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Synthesis of Symmetrical *C*- and Pseudo-symmetrical *O*-Linked Disaccharide Analogs for Arabinosyltransferase Inhibitory Activity in *Mycobacterium tuberculosis*

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Abstract

Herein we report the synthesis of symmetrical *C*-linked and pseudo-symmetrical *O*-linked disaccharides structurally related to Ara*f* motifs present in the cell wall of MTB. Their activity in a competition-based arabinosyltransferase assay using [^{14}C]-DPA as the glycosyl donor is also presented. In addition, *in vitro* inhibitory activity for the disaccharides was determined in a colorimetric broth microdilution assay system against MTB H_{37}Ra and *Mycobacterium avium*.

The development of multi-drug resistant strains of *Mycobacterium tuberculosis* (MTB)[1,2] and co-infection with HIV[3] has limited TB treatment options, initiating a worldwide effort to discover new biochemical targets and selective inhibitors. The mycobacterial cell wall remains an excellent target, focusing discovery efforts on new proteins involved in the biogenesis of this critical bacterial barrier.[4] The cell wall of MTB allows the bacterium to elude cellular defenses and thrive within macrophages of the host. Particular components of that barrier, arabinofuranose (Ara*f*), galactofuranose (gal*f*) and rhamnopyranose (rha*f*), and several of the attendant synthetic enzymes are not found in humans, and they offer the potential for development of highly selective and potent new drugs.

The major components of the mycobacterial integument are the mycolyl arabinogalactan – peptidoglycan complexes (mAGPs) and lipoarabinomannan (LAM) associated lipoglycans.[5] The arabinan portion of the cell wall is composed of Ara*f* homopolymers with different linkages viz. α(1→5), α(1→2) and α(1→3), and requires several different sugar processing enzymes, or arabinosyltransferases (AraT's), for its complete genesis.[5,6] Several synthetic *O*- and *S*-alkyl arabinofuranoside acceptors have been prepared for the development of arabinosyl-transferase assays[7] and other biological and structural studies based on the unbranched and highly branched polysaccharides of AG and LAM.[8–10]

As part of ongoing programs to find carbohydrate-based antimycobacterial agents targeting biogenesis of the mycobacterial cell wall polysaccharides, we and others have synthesized several analogs of α(1→5) Ara*f* disaccharides.[9b,11,12] We have reported the synthesis and

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antimycobacterial activity of analogs (Figure 1) with substitution at the non-reducing terminus (ring B).

We designed *O*-linked and *C*-linked disaccharide analogs (**3** and **4**) that also possess *C*-substitution at the anomeric center of the reducing terminus. This substitution is based on the *N*,*N*-dicyclohexyl-methylamino substitution of **2** at the 5′-position that showed the best activity among reported derivatives.[11] C-sugars and *C*-linked disaccharides offer advantages as enzyme probes and inhibitors, and as drugs. Most importantly, this linkage prevents glycosidase-mediated cleavage. We report the synthesis and inhibitory data of pseudo-symmetrical and symmetrical disaccharides **3** and **4** respectively.

In our study of the Ara*f* 1-5 linkages, it was noted that the simple O-linked disaccharide core is pseudo-symmetrical around the central -O-C- bond. Hence, we targeted **3** and **4** to incorporate the *N*,*N*-dicyclohexyl group of the active compound **2** at both ends of the targets to take advantage of this symmetry to potentially increase binding efficiency. Compound **4** contains a true C_2-symmetry axis as does the intermediate **17** that may also offer the advantage of reduced degrees of freedom around the disaccharide linkage that could further improve binding efficiency.

Several groups have reported *C*-linked glycoside analogs of the α-D-Ara*f*-(1→5)-α-D-Ara*f* motif found in the cell wall of mycobacteria using various approaches.[13–16] We describe the synthesis of targets **3** and **4** through coupling of a 5-azidoarabinosyl donor with a 1-azido D-mannitol derivative and C–C bond formation by Wittig olefination[14] respectively. These syntheses began with 2,5-anhydro-1-azido-1-deoxy-D-mannitol (**5**) prepared from D-glucosamine hydrochloride by diazotization-mediated ring contraction and selective monotosylation followed by introduction of the azido group using NaN_3.[17] Compound **5** was persilylated to produce **6** which on selective desilylation at the 6-position using a trifluoroacetic acid-water mixture (1:1) in dry THF at −4°C produced **7** as shown in Scheme 1.

The synthesis of disaccharide **3** was achieved by coupling of *p*-thiotolyl 1,5-dideoxy-5-azido-2,3-di-*O*-acetyl-α-D-arabinofuranoside (**8**),[11] with 2,5-Anhydro-1-azido-3,4-di-*O*-*tert*-butyldimethylsilyl-1-deoxy-D-mannitol (**7**) in the presence of NIS and the Lewis acid promoter triflic acid to produce **9** (Scheme 2). After several column purifications, a slight trace of unreacted **8** was present necessitating deacetylation to yield the diazido disaccharide **10** as a pure, colorless oil. *N*,*N*-dialkylation of **10** via reductive alkylation with cyclohexane carboxyaldehyde in MeOH over 10% Pd/C at room temperature under H_2 atmosphere gave **11** in 74% yield as a colorless oil after purification. Desilylation of **11** in a trial reaction with $Bu_4N^+F^-$ produced only a poor yield (48%) of **3**. The synthesis of **3** was achieved by desilylation of **11** using $Et_4N^+F^-$ in THF in 88% yield after purification.

The attempted synthesis of *C*-linked disaccharide **4** *via* Wittig olefination[18] to give a *C*-linked diazido disaccharide similar to **9** was unsuccessful. Disaccharide **4** was produced using Wittig olefination as shown in Scheme 3. Azido saccharide **7** was first converted to the *N*,*N*-dicyclohexylmethylamino derivative **12**, ultimately yielding **14** and **15** for coupling. Compound **12** was converted to 6-iodomannitol derivative **13** by heating with iodine, PhP_3, and imidazole. After purification, **13** was heated with neat Ph_3P to produce the triphenylphosphonium iodide **14**. Compound **12** was alternatively oxidized with PCC in CH_2Cl_2 to aldehyde **15** that was used directly in the coupling without purification.[19] The two saccharides **14** and **15** were coupled in the presence of BuLi at −30°C to give a mixture of olefin **16** (*E*/*Z* ratio 96:4 by NMR) after purification. Deblocking of **16** with $Et_4N^+F^-$ in THF and purification produced **17** in 86% yield as an *E*/*Z* mixture. Reduction of **17** produced the symmetrical *C*-linked disaccharide **4** in 62% yield.

All compounds were characterized by ESIMS analysis and ^{1}H NMR spectroscopy.[20] nOe, and D_2O exchange experiments were performed as needed to confirm NMR assignments.

Activity was determined in the cell-free enzymatic arabinosyltransferase acceptor assay[7] in the presence of membranes and is based on inhibition of [^{14}C]Ara*f* incorporation from [^{14}C] DPA by the control α(1→5)-linked 1-*O*-octyl arabinofuranosyl disaccharide.[11] Disaccharide analogs **3**, **4**, and **17** showed inhibitory activity at a concentration of 3.6 mM (with control acceptor at 0.4 mM) and specific IC_{50} values were 2.80, 3.44 and 4.15 mM respectively. Bacterial growth inhibition was determined versus MTB H_{37}Ra (ATCC 25177) and *Mycobacterium avium* (NJ 211) at the initial concentrations of 1.28 and 12.8 μg/mL.[21] Initial activity was confirmed using half-log dilutions at 16, 8, and 4 ug/mL to determine an MIC as reported.[21] Ethambutol showed a MIC in the range 2 – 4 μg/mL. Compounds **3** and **17** showed a modest MIC of 8 μg/mL, **4** and **10** gave an MIC of 16 μg/mL and **11** a MIC of >12.8 μg/mL against MTB. Against *M. avium*, however, compound **17** showed a MIC of 8 μg/mL, and **3** and **4** a MIC of 16 μg/mL. The blocked analogs **10** and **11** were inactive at 12.8 μg/mL. In conclusion, we report efficient syntheses of *O*- and *C*linked disaccharides **3**, **4** and **17** and their inhibitory activity against MTB.

Acknowledgments

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19. Compound formation was monitored by ESI-MS that showed m/z at 583 $[M+H]^+$.
20. Selected data: Compound 6. ^{1}H NMR ($CDCl_3$): δ 4.13 (s, 1H, H-3), 3.97 – 4.04 (m, 3H, H-2, H-4, H-5), 3.66 (d, 2H, *J* = 7.4 Hz H_2-6), 3.46 (dd, 1H, *J* = 7.0, 12.3 Hz, H-1a), 3.32 (dd, 1H, *J* = 6.7, 12.3 Hz, H-1b), 0.893 (s, 9H, 3xCH_3), 0.890 (s, 9H, 3xCH_3), 0.89 (s, 9H, 3xCH_3), 0.10 (12H, s, 4xCH_3), 0.05 (6H, s, 2xCH_3). ESIMS: *m/z* calcd for $C_{24}H_{53}N_3O_4Si_3$ 532.3422, found 532.3418 $[M+H]^+$. Compound 7. ^{1}H NMR ($CDCl_3$): δ 4.10 – 4.06 (m, 2H, H-2, H-5), 4.05 – 4.00 (m, 2H, H-3, H-4), 3.71 (dd, 2H, *J* = 4.5, 5.7 Hz, H_2-6), 3.50 (dd, 1H, *J* = 7.0, 12.4 Hz, H-1a), 3.36 (dd, 1H, *J* = 6.8, 12.4 Hz, H-1b), 2.38 (t, 1H, *J* = 5.7 Hz, 6-OH), 0.91, 0.90 (s, 9H, 3xCH_3), 0.90 (s, 9H, 3xCH_3), 0.12 (3H, s, CH_3), 0.11 (3H, s, CH_3), 0.10 (3H, s, CH_3), 0.09 (3H, s, CH_3). ESI-MS: *m/z* calcd for $C_{18}H_{39}N_3O_4Si_2$ 418.2557, found 418.2551 $[M+H]^+$. Compound 11. ^{1}H NMR ($CDCl_3$): δ 5.01 (1H, s, H-1′), 4.76 (1H, d, *J* = 1.4 Hz, H-1), 4.17 (1H, br s, H-4′), 4.03 – 3.97 (3H, m, H-2, H-4, H-2′), 3.83 – 3.76 (3H, m, H-3, H-5a, H-3′), 3.68 – 3.58 (1H, m, OCH_2), 3.59 (1H, dd, *J* = 3.2 Hz, *J* = 10.4 Hz, H-5b), 3.35 – 3.28 (1H, m, OCH_2), 2.71 – 2.60 (2H, m, H_2-5′), 2.44 (2H, dd, *J* = 7.7, 12.6 Hz, NCH_2), 2.16 (2H, dd, *J* = 5.2, 12.6 Hz, NCH_2), 1.87 – 1.60 (4H, m, cyclohexyl CH_2′s), 1.57 –1.50 (10H, m, cyclohexyl), 1.46 – 1.41 (2H, m, CH_2), 1.37 (10H, br s, 5xCH_2), 1.20 – 1.08 (8H, m, cyclohexyl), 0.90 – 0.86 (21H, m, 7xCH_3), 0.09, 0.07, 0.06 (each s, 4xCH_3). ESIMS: *m/z* calcd. for $C_{51}H_{98}N_2O_7Si_2$ 907.6990, found 907.6998 $[M+H]^+$. Compound 3. ^{1}H NMR (CD_3OD): δ 4.95 (1H, dd, *J* = 1.6 Hz, H-1′), 4.83 (1H, d, *J* = 1.7 Hz, H-1), 4.04 (1H, ddd, *J* = 3.5, 6.2, 6.6 Hz, H-4′), 4.00 (1H, dd, *J* = 1.6 Hz, *J* = 3.8 Hz, H-2′), 4.03 – 3.99 (1H, m, H-4), 3.94 (1H, dd, *J* = 1.7, 3.9 Hz, H-2), 3.87 (1H, dd, *J* = 3.8, 6.6 Hz, H-3′), 3.86 – 3.79 (2H, m, H-3, H-5a), 3.73 – 3.65 (1H, m, OCH_2), 3.65 (1H, dd, *J* = 3.6, 11.1 Hz, H-5b), 3.50 (1H, dd, *J* = 3.3, 13.3 Hz, H-5′a), 3.44 – 3.36 (2H, m, OCH_2), 3.37 (1H, dd, *J* = 6.2, 13.3 Hz, H-5′b), 1.62 – 1.53 (2H, m, CH_2), 1.30 (10H, br s, 5xCH_2), 0.92 – 0.87 (3H, m, CH_3). ESIMS: m/z calcd. for $C_{18}H_{33}N_3O_8Na$ 442.2165, found 442.2176 $[M+Na]^+$. Compound 12. ^{1}H NMR ($CDCl_3$): δ 4.00 (3H, m, H-3, H-4, H-5), 3.96 (1H, dd, *J* = 5.5, 8.1 Hz, H-2), 3.68 (1H, d, *J* = 4.1 Hz, H-6a), 2.72 (1H, dd, *J* = 8.1, 13.6 Hz, H-1a), 2.43 (1H, dd, *J* = 5.5, 13.6 Hz, H-1b), 2.18 (2H, m, NCH_2), 1.93 – 1.10 (22H, m, Cyclohexyl), 0.90, 0.89 (each 9H, s, 6xCH_3), 0.12 (3H, s, CH_3), 0.11 (6H, s, 2xCH_3), 0.80 (3H, s, CH_3). ESIMS: *m/z* calcd. for $C_{32}H_{65}NO_4Si_2$ 584.4530, found 584.4534 $[M+H]^+$. Compound 13. ^{1}H NMR ($CDCl_3$): δ 4.24 (1H, s, H-4), 4.14 (1H, dd, *J* = 5.3, 10.4 Hz, H-5), 4.04 (1H, dd, *J* = 5.1, 8.5 Hz, H-2), 3.96 (1H, s, H-3), 3.44 (1H, dd, *J* = 9.4, 10.4 Hz, H-6a), 3.22 (1H, dd, *J* = 5.3, 9.4 Hz, H-6b), 2.67 (1H, dd, *J* = 8.5, 13.4 Hz, H-1a), 2.39 (1H, dd, *J* = 5.1, 13.4 Hz, H-1b), 2.19 (1H, dd, *J* = 8.1, 12.6 Hz, NCH_2), 2.12 (1H, dd, *J* = 5.7, 12.8 Hz, NCH_2), 1.85 – 1.10 (20H, m, cyclohexyl) 0.92 – 0.76 (4H, m, cyclohexyl), 0.91 (9H, s, 3xCH_3), 0.89 (9H, s, 3xCH_3), ESIMS: *m/z* calcd. for $C_{32}H_{64}INO_3Si_2$ 694.3549, found 694.3539 $[M+H]^+$. Compound 14. ^{1}H NMR ($CDCl_3$): δ 7.89 – 7.82 (4H, m, Ar), 7.76 – 7.74 (2H, m, Ar), 7.71 – 7.62 (6H, m, Ar), 7.55 – 7.52 (1H, m, Ar), 7.49 – 7.43 (2H, m, Ar), 4.68 (1H, m, H-6a), 4.42 (1H, s, H-4), 4.29 (1H, m, H-5), 3.39 (1H, s, H-3), 3.85 (1H, m, H-6b), 3.71 (1H, dd, *J* = 5.6, 7.1 Hz, H-2), 2.46 (1H, dd, *J* = 7.1, 13.8 Hz, H-1a), 2.39 (1H, dd, *J* = 5.6, 13.8 Hz, H-1b), 1.95 (1H, dd, *J* = 6.3, 12.0 Hz, NCH_2), 2.46 (1H, dd, *J* = 7.4, 12.0 Hz, NCH_2), 1.71 – 1.56 (10H, m, cyclohexyl), 1.31 – 1.03 (10H, m, cyclohexyl), 0.93 (9H, s, 3xCH_3), 0.82 (9H, s, 3xCH_3), 0.71 – 0.61 (2H, m, cyclohexyl), 0.23 (3H, s, CH_3), 0.21 (3H, s, CH_3), 0.18 (6H, s, 2xCH_3). ESIMS: *m/z* calcd. for $C_{50}H_{79}NO_3IPSi_2$ 825.5335, found 825.5330 $[M-I]^+$. Compound 16. ^{1}H NMR ($CDCl_3$): δ 5.66 (2H, dd, *J* = 2.0, 6.6 Hz, H-6, H-7), 4.54 (2H, d, *J* = 6.6, 13.2 Hz, H-5, H-8), 3.99 (2H, s, H-3, H-10), 3.97 (2H, dd, *J* = 4.5, 8.7 Hz, H-2, H-11), 3.91 (2H, s, H-4, H-9), 2.76 (2H, dd, *J* = 8.7, 13.4 Hz, H-1a, H-12a), 2.34 (2H, dd, *J* = 4.6, 13.4 Hz, H-1b, H-12b), 2.20 (2H, dd *J* = 8.6, 12.6 Hz, NCH_2), 2.12 (2H, dd *J* = 5.7, 12.6 Hz, NCH_2), 1.91 – 1.11 (40H, m, cyclohexyl), 0.93 (18H, s, 6xCH_3), 0.87 (18H, s, 6xCH_3), 0.92 – 0.75 (4H, m, cyclohexyl), 0.11 (6H, s, 2xCH_3), 0.10 (6H, s, 2xCH_3), 0.073 (6H, s, 2xCH_3), 0.070 (6H, s, 2xCH_3). ESIMS: *m/z* calcd. for $C_{64}H_{126}N_2O_6Si_4$ 1131.8765, found 1131.8756 $[M+H]^+$. Compound 17. ^{1}H NMR ($CDCl_3$): δ 5.84 (2H, dd, *J* = 1.1, 4.7 Hz, H-6, H-7), 4.59 (2H, dd, *J* = 4.7, 13.4 Hz, H-5, H-8), 3.99 (2H, dd, *J* = 3.9, 6.7 Hz, H-2, H-11), 3.98 (4H, s, H-3, H-4, H-9, H-10), 2.67 (2H, dd, *J* = 6.7, 13.2 Hz, H-1a, H-12a), 2.56 (2H, dd, *J* = 2.9, 13.2 Hz, H-1b, H-12b), 2.28 (2H, dd, *J* = 8.3, 12.8 Hz, NCH_2), 2.14 (2H, dd, *J* = 5.4, 12.8 Hz, NCH_2), 1.82 – 1.09 (44H, m, cyclohexyl, 4xOH), 0.91 – 0.78 (4H, m, cyclohexyl). ESIMS: *m/z* calcd. for $C_{40}H_{70}N_2O_6$ 675.5306, found 675.5317 $[M+H]^+$. Compound 4. ^{1}H NMR (DMSO-d_6, D_2O exchanged): δ 3.75 (8H, m, H-2, H-3, H-4, H-5, H-8, H-9, H-10, H-11), 2.53 (2H, m, H-1a, H-12a), 2.35 (2H, dd, *J* = 7.6, 13.6 Hz, H-1b, H-12b), 2.20 (2H, dd, *J* = 8.2, 12.5 Hz, NCH_2), 2.12 (2H, dd,

J = 6.6, 12.5 Hz, NCH_2), 1.85 – 1.08 (40H, m, cyclohexyl), 0.88 – 0.71 (4H, m, cyclohexyl). ESIMS: *m/z* calcd. for $C_{40}H_{72}N_2O_6$ 677.5463, found 677.5466 $[M+H]^+$.

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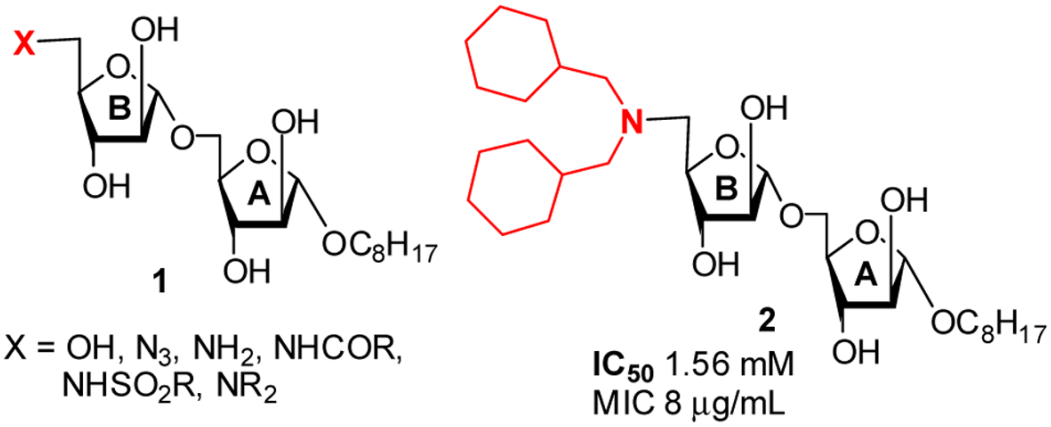


Figure 1.
5′-substituted Araf α(1→5) Araf disaccharides

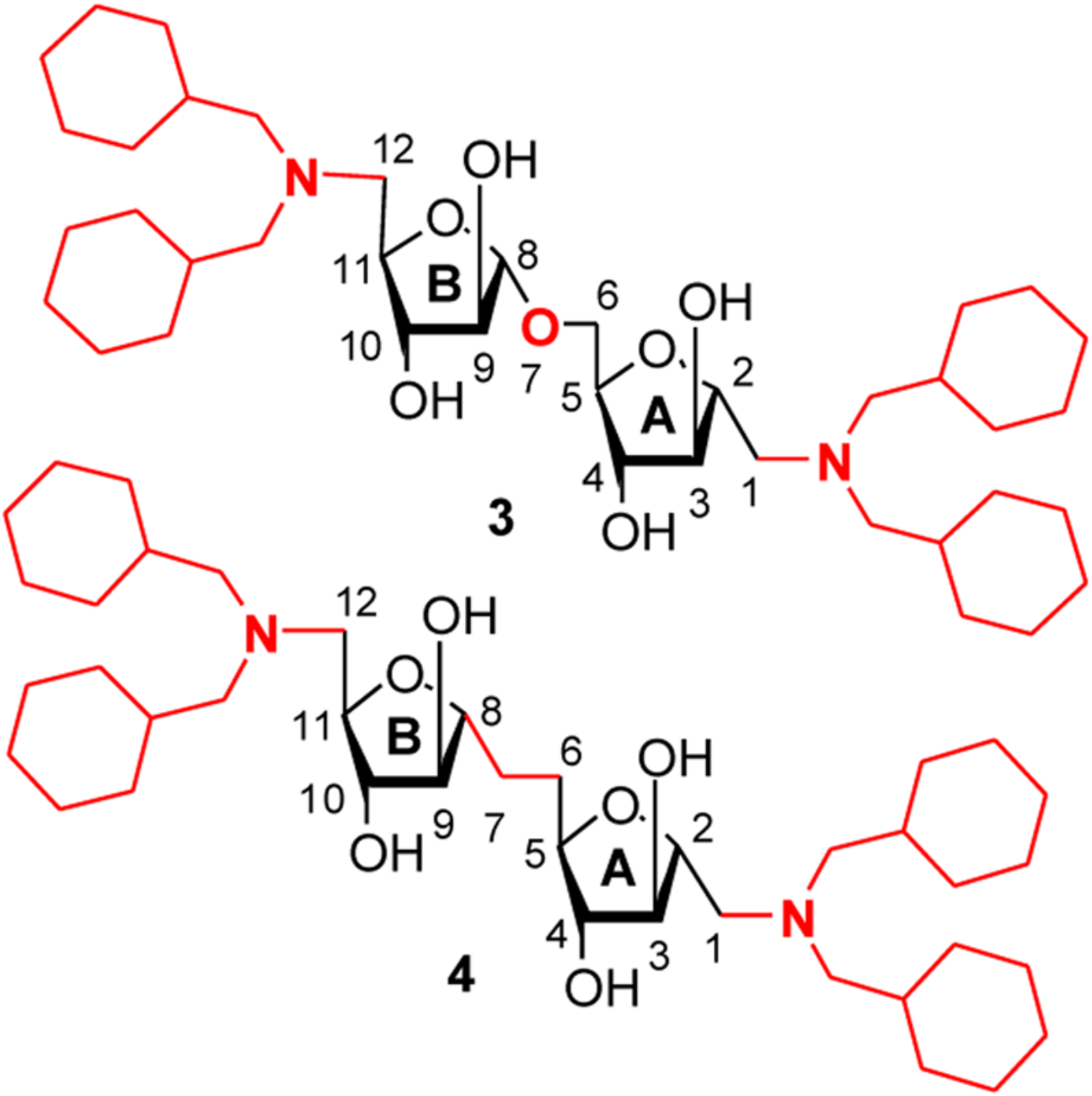
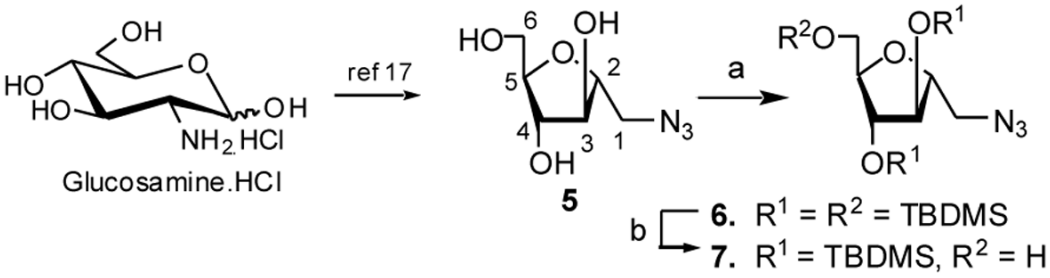
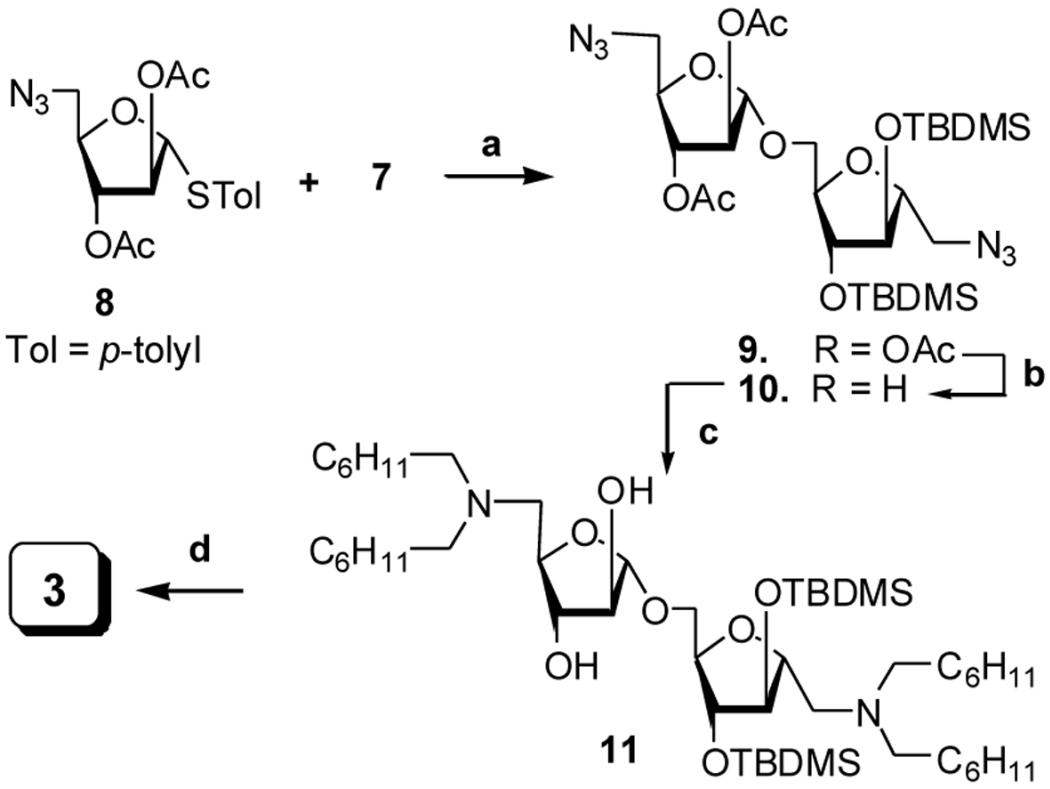


Figure 2.
Target *O*- and *C*-linked Disaccharides

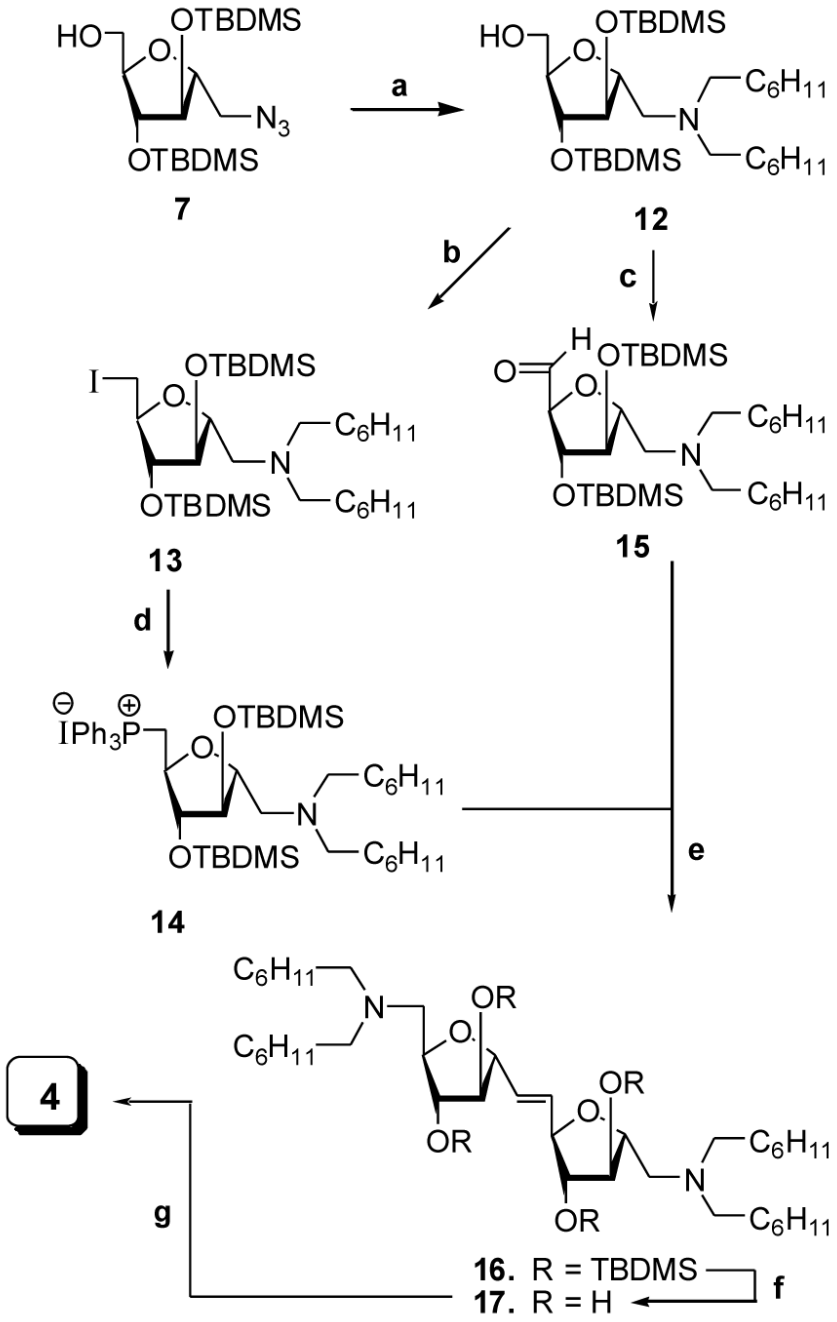


Scheme 1.
(a) TBDMSCl, imidazole, DMF, 50 °C, 18 h; (b) TFA-Water (1:1), THF, −4 °C, 4 h, 85% (in 2 steps).



Scheme 2.

Reagents and conditions. (a) NIS, TfOH, CH_2Cl_2, −20 °C, 15 min; (b) 7N NH_3/MeOH, MeOH, rt, overnight, 85% (in 2 steps); (c) $C_6H_{11}CHO$, 10% Pd/C, MeOH, rt, 4h, 74%; (d) $Et_4N^+F^-$, THF, rt, overnight, 88%.



Scheme 3.

Reagents & Conditions. (a) $C_6H_{11}CHO$, Pd/C, MeOH, rt, 4h, 95%; (b) I_2, imidazole, Ph_3P, toluene, 80 °C, 1 h, 56%; (c) PCC, CH_2Cl_2, rt, 4h, 85%; (d) PPh_3, 120 °C, 4 h, 67%; (e) THF-HMPA, BuLi, −30 °C, 2 h, 55%; (f) $Et_4N^+F^-$, THF, rt, overnight, 86%; (g) $Pd(OH)_2$, H_2, EtOAc-MeOH (1:1), rt, 4h, 62%.