, $J_{2,3}$ = $J_{3,4}$ 9.8 Hz, H-3), 3.45~3.31 (m, 2 H, H-2 & H-4). ^{13}C NMR

(CD_3OD, 100 MHz): δ 109.5 (d, $J_{C,F}$ 223.0 Hz), 77.1 (d, $J_{C,F}$ 3.0 Hz), 73.0 (d, $J_{C,F}$ 25.0 Hz), 70.3, 69.0, 62.9. ^{19}F-NMR (CD_3OD, 282 MHz): δ -152.7. ESI-HRMS: Calcd for $[C_6H_{10}N_3FO_4 - H]^-$: 206.0577; Found m/z: 206.0581.

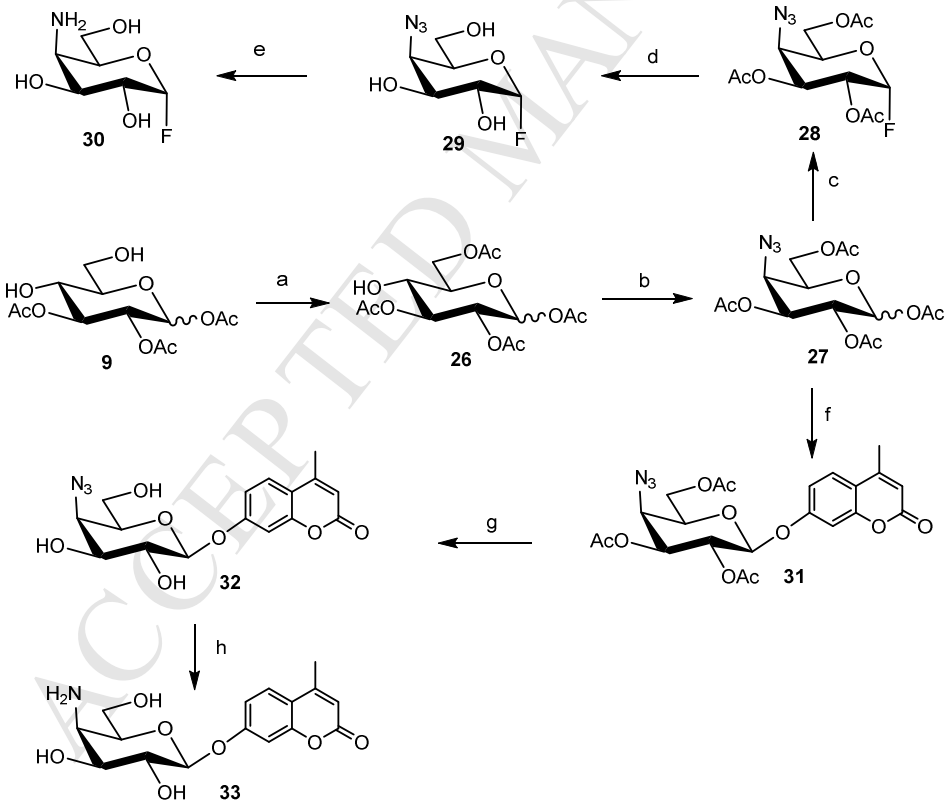
3-Amino-3-deoxy-α-D-glucopyranosyl fluoride (**22**): See general procedure C, **22** was obtained as a foam in 96% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.56 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.6 Hz, H-1), 3.78 (dd, 1 H, $J_{5,6a}$ 1.6 Hz, $J_{6a,6b}$ 11.6 Hz, H-6a), 3.73 (m, 1 H, H-5), 3.68 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 3.43 (dddd, 1 H, $J_{2,3}$ 10.4 Hz, $J_{H,F}$ 26.4 Hz, H-2), 3.31 (t, $J_{3,4} = J_{4,5}$ 9.2 Hz, H-4), 2.96 (t, 1 H, H-3). ^{13}C NMR (CD_3OD, 100 MHz): δ 107.0 (d, $J_{C,F}$ 223.0 Hz), 74.9 (d, $J_{C,F}$ 3.0 Hz), 71.7 (d, $J_{C,F}$ 24.0 Hz), 68.9, 60.9, 54.6. ^{19}F-NMR (D_2O, 282 MHz): δ -150.8. ESI-HRMS: Calcd for $[C_6H_{12}NFO_4 + H]^+$: 182.0829; Found m/z: 182.0827.

4-Methylumbelliferyl 3-azido-3-deoxy-2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (**23**): See general procedure D, eluent (2:1 petroleum ether-EtOAc), **3-azido-3-deoxy-2,4,6-tri-*O*-acetyl-D-glucopyranose** was obtained as a colorless syrup in 71% yield. See general procedure E, eluent (2:1 & 3:2 petroleum ether-EtOAc), **23** was obtained as a white solid in 48% yield (overall yield: 34%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, 1 H, *J* 8.4 Hz, Ar-H), 6.91 (m, 2 H, Ar-H), 6.19 (d, 1 H, *J* 0.8 Hz, Ar-H), 5.22 (dd, 1 H, $J_{2,3}$ 10.0 Hz, H-2), 5.20 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.06 (t, 1 H, $J_{3,4} = J_{4,5}$ 10.0 Hz, H-4), 4.25 (dd, 1 H, $J_{5,6a}$ 6.0 Hz, $J_{6a,6b}$ 12.4 Hz, H-6a), 4.17 (dd, 1 H, $J_{5,6b}$ 2.4 Hz, H-6b), 3.88 (dddd, 1 H, H-5), 3.77 (t, 1 H, H-3), 2.41 (d, *J* 1.2 Hz, 3 H, Ar-CH_3), 2.16 (s, 3 H, CH_3CO), 2.15 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 169.3, 169.1, 160.9, 159.3, 155.0, 152.4, 125.9, 115.7, 114.3, 113.1, 103.9, 98.7, 73.4, 70.8, 68.4, 64.2, 62.0, 20.84, 20.79, 20.76, 18.8. ESI-HRMS: Calcd for $[C_{22}H_{23}N_3O_{10} + Na]^+$: 512.1281; Found m/z: 512.1281.

4-Methylumbelliferyl 3-azido-3-deoxy-β-D-glucopyranoside (**24**): See general procedure F, **24** was obtained as a white solid in 97% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.71 (d, 1 H, *J* 9.4 Hz, Ar-H), 7.04 (m, 2 H, Ar-H), 6.24 (s, 1 H, Ar-H), 5.15 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 3.70~3.23 (m, 6 H, remaining protons of sugar ring), 2.31 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 159.8, 159.4, 153.9, 153.0, 126.1,

113.9, 113.0, 111.4, 102.8, 99.2, 77.0, 70.9, 69.0, 67.5, 59.6, 17.7. ESI-HRMS: Calcd for $[C_{16}H_{17}N_3O_7 + Na]^+$: 386.0963; Found m/z: 386.0964.

4-Methylumbelliferyl 3-amino-3-deoxy-β-D-glucopyranoside (**25**): See general procedure G, **25** was obtained as a white solid in 99% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.70 (d, 1 H, *J* 9.2 Hz, Ar-H), 7.04 (m, 2 H, Ar-H), 6.24 (s, 1 H, Ar-H), 5.07 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 4.02 (d, 1 H, $J_{6a,6b}$ 7.6 Hz, H-6a), 3.45 (m, 2 H, H-5 & H-6b), 3.25 (dd, 1 H, H-2), 3.15 (t, 1 H, $J_{4,5}$ 9.0 Hz, H-4), 2.72 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.6 Hz, H-3), 2.40 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.7, 155.0, 154.0, 127.1, 114.7, 114.0, 112.3, 103.8, 100.8, 78.7, 72.8, 69.5, 61.0, 59.3, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{19}NO_7 + Na]^+$: 360.1053; Found m/z: 360.1059.



Scheme 4. Reagents and conditions: a). CH_2Cl_2, TEA, 1-(acetoxy)-benzotriazole, rt, 79%. b) CH_2Cl_2, pyridine, Tf_2O, 0 °C; DMF, NaN_3, rt; 91%. c) CH_2Cl_2, Ac_2O, HF/pyridine, 0 °C, 86%. d) MeOH, NH_3, 0 °C, 98%. e) MeOH, Pd/C, H_2, rt, 98%. f) DMF,

hydrazine acetate, rt; CH_2Cl_2, TCA, DBU, -20~0 °C; DCM, 4 Å molecular sieves, Mu, $BF_3{\cdot}Et_2O$, -40~-30 °C; 32%. g) MeOH, Na, rt, 92%. h) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 90%.

1,2,3,6-Tetra-*O*-acetyl-D-glucopyranose (**26**): To a solution of **9** (4.7 g, 15.4 mmol) in anhydrous CH_2Cl_2 (100 mL) and Et_3N (3.2 mL) was added 1-(acetoxy)-benzotriazole [29] (3.26 g, 18.4 mmol, 1.2 equiv) in one portion [30, 31], and the mixture was stirred for 5 h at room temperature under N_2. After completion, the mixture was diluted with CH_2Cl_2 (50 mL), washed with brine (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (55:45, petroleum ether-EtOAc) to afford **26** as a syrup (4.27 g, 79%; α/β = 1/1.3). ESI-MS: Calcd for $[C_{14}H_{20}O_{10} + Na]^+$: 371.1; Found m/z: 371.2.

4-Azido-4-deoxy-1,2,3,6-tetra-*O*-acetyl-D-galactopyranose (**27**): To a solution of **26** (4.23 g, 12.2 mmol) in dry CH_2Cl_2 (120 mL) and dry pyridine (20 mL), stirred at 0 °C under N_2, was added triflic anhydride (4.4 mL, 26.2 mmol, 2.1 equiv) dropwise, and the mixture stirred for 1 h under the same conditions. After completion, the reaction mixture was diluted with CH_2Cl_2 (150 mL), washed with cold 1 M HCl (2 x 200 mL), cold saturated $NaHCO_3$ (200 mL) and cold brine (200 mL), dried over $MgSO_4$, filtered and concentrated to afford a brownish foam. To the brownish foam were added dry DMF (50 mL) and NaN_3 (6.88 g, 105.8 mmol, 8.7 equiv), and the reaction mixture stirred vigorously for 1.5 h at room temperature under N_2. The reaction mixture was diluted with EtOAc (500 mL), washed with water (2 x 250 mL) and brine (250 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (65:35, petroleum ether-EtOAc) to afford **27** as a syrup (91%; α/β = 1/1.23). ESI-MS: Calcd for $[C_{14}H_{19}N_3O_9 + Na]^+$: 396.1; Found m/z: 396.2.

4-Azido-4-deoxy-2,3,6-tri-*O*-acetyl-α-D-galactopyranosyl fluoride (**28**): See the general procedure A, the reaction mixture was stirred overnight at 0 °C, **28** was obtained as a colorless syrup in 86%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 53.2 Hz, H-1), 5.48 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 5.31 (dddd, 1 H, $J_{2,3}$ 10.8 Hz, $J_{H,F}$ 23.6 Hz, H-2), 4.36~4.25 (m, 4 H, H-4,5,6), 2.21 (s, 3 H, CH_3CO), 2.18 (s, 3 H,

CH_3CO), 2.16 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 170.2 (2 C), 104.3 (d, $J_{C,F}$ 227.6 Hz), 69.3, 68.7 (d, $J_{C,F}$ 3.5 Hz), 67.6 (d, $J_{C,F}$ 23.7 Hz), 62.6, 60.3, 20.9, 20.7, 20.6. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -151.6. ESI-HRMS: Calcd for $[C_{12}H_{16}N_3FO_7 + Na]^+$: 356.0870; Found m/z: 356.0860.

4-Azido-4-deoxy-α-D-galactopyranosyl fluoride (**29**): See general procedure B, the mixture was stirred overnight at 0 °C. The resulting residue was purified by flash column chromatography to afford **29** as a colorless syrup in 98% yield. ^1H NMR (CD_3OD, 400 MHz): δ 5.55 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 54.0 Hz, H-1), 4.08~4.03 (m, 3 H, H-3,4,5), 3.79 (dddd, 1 H, $J_{2,3}$ 9.2 Hz, $J_{H,F}$ 26.0 Hz, H-2), 3.68(d, 2 H, $J_{5,6}$ 6.4 Hz, H-6). ^{13}C NMR (CD_3OD, 100 MHz): δ 107.7 (d, $J_{C,F}$ 223.6 Hz), 71.7 (d, $J_{C,F}$ 2.7 Hz), 69.9, 68.7 (d, $J_{C,F}$ 24.2 Hz), 63.0, 60.9. ^{19}F-NMR (CD_3OD, 282 MHz): δ -153.5. ESI-HRMS: Calcd for $[C_6H_{10}N_3FO_4 - H]^-$: 206.0577; Found m/z: 206.0579.

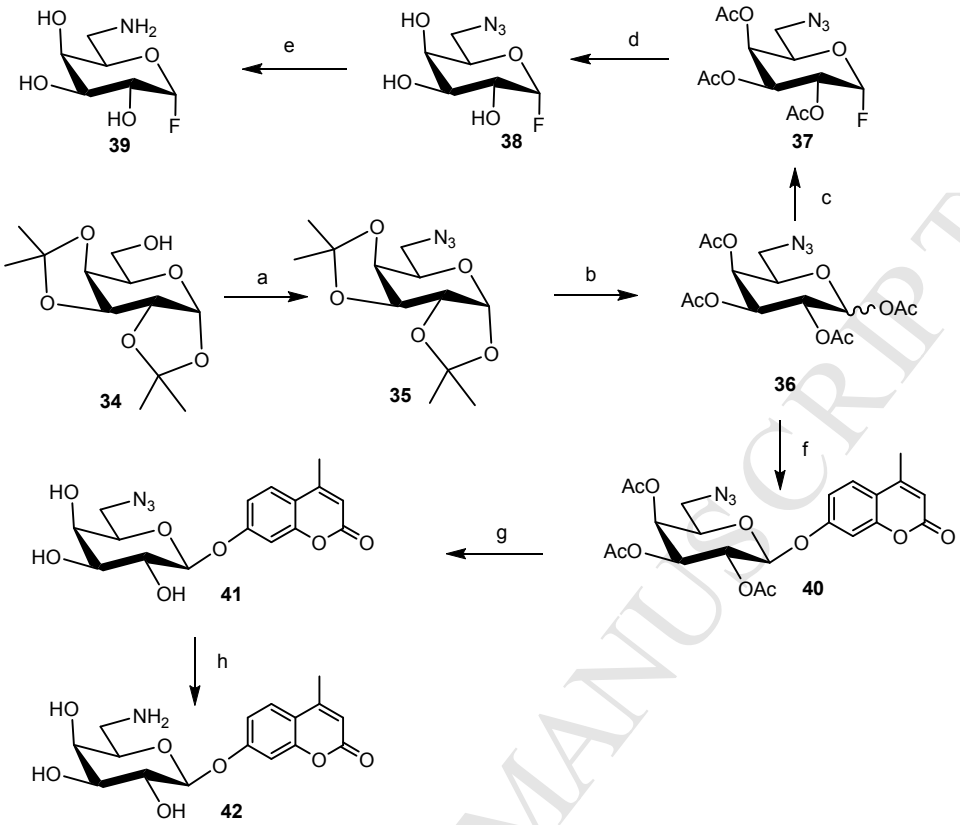
4-Amino-4-deoxy-α-D-galactopyranosyl fluoride (**30**): See general procedure C, **30** was obtained as a white solid in 98% yield. ^1H NMR (CD_3OD, 400 MHz): δ 5.60 (dd, 1 H, $J_{1,2}$ 3.2 Hz, $J_{H,F}$ 54.0 Hz, H-1), 4.08 (m, 1 H, H-5), 3.90 (dd, 1 H, $J_{5,6a}$ 4.4 Hz, $J_{6a,6b}$ 10.4 Hz H-6a), 3.80~3.69 (m, 3 H, H-2, 3, 6b), 3.38 (brs, 1 H, H-4). ^{13}C NMR (CD_3OD, 100 MHz): δ 107.7 (d, $J_{C,F}$ 224.0 Hz), 71.8 (d, $J_{C,F}$ 3.0 Hz), 68.5, 68.2 (d, $J_{C,F}$ 24.0 Hz), 61.1, 52.5. ^{19}F-NMR (D_2O, 282 MHz): δ -151.9. ESI-HRMS: Calcd for $[C_6H_{12}NFO_4 + H]^+$: 182.0829; Found m/z: 182.0822.

4-Methylumbelliferyl 4-azido-4-deoxy-2,3,6-tri-*O*-acetyl-β-D-galactopyranoside (**31**): See general procedure D, eluent (2:1 petroleum ether-EtOAc), **4-azido-4-deoxy-2,3,6-tri-*O*-acetyl-D-galactopyranose** was obtained as a colorless syrup in 73% yield. See general procedure E, eluent (2:1 & 3:2 petroleum ether-EtOAc), **23** was obtained as a white solid in 43% yield (overall yield: 31%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, 1 H, *J* 9.1 Hz, Ar-H), 6.95 (m, 2 H, Ar-H), 6.22 (d, 1 H, *J* 0.9 Hz, Ar-H), 5.60 (dd, 1 H, $J_{2,3}$ 10.4 Hz, H-2), 5.25 (dd, 1 H, $J_{3,4}$ 3.7 Hz, H-3), 5.10 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.38 (dd, 1 H, $J_{5,6a}$ 7.0 Hz, $J_{6a,6b}$ 11.6 Hz, H-6a), 4.29 (dd, 1 H, $J_{5,6b}$ 5.8 Hz, H-6b), 4.18 (brd, 1 H, H-4), 4.03 (m, 1 H, H-5), 2.44 (d, *J* 0.9 Hz, 3 H, Ar-CH_3), 2.20 (s, 3 H, CH_3CO), 2.19 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO). ^{13}C NMR (d_6-acetone, 100 MHz): δ 170.0, 169.4,

169.2, 159.9, 159.6, 155.0, 152.7, 126.4, 115.3, 113.6, 112.7, 103.8, 98.4, 72.6, 71.3, 68.8, 62.7, 60.4, 20.0, 19.9, 19.7, 17.8. ESI-HRMS: Calcd for $[C_{22}H_{23}N_3O_{10} + Na]^+$: 512.1281; Found m/z: 512.1296.

4-Methylumbelliferyl 4-azido-4-deoxy-β-D-galactopyranoside (**32**): See general procedure F, **32** was obtained as a white solid in 92% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.68 (d, 1 H, *J* 9.6 Hz, Ar-H), 7.01 (m, 2 H, Ar-H), 6.22 (d, 1 H, *J* 0.8 Hz, Ar-H), 5.03 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 3.93 (brd, 1 H, H-4), 3.84 (m, 1 H, H-5), 3.80 (dd, 1 H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 4.0 Hz, H-3), 3.54 (m, 1 H, H-2), 3.45 (m, 2 H, H-6), 2.38 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 159.8, 159.4, 153.9, 153.0, 126.0, 113.7, 113.0, 111.3, 102.6, 99.6, 72.7, 72.4, 69.8, 61.8, 59.6, 17.7. ESI-HRMS: Calcd for $[C_{16}H_{17}N_3O_7 + Na]^+$: 386.0964; Found m/z: 386.0961.

4-Methylumbelliferyl 4-amino-4-deoxy-β-D-galactopyranoside (**33**): See general procedure G, **33** was obtained as a white solid in 90% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.70 (d, 1 H, *J* 9.6 Hz, Ar-H), 7.04 (m, 2 H, Ar-H), 6.24 (s, 1 H, Ar-H), 4.99 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 3.78 (m, 1 H, H-5), 3.70~3.30 (m, 4 H, H-2, H-3 & H-6), 3.03 (brs, 1 H, H-4), 2.40 (s, 3 H, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.7, 155.0, 154.1, 127.1, 114.7, 114.0, 112.3, 103.7, 101.3, 75.5, 72.8, 70.6, 61.1, 52.3, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{19}NO_7 + H]^+$: 338.1240; Found m/z: 338.1238.



Scheme 5. Reagents and conditions: a) CH_2Cl_2, pyridine, Tf_2O, 0 °C; DMF, NaN_3, rt; 75%. b) AcOH/H_2O (2/1), 80 °C; pyridine, Ac_2O, rt; 92%. c) CH_2Cl_2, HF/pyridine, 0 °C; 78%. d) MeOH, NH_3, 0 °C; 95%. e) MeOH, Pd/C, H_2, rt, 96%. f) CH_2Cl_2, EtOAc, Ac_2O, $TiBr_4$, rt; CH_2Cl_2, 1 M NaOH, TBAB, Mu, rt; 58%. g) MeOH, Na, rt; 89%. h) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 94%.

6-Azido-6-deoxy-1,2,3,4-di-*O*-isopropylidene-α-D-galactopyranose (**35**): To a solution of **34** (0.91 g, 3.5 mmol) in dry CH_2Cl_2 (15 mL) and dry pyridine (6 mL), stirred at 0 °C under N_2, was added triflic anhydride (1.2 mL, 7.1 mmol, 2 equiv) dropwise, and the reaction mixture was stirred for 1 h under the same conditions. After completion, the mixture was diluted with DCM (70 mL), washed with cold saturated $NaHCO_3$ (40 mL) and cold brine (40 mL), dried over $MgSO_4$, filtered and evaporated, co-evaporated twice with toluene, and dried under vacuum for 1 h to afford a brownish foam. To this foam were added dry DMF (10 mL) and NaN_3 (0.7 g, 10.8 mmol, 3 equiv), and the reaction mixture stirred vigorously for 1.5 h at room temperature under N_2. The reaction mixture

was diluted with EtOAc (100 mL), washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (9:1, petroleum ether-EtOAc with 1% Et_3N) to afford **35** as a colorless syrup (748 mg, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.53 (d, 1 H, $J_{1,2}$ 5.2 Hz, H-1), 4.62 (dd, 1 H, $J_{3,4}$ 7.6 Hz, H-3), 4.32 (dd, 1 H, $J_{2,3}$ 2.4 Hz, H-2), 4.18 (dd, 1 H, $J_{4,5}$ 2.0 Hz, H-4), 3.90 (m, 1 H, H-5), 3.50 (dd, 1 H, $J_{5,6a}$ 8.0 Hz, $J_{6a,6b}$ 12.8 Hz, H-6a), 3.35 (dd, 1 H, $J_{5,6b}$ 5.4 Hz, H-6b), 1.54 (s, 3 H, CH_3C), 1.45 (s, 3 H, CH_3C), 1.333 (s, 3 H, CH_3C), 1.327 (s, 3 H, CH_3C). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.7, 108.9, 96.5, 71.3, 70.9, 70.5, 67.1, 50.8, 26.14, 26.05, 25.0, 24.5. ESI-HRMS: Calcd for $[C_{12}H_{19}N_3O_5 + Na]^+$: 308.1222; Found m/z: 308.1227.

6-Azido-6-deoxy-1,2,3,4-tetra-*O*-acetyl-D-galactopyranose (**36**): A mixture of **35** (9.05 g, 31.8 mmol), AcOH (120 mL) and H_2O (60 mL) was stirred for 27 h at 80 °C, evaporated and co-evaporated with toluene twice, then dried under vacuum for 2 h to afford a syrup. To this syrup were added pyridine (120 mL) and Ac_2O (60 mL), and the mixture stirred overnight at room temperature. After evaporation, ice-water was added and the mixture was stirred for 0.5 h, extracted with EtOAc (2 x 250 mL). The organic phase was washed with 1 M HCl (2 x 250 mL), water (250 mL), saturated $NaHCO_3$ (2 x 250 mL) and brine (250 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (3:1, petroleum ether-EtOAc) to afford **36** as a syrup (10.84 g, 92%; α/β=1/1.38). ESI-MS: Calcd for $[C_{14}H_{19}N_3O_9 + Na]^+$: 396.1; Found m/z: 396.0.

6-Azido-6-deoxy-2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl fluoride (**37**): See the general procedure A, the reaction mixture was stirred overnight at 0 °C, **37** was obtained as a colorless syrup in 78% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.82 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.2 Hz, H-1), 5.50 (brd, 1 H, H-4), 5.36 (dd, 1 H, $J_{3,4}$ 2.8 Hz, H-3), 5.19 (dddd, 1 H, $J_{2,3}$ 10.8 Hz, $J_{H,F}$ 24.0 Hz, H-2), 4.31 (m, 1 H, H-5), 3.49 (dd, 1 H, $J_{5,6a}$ 7.2 Hz, $J_{6a,6b}$ 12.8 Hz, H-6a), 3.26 (dd, 1 H, $J_{5,6b}$ 5.2 Hz, H-6b), 2.18 (s, 3 H, CH_3CO), 2.13 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 170.1, 169.9, 104.3 (d, $J_{C,F}$ 227.0 Hz), 70.2 (d, $J_{C,F}$ 3.0 Hz), 68.1, 67.4 (d, $J_{C,F}$ 24.0 Hz), 67.1, 50.5, 20.8, 20.7 (2 C). ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -150.6. ESI-HRMS: Calcd for

$[C_{12}H_{16}N_3FO_7 + Na]^+$: 356.0870; Found m/z: 356.0869.

6-Azido-6-deoxy-α-D-galactopyranosyl fluoride (**38**): See general procedure B, the mixture was stirred overnight at 0 °C. The resulting residue was purified by flash column chromatography to afford **38** as a colorless syrup in 95% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.62 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.2 Hz, H-1), 4.10 (dd, 1 H, H-5), 3.93 (brd, 1 H, $J_{3,4}$ 2.0 Hz, H-4), 3.83~3.70 (m, 2 H, $J_{2,3}$ 10.4 Hz, $J_{H,F}$ 25.2 Hz, H-2 & H-3), 3.52 (dd, 1 H, $J_{5,6a}$ 8.8 Hz, $J_{6a,6b}$ 12.8 Hz, H-6a), 3.41 (dd, 1 H, $J_{5,6b}$ 4.8 Hz, H-6b). ^{13}C NMR (D_2O, 100 MHz): δ 107.5 (d, $J_{C,F}$ 223.0 Hz), 71.9 (d, $J_{C,F}$ 3.0 Hz), 69.1, 68.8, 67.8 (d, $J_{C,F}$ 24.0 Hz), 50.9. ^{19}F-NMR (CD_3OD, 282 MHz): δ -152.3. ESI-HRMS: Calcd for $[C_6H_{10}N_3FO_4 - H]^-$: 206.0577; Found m/z: 206.0584.

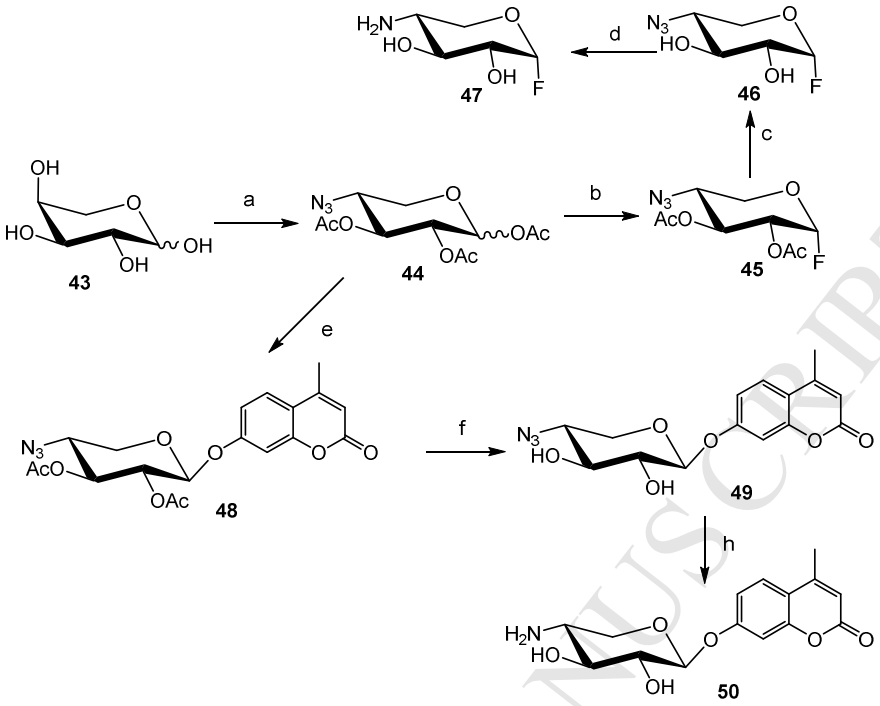
6-Amino-6-deoxy-α-D-galactopyranosyl fluoride (**39**): See general procedure C, **39** was obtained as a white solid in 96% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.61 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 53.6 Hz, H-1), 3.98 (dd, 1 H, H-5), 3.93 (brd, 1 H, $J_{3,4}$ 2.8 Hz, H-4), 3.82~3.69 (m, 2 H, $J_{2,3}$ 10.0 Hz, $J_{H,F}$ 25.0 Hz, H-2 & H-3), 2.92 (dd, 1 H, $J_{5,6a}$ 8.4 Hz, $J_{6a,6b}$ 13.6 Hz, H-6a), 2.85 (dd, 1 H, $J_{5,6b}$ 3.6 Hz, H-6b). ^{13}C NMR (D_2O, 100 MHz): δ 107.5 (d, $J_{C,F}$ 222.0 Hz), 72.5, 69.4, 69.0, 67.9 (d, $J_{C,F}$ 25.0 Hz), 40.8. ^{19}F-NMR (D_2O, 282 MHz): δ -152.3. ESI-HRMS: Calcd for $[C_6H_{12}NFO_4 + H]^+$: 182.0829; Found m/z: 182.0827.

4-Methylumbelliferyl 6-azido-6-deoxy-2,3,4-tri-*O*-acetyl-β-D-galactopyranoside (**40**): To a solution of **36** (1.14 g, 3.1 mmol) in dry CH_2Cl_2 (17 mL), dry EtOAc (1.7 mL) and Ac_2O (0.3 mL), stirred at room temperature under N_2, was added $TiBr_4$ (2.25 g, 6.1 mmol, 2 equiv), and the reaction mixture stirred for 2 days under the same conditions [32]. An additional 10% of $TiBr_4$ was added each day until completion. The reaction mixture was diluted with CH_2Cl_2 (125 mL), washed with cold water (2 x 80 mL), cold brine (80 mL), dried over $MgSO_4$, filtered and concentrated, and dried under vacuum for 2 h to afford a foam. To the foam were added CH_2Cl_2 (16 mL), 1 M NaOH (8 mL), Mu (1.1 g, 6.2 mmol, 2 equiv) and tetra-n-butylammonium bromide (TBAB, 1 g), and the reaction mixture stirred vigorously overnight at room temperature [33]. The reaction mixture was diluted with CH_2Cl_2 (125 mL), washed with 1 M NaOH (2 x 60 mL),

saturated $NaHCO_3$ (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (2:1 petroleum ether-EtOAc) to afford **40** as a white solid (0.86 g, 58%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, 1 H, *J* 9.2 Hz, Ar-H), 6.98 (m, 2 H, Ar-H), 6.20 (d, 1 H, *J* 1.2 Hz, Ar-H), 5.50 (dd, 1 H, $J_{2,3}$ 10.8 Hz, H-2), 5.45 (brd, 1 H, H-4), 5.17 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.14 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 3.99 (m, 1 H, H-5), 3.58 (dd, 1 H, $J_{5,6a}$ 8.0 Hz, $J_{6a,6b}$ 13.2 Hz, H-6a), 3.28 (dd, 1 H, $J_{5,6b}$ 4.8 Hz, H-6b), 2.41 (d, *J* 1.2 Hz, 3 H, Ar-CH_3), 2.22 (s, 3 H, CH_3CO), 2.08 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 170.1, 169.5, 160.0, 159.3, 155.0, 152.3, 126.0, 115.8, 113.7, 113.4, 104.6, 99.2, 73.3, 70.7, 68.4, 67.7, 50.7, 20.84, 20.8, 20.7, 18.8. ESI-HRMS: Calcd for $[C_{22}H_{23}N_3O_{10} + Na]^+$: 512.1281; Found m/z: 512.1277.

4-Methylumbelliferyl 6-azido-6-deoxy-β-D-galactopyranoside (**41**): See general procedure F, **41** was obtained as a white solid in 89% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.70 (d, 1 H, *J* 8.8 Hz, Ar-H), 7.03 (m, 2 H, Ar-H), 6.23 (d, 1 H, *J* 0.8 Hz, Ar-H), 5.08 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.94 (m, 1 H, H-5), 3.65 (brd, 1 H, H-4), 3.61 (dd, 1 H, $J_{2,3}$ 9.6 Hz, H-2), 3.54 (m, 1 H, H-6a), 3.47 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 3.26 (dd, 1 H, $J_{5,6b}$ 3.6 Hz, $J_{6a,6b}$ 12.8 Hz, H-6b), 2.39 (d, 3 H, *J* 0.8 Hz, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.5, 155.0, 154.1, 127.0, 114.7, 114.0, 112.2, 103.6, 100.7, 74.7, 73.1, 70.2, 69.2, 51.7, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{17}N_3O_7 + H]^+$: 364.1145; Found m/z: 364.1146.

4-Methylumbelliferyl 6-amino-6-deoxy-β-D-galactopyranoside (**42**): See general procedure G, **42** was obtained as a white solid in 94% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.69 (d, 1 H, *J* 9.6 Hz, Ar-H), 7.05 (m, 2 H, Ar-H), 6.23 (s, 1 H, Ar-H), 4.97 (d, 1 H, $J_{1,2}$ 8.0 Hz, H-1), 3.73~3.57 (m, 3 H, H-2,4 & 5), 3.43 (dd, 1 H, $J_{2,3}$ 9.6 Hz, $J_{3,4}$ 3.2 Hz, H-3), 2.81 (d, 2 H, $J_{5,6}$ 6.0 Hz, H-6), 2.39 (d, 3 H, *J* 0.4 Hz, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.7, 155.1, 153.9, 127.0, 114.6, 113.9, 112.3, 103.6, 101.1, 75.9, 73.8, 70.7, 69.2, 42.1, 18.7. ESI-HRMS: Calcd for $[C_{16}H_{19}NO_7 + H]^+$: 338.1240; Found m/z: 338.1238.



Scheme 6. Reagents and conditions: a) pyridine, BzCl, 0 °C; CH_2Cl_2, pyridine, Tf_2O, 0 °C; DMF, NaN_3, rt; MeOH, NaOMe, rt; pyridine, Ac_2O, rt; 33%. b) CH_2Cl_2, Ac_2O, HF/pyridine, 0 °C, 87%; c) MeOH, NH_3, 0 °C, 99%. d) MeOH, Pd/C, H_2, rt. e) DMF, hydrazine acetate, rt; CH_2Cl_2, TCA, DBU, -20~0 °C; CH_2Cl_2, Mu, $BF_3{\cdot}Et_2O$, -40~-20 °C, 4Å molecular sieves; 41%. f) CH_2Cl_2, MeOH, Na, rt, 98%. g) THF/H_2O (4/1), Ph_3P, silica gel, 50 °C, 94%

4-Azido-4-deoxy-2,3-di-*O*-acetyl-α-D-xylosyl fluoride (**45**): See the general procedure A, a solution of **4-azido-4-deoxy-1,2,3-tri-*O*-acetyl-D-xylose** [34, 35] in dry CH_2Cl_2 and HF/Pyridine was stirred for 24 h at 0 °C. After flash column chromatography (9:1 petroleum ether-EtOAc), **45** was obtained as a white solid in 87% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.66 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 52.8 Hz, H-1), 5.41 (t, 1 H, $J_{3,4}$ 9.6 Hz, H-3), 4.87 (dddd, 1 H, $J_{2,3}$ 10.0 Hz, $J_{H,F}$ 24.0 Hz, H-2), 3.92 (dd, 1 H, $J_{4,5a}$ 2.4 Hz, $J_{5a,5b}$ 5.6 Hz, H-5a), 3.76~3.73 (m, 2 H, H-4 & H-5b), 2.12 (s, 3 H, CH_3CO), 2.10 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 169.8, 104.3 (d, $J_{C,F}$ 228.0 Hz), 70.6 (d, $J_{C,F}$ 24.0 Hz), 70.1, 61.5 (d, $J_{C,F}$ 4.0 Hz), 58.8, 20.8, 20.7. ^{19}F-NMR ($CDCl_3$, 282 MHz): δ -150.9. ESI-HRMS: Calcd for $[C_9H_{12}N_3FO_5 + Na]^+$: 284.0659; Found m/z: 284.0655.

4-Azido-4-deoxy-α-D-xylosyl fluoride (**46**): See general procedure B, the mixture was stirred overnight at 0 °C. The resulting residue was purified by flash column chromatography (50:1 & 15:1 CH_2Cl_2-MeOH) to afford **46** as white crystals in 99% yield. ^{1}H NMR (CD_3OD, 400 MHz): δ 5.51 (dd, 1 H, $J_{1,2}$ 2.8 Hz, $J_{H,F}$ 53.6 Hz, H-1), 3.80 (dd, 1 H, $J_{4,5a}$ 2.8 Hz, $J_{5a,5b}$ 5.6 Hz, H-5a), 3.68 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.2 Hz, H-3), 3.56 ~ 3.52 (m, 2 H, H-4 & H-5b), 3.48 (dddd, 1 H, $J_{H,F}$ 23.2 Hz, H-2), 3.41 (dd, 1 H, $J_{5,6b}$ 4.8 Hz, H-6b). ^{13}C NMR (CD_3OD, 100 MHz): δ 107.8 (d, $J_{C,F}$ 225.0 Hz), 72.4, 72.0 (d, $J_{C,F}$ 25.0 Hz), 61.6 (d, $J_{C,F}$ 4.0 Hz), 61.2. ^{19}F-NMR (D_2O, 282 MHz): δ -152.8. ESI-HRMS: Calcd for $[C_5H_8N_3FO_3 - H]^-$: 176.0471; Found m/z: 176.0476.

4-Amino-4-deoxy-α-D-xylosyl fluoride (**47**): See general procedure C, the mixture was stirred overnight at room temperature. The resulting residue was purified by flash column chromatography (9:1 & 5:1 CH_2Cl_2-MeOH with 1% Et_3N) to afford **47** as a syrup in 98% yield. ^{1}H NMR (D_2O, 400 MHz): δ 5.65 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{H,F}$ 53.3 Hz, H-1), 3.84 (dd, 1 H, $J_{4,5a}$ 3.8 Hz, $J_{5a,5b}$ 11.6 Hz, H-5a), 3.65 (t, 1 H, $J_{2,3} = J_{3,4}$ 11.3 Hz, H-3), 3.64~3.53 (m, 2 H, H-2 & H-5b), 2.98 (m, 1 H, H-4). ^{13}C NMR (D_2O, 100 MHz): δ 108.0 (d, $J_{C,F}$ 223.9 Hz), 72.3, 71.4 (d, $J_{C,F}$ 24.5 Hz), 63.6 (d, $J_{C,F}$ 3.1 Hz), 51.1. ^{19}F-NMR (D_2O, 282 MHz): δ -152.2. ESI-HRMS: Calcd for $[C_5H_{10}NFO_3 + H]^+$: 152.0723; Found m/z: 152.0723.

4-Methylumbelliferyl 4-azido-4-deoxy-2,3-di-*O*-acetyl-β-D-xyloside (**48**): See general procedure D, eluent (2:1 petroleum ether-EtOAc), **4-azido-4-deoxy-2,3-di-*O*-acetyl-D-xylose** was obtained as a colorless syrup in 56% yield. See general procedure E, eluent (3:1 petroleum ether-EtOAc), **48** was obtained as a white solid in 74% yield (overall yield: 41%). ^{1}H NMR (d_6-acetone, 400 MHz): δ 7.72 (d, 1 H, J 8.4 Hz, Ar-H), 7.01 (m, 2 H, Ar-H), 6.19 (d, 1 H, J 1.2 Hz, Ar-H), 5.54 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 5.27 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.2 Hz, H-3), 5.13 (dd, 1 H, H-2), 4.24 (dd, 1 H, $J_{4,5a}$ 5.6 Hz, $J_{5a,5b}$ 12.0 Hz, H-5a), 4.03 (m, 1 H, H-4), 3.79 (dd, 1 H, $J_{4,5b}$ 10.4 Hz, H-5b), 2.45 (d, J 1.2 Hz, 3 H, Ar-CH_3), 2.09 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.0, 169.7, 160.9, 159.2, 155.0, 152.3, 125.9, 115.7, 113.7, 113.3, 104.5, 98.6, 72.6, 70.6, 63.3, 58.3, 20.82, 20.76, 18.8. ESI-HRMS: Calcd for $[C_{19}H_{19}N_3O_8 + Na]^+$: 440.1070; Found m/z: 440.1068.

4-Methylumbelliferyl 4-azido-4-deoxy-β-D-xyloside (**49**): See general procedure F, **49** was obtained as a white solid in 98% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.71 (d, 1 H, *J* 9.6 Hz, Ar-H), 7.01 (m, 2 H, Ar-H), 6.24 (d, 1 H, *J* 1.2 Hz, Ar-H), 5.09 (d, 1 H, $J_{1,2}$ 7.6 Hz, H-1), 3.88 (dd, 1 H, $J_{4,5a}$ 4.8 Hz, $J_{5a,5b}$ 10.8 Hz, H-5a), 3.58~3.41 (m, 3 H, H-3, 4 & 5b), 3.34 (dd, 1 H, $J_{2,3}$ 8.8 Hz, H-2), 2.39 (d, 3 H, *J* 0.8 Hz, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.7, 160.3, 154.9, 154.0, 127.2, 114.9, 113.9, 112.4, 103.7, 100.5, 75.3, 73.5, 63.7, 61.5, 18.7. ESI-HRMS: Calcd for $[C_{15}H_{15}N_3O_6 + Na]^+$: 356.0859; Found m/z: 356.0864.

4-Methylumbelliferyl 4-amino-4-deoxy-β-D-xyloside (**50**): See general procedure G, **50** was obtained as a white solid in 94% yield. ^{1}H NMR (d_6-DMSO + D_2O, 400 MHz): δ 7.70 (d, 1 H, *J* 9.2 Hz, Ar-H), 7.03 (m, 2 H, Ar-H), 6.24 (s, 1 H, Ar-H), 5.02 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 3.78 (dd, 1 H, $J_{4,5a}$ 5.2 Hz, $J_{5a,5b}$ 11.2 Hz, H-5a), 3.37~3.26 (m, 2 H, H-2, & H-5b), 3.18 (t, 1 H, $J_{2,3} = J_{3,4}$ 8.8 Hz, H-3), 2.70 (m, 1 H, H-4), 2.39 (d, 3 H, *J* 0.8 Hz, Ar-CH_3). ^{13}C NMR (d_6-DMSO + D_2O, 100 MHz): δ 160.8, 160.5, 154.9, 154.0, 127.1, 114.8, 114.0, 112.3, 103.7, 101.2, 76.5, 73.6, 66.5, 52.9, 18.7. ESI-HRMS: Calcd for $[C_{15}H_{17}NO_6 + H]^+$: 308.1134; Found m/z: 308.1131.

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Highlights:

-Common strategy for synthesis of azido glycosides and amino glycosides

-Synthesis of the corresponding alpha-glycosyl fluorides via common intermediates

-Approach provides access to clickable oligo- and polysaccharides