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Stereoselective β-Mannosylation via Anomeric *O*-Alkylation with L-Sugar-Derived Electrophiles

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Abstract

A total synthesis of the trisaccharide repeat unit of *Salmonella* serogroup E1 *O*-antigen is reported. This synthesis features a key β-mannosylation reaction via cesium carbonate-mediated anomeric *O*-alkylation of a partially protected D-mannose with an L-fucose-derived electrophile for the first time.

Introduction

Carbohydrate epitopes expressed on bacterial cell surfaces, e.g. capsular polysaccharides (CPS), may act as antibody recognition components and potential targets for the development of effective therapeutic vaccines against bacterial infections.[1] Due to their scarcity and high heterogeneity, it is difficult to isolate large amounts of pure and structurally well-defined microbial oligosaccharides from natural sources for biological studies. As of now, chemical synthesis remains as a reliable approach to access sufficient quantities and good purity of bacterial carbohydrate molecules. Structurally, microbial glycans often consists of unusual and highly complex monosaccharides as well as challenging glycosidic linkages. Therefore, development of efficient glycosylation methods and strategies is vital to supply these bacterial oligosaccharides for biomedical purposes.

The *O-antigen* repeating unit of *Salmonella* serogroup E1,[2] →6)-β-D-Man-(l→4)-α-L-Rha-(1→3)-α-D-Gal-(l→ (**1**, *cf.* **Figure 1**), is a trisaccharide containing a β-mannosidic linkage[3] that belongs to a family of *Salmonella* serogroups. This trisaccharide has previously been synthesized by the Thorson group using chemoenzymatic methods involving a recombinant β-(1→4)-mannosyltransferase.[4] While enzymatic method was used for construction of the key β-mannosidic linkage, currently it is not amenable to the large-scale synthesis. In addition, Crich and Li reported a chemical synthesis of this trisaccharide later in 2002 using 4,6-*O*-benzylidene protected D-mannosyl thioglycoside donors.[5] As a class of 1,2-*cis*-glycosidic linkages,[6] β-mannosides are difficult to construct due to the steric effect of the axial C2-substituents and the absence of anomeric effect.[7],[8] Recently, our group developed a β-mannosylation method involving Cs_2CO_3-

mediated anomeric *O*-alkylation of partially protected mannoses with suitable electrophiles.[9] Thus far, only D-sugar-derived triflates[10,11] have been studied for anomeric *O*-alkylation of various types of D-mannoses in this β-mannosylation.[9,12] As part of our program to study anomeric *O*-alkylation for stereoselective synthesis of oligosaccharides, we were interested in exploring the use of L-sugar-derived triflates for anomeric *O*-alkylation of D-mannoses and its application in the synthesis of an analogue (**2**, **Figure 1**) of this trisaccharide repeat unit of *Salmonella* serogroup E1.

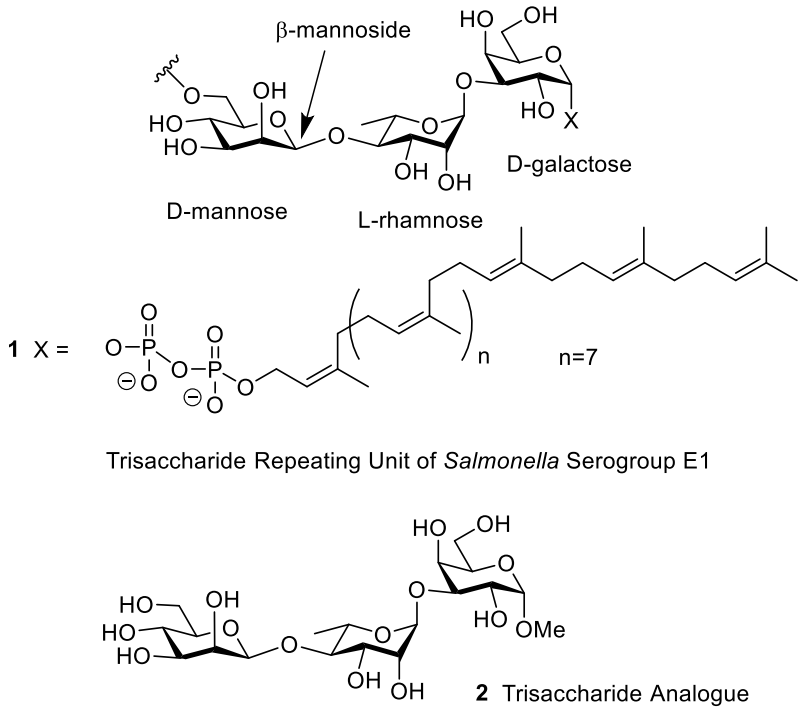
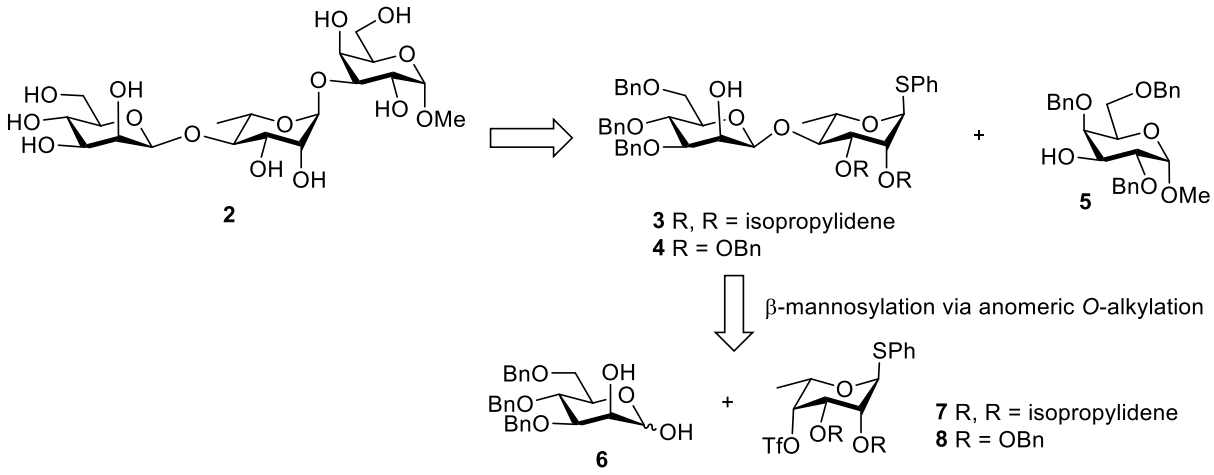


Figure 1. The structure of a trisaccharide repeating unit of *Salmonella* serogroup E1 (**1**) and its analogue (**2**).

Results and Discussion

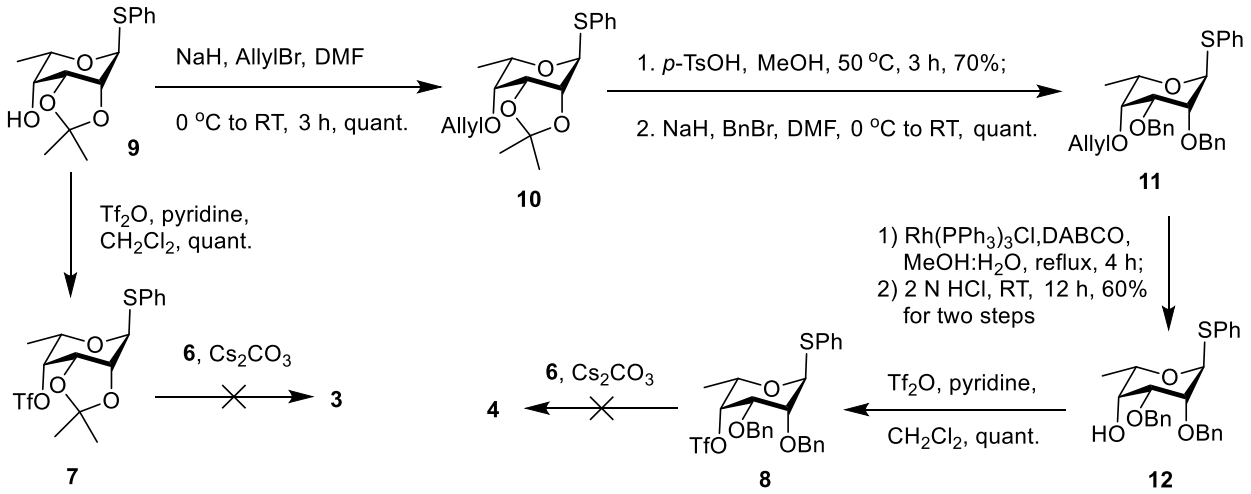
As depicted in **Scheme 1**, in our original plan trisaccharide analogue **2** will be prepared by standard glycosylation of disaccharide thioglycoside donors **3** or **4** with D-galactose-derived acceptor **5**. Disaccharide donors **3** or **4** may be obtained via Cs_2CO_3-mediated β-selective anomeric *O*-alkylation of known partially protected D-mannose **6**[9] with L-sugar-derived triflate **7** or **8**.

Scheme 1. Synthetic strategy for trisaccharide (**2**).



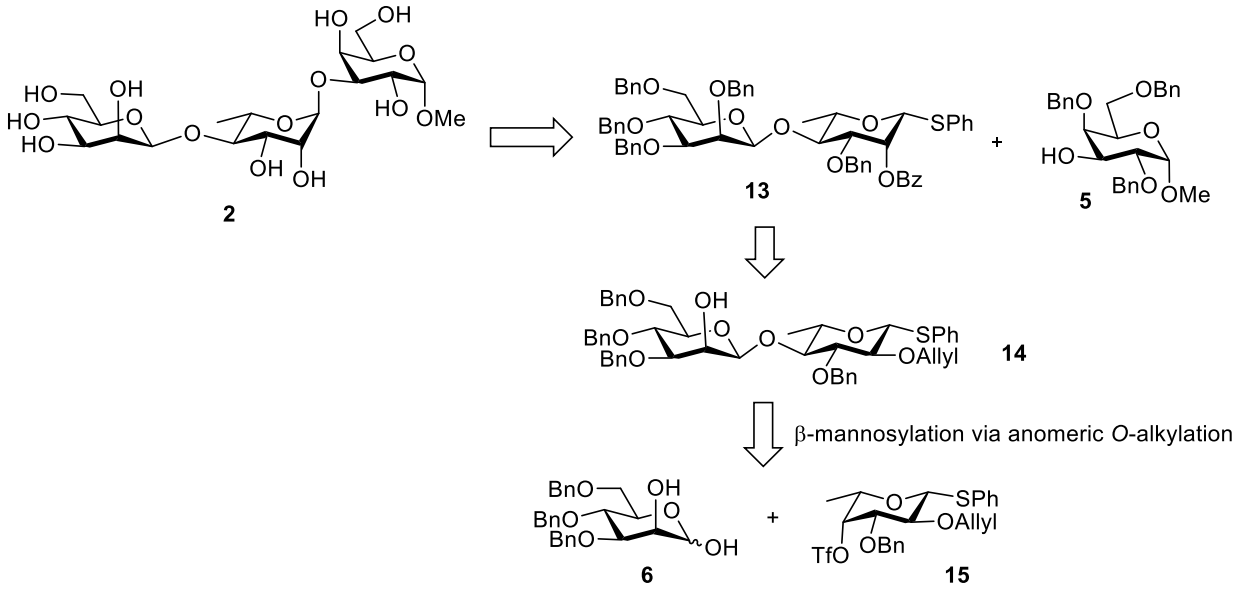
Starting from known 6-deoxy-L-talose-derived thioglycoside **9**,[13] C4-triflate **7** was prepared in quantitative yield via a one-step triflation (**Scheme 2**). Unfortunately, Cs_2CO_3-mediated anomeric *O*-alkylation of partially protected D-mannose **6** with 6-deoxy-L-talose-derived C4-triflate **7** under various conditions did not afford any desired β-linked disaccharide **3**. It was surmised that removal of the isopropylidene moiety may help alleviate the strain of bicyclic **7** and improve its reactivity. Therefore, we turned to synthesize its monocyclic counterpart, triflate **8**. Thus, the C4-alcohol of thioglycoside **9** was protected as its allyl ether **10** which subsequently underwent acetonide cleavage and benzylation of the resulting 2,3-diol to afford fully protected thioglycoside **11**. Next, $Rh(PPh_3)_3Cl$-catalyzed isomerization of the allyl ether to the corresponding propenyl ether followed by acid-mediated hydrolysis furnished **12** in which the liberated C4-alcohol was subsequently converted to its triflate (**8**). Disappointingly, the key Cs_2CO_3-mediated anomeric *O*-alkylation of partially protected D-mannose **6** with 6-deoxy-L-talose-derived C4-triflate **8** under various conditions failed to afford any desired β-linked disaccharide **4**. In both cases, elimination of triflates **7** or **8**was found to be the major problem.[9, 14] Initially, we suspected that the conformation of **7** or **8** containing three axial substituents may not adopt $^1C_4$ conformation due to severe 1,3-diaxial interactions. As a result, triflate **7** or **8** becomes unreactive as the C4-triflate substituent may no longer be axial in the distorted conformation. However, extensively 2D NMR studies did not support our hypothesis. While it is unclear why that happened, it is possible that triflate **7** or **8** may undergo conformation change from $^1C_4$ to $^{1,4}B$ and the sulfur atom attached to the anomeric carbon may intramolecularly attack the C4-triflate to form a cyclic sulfonium intermediate which further decomposes.[15]

Scheme 2. Attempted anomeric *O*-alkylation of D-mannose with 6-deoxy-L-talose-derived C4-triflates **7** and **8**.



Based on these results, our synthetic strategy was revised as shown in **Scheme 3**. Instead of using 6-deoxy-L-talose-derived C4-triflates, we decided to study anomeric *O*-alkylation of D-mannose **6** with an L-fucose-derived C4-triflate **15** as the electrophile in order to prepare disaccharide **14**. Subsequent inversion of C2-stereochemistry of **14** followed by protecting group manipulations should afford disaccharide **13**. A final glycosylation of disaccharide thioglycoside donor **13** with D-galactose-derived acceptor **5** under traditional conditions should furnish trisaccharide **2** after global deprotection.

Scheme 3. Revised synthetic strategy for trisaccharide (**2**).



L-Fucose-derived triflate **15** was readily available in three steps from known L-fucose-derived thioglycoside **16**:[16] 1) treatment of **16** with dibutyltin oxide to form the 3,4-*O*-stannylene acetal; 2) regioselective benzylation to afford its corresponding C3-*O*-benzyl ether **17**; and 3) triflation of the C4-free alcohol (**Scheme 4**). Gratifyingly, under optimal condition the key Cs_2CO_3-mediated anomeric *O*-alkylation of partially protected mannose **6** with an L-fucose-derived C4-triflate **15**

(3.0 eq.) furnished desired β-linked disaccharide **14** in moderate yield (50%, β only). Not surprisingly, elimination of triflates **15** was found to be the major competitive reaction.[9, 14] Extensive studies revealed that this reaction performed at 0.08M concentration produced disaccharide **14** in highest yield and changing other parameters including solvents and temperature did not further improve the yield (**Table 1**). In comparison, it was found that Cs_2CO_3-mediated anomeric *O*-alkylation of mannose **6** with 2.5 eq. of a D-fucose-derived triflate *ent*-**15**, prepared following the same procedure as **15**, furnished desired β-linked disaccharide **18** in 81% (β only, **Scheme 5**). It is worth noting that, under the exactly the same condition, Cs_2CO_3-mediated anomeric *O*-alkylation of mannose **6** with 2.5 eq. of an L-fucose-derived triflate **15** afforded desired β-linked disaccharide **14** in only 35% yield (β only, entry 1, **Table 1**). These results suggested that anomeric *O*-alkylation of D-mannose **6** with L-fucose-derived triflate **15** may be a "mismatched" case, while D-mannose **6** and D-fucose-derived triflate *ent*-**15** are "matched pairs."[9] Next, benzylation of the C2'-alcohol of **14** afforded disaccharide **19** which underwent de-allylation to produce **20** bearing the free equatorial C2-alcohol. Unfortunately, various attempts to epimerize the C2-stereocenter, i.e. isomerization of **20** to **21** bearing an axial C2-alcohol, were unreproducible or unsuccessful. For instance, Swern oxidation of the C2-equatorial alcohol of **20** followed by reduction oftentimes resulted in the epimerization of the C1-stereochemistry, i.e. the β-thioglycoside was isomerized to the α-thioglycoside, while the C2-equatorial alcohol remained unchanged.

Scheme 4. Anomeric *O*-alkylation of D-mannose with L-fucose-derived triflate **15**.

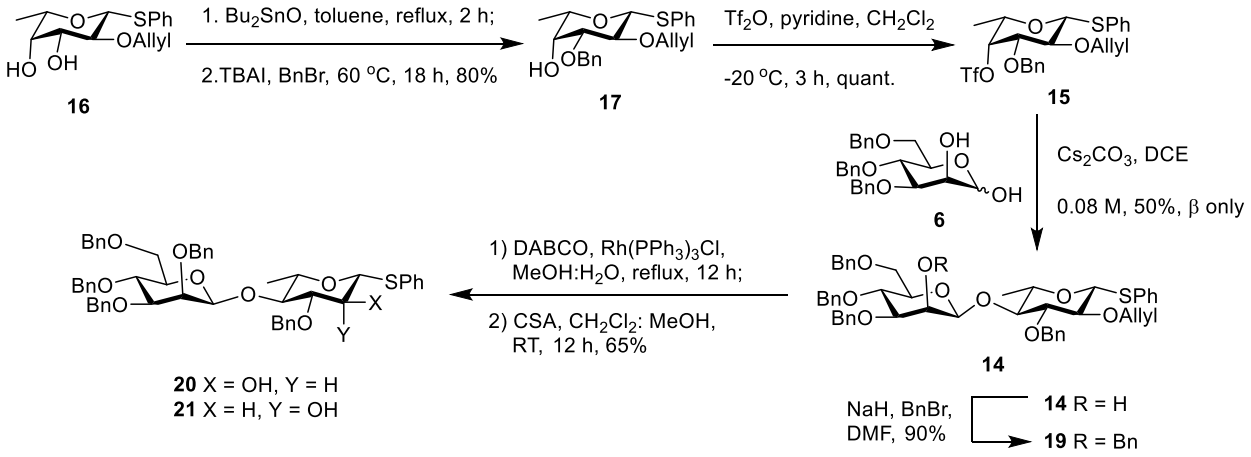
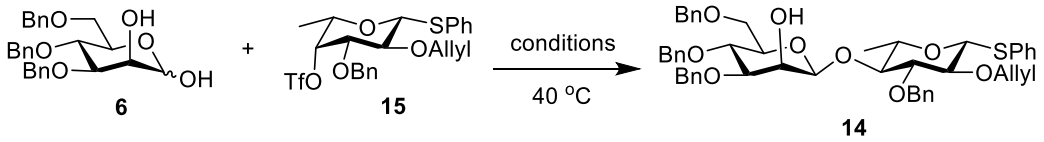


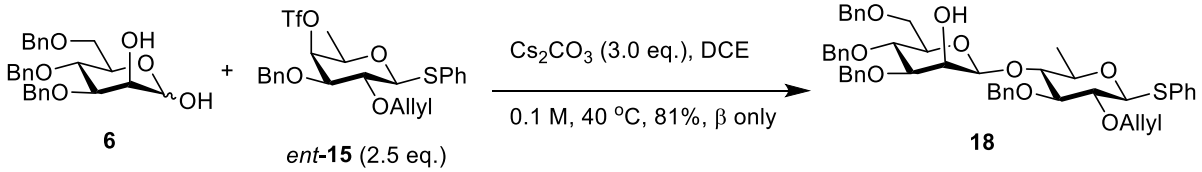
Table 1. Reaction optimization.



Entry	Triflate 15 (eq.)	Cs_2CO_3 (eq.)	Concentration of 6	yield (β only)
1	2.5	3.0	0.1 M	35%

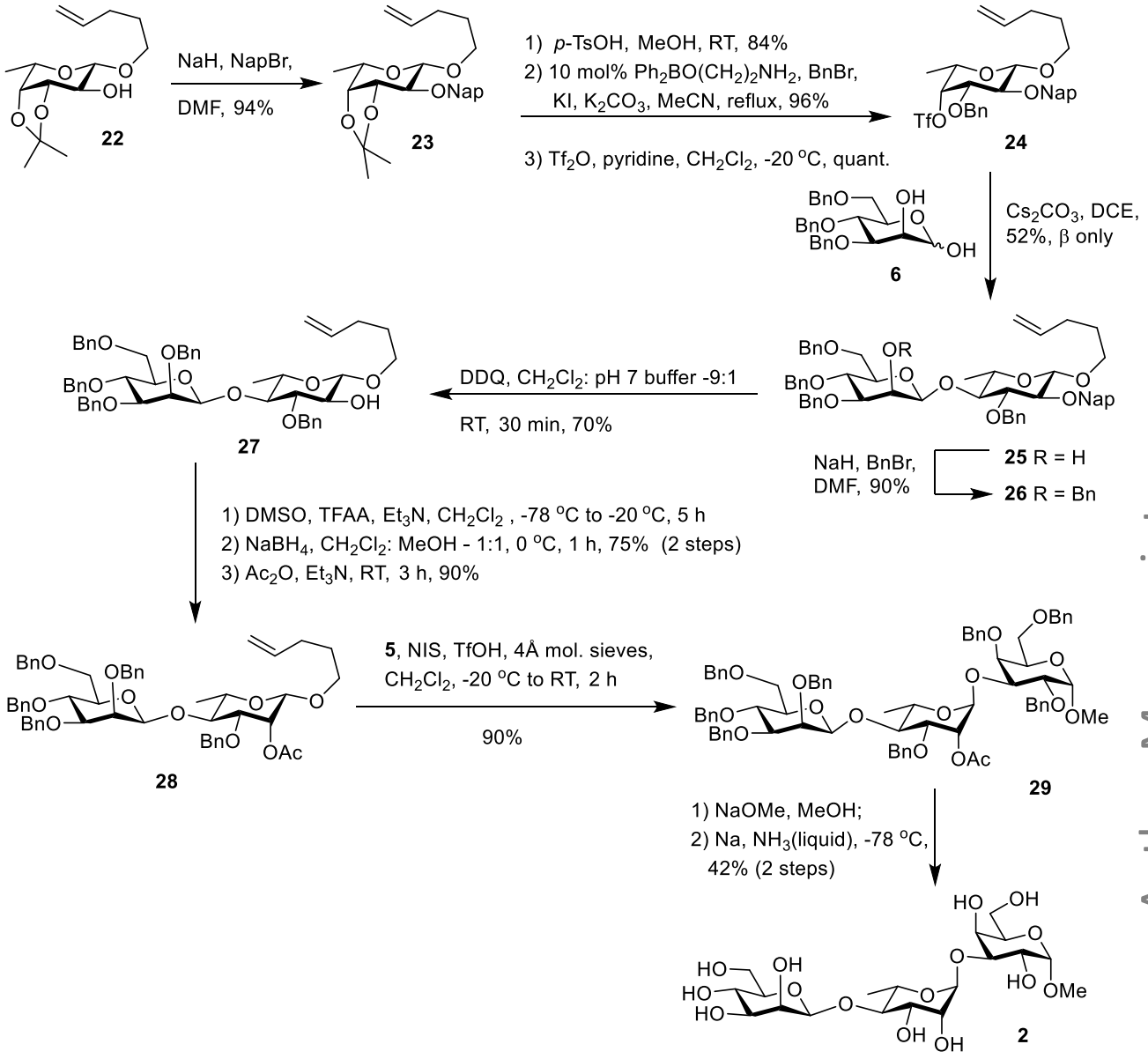
2	3.0	3.5	0.1 M	43%
3	3.0	3.5	0.125 M	31%
4	3.0	3.5	0.08 M	50%
5	3.0	3.5	0.067 M	49%
6	3.0	3.5	0.05 M	24%

Scheme 5. Anomeric *O*-alkylation of D-mannose with D-fucose-derived triflate *ent*-**15**.



It was believed that, after the equatorial C2-alcohol of reducing end thioglycoside **20** was oxidized to the corresponding ketone, the anomeric proton located on the α-carbon became quite acidic. Deprotonation followed by re-protonation led to the epimerization to the more stable α-thioglycoside. Hence, changing the more polarizable sulfur atom to an oxygen atom, e.g. n-pentenyl glycoside, should decrease the acidity and suppress the epimerization. In practice, known partially protected n-pentenyl β-L-fucoside **22** [17] was converted into its corresponding 2-naphthylmethyl (Nap) ether **23** which underwent sequential isopropylidene ring opening, borinic acid-catalyzed[18] regioselective benzylation of the C3-alcohol, and triflation of the free C4-alcohol to furnish triflate **24** (**Scheme 6**). Next, cesium carbonate-mediated anomeric *O*-alkylation of mannose **6** with triflate **24** afforded desired β-linked disaccharide **25** in 52% yield (β only). Benzylation of the C2'-alcohol of the mannoside moiety of **25** produced **26** which upon DDQ-mediated Nap ether cleavage furnished the free C2-alcohol **27**. Swern oxidation of the equatorial C2-alcohol in **27** afforded the corresponding ketone which was subsequently reduced by sodium borohydride to provide the axial alcohol (75% yield over two steps). This axial alcohol was acetylated to form C2-axial acetate **28** which served as the glycosyl donor for 2+1 coupling. Indeed, standard NIS/TfOH-mediated glycosylation of disaccharide donor **28** with D-galactose-derived acceptor **5** afforded desired trisaccharide **29** in 90% yield (α only). After deacetylation of **29**, the resulting intermediate was subjected to Birch reduction for global cleavage of all benzyl ethers. The final target trisaccharide **2** was obtained in 42% yield over two steps after gel purification.

Scheme 6. Synthesis of trisaccharide (**2**).



Conclusions

We have described a total synthesis of the trisaccharide repeat unit of *Salmonella* serogroup E1 *O*-antigen. Key steps include a β-mannosylation reaction via anomeric *O*-alkylation of a partially protected D-mannose with an L-fucose-derived C4-triflate electrophile as well as stereochemical inversion of the equatorial C2-alcohol. Interestingly, while D-mannose and a D-fucose-derived C4-triflate were found to be "match" pairs in this anomeric *O*-alkylation, a corresponding L-fucose-derived triflate was a "mismatch" for D-mannose.

Experimental Section

Methyl 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl-(1→4)-2-*O*-acetyl-3-*O*-benzyl-β-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (29): To a mixture of 4-penten-1-yl 2,3,4,6-tetra-*O*-benzyl-*β*-D-mannopyranosyl-(1 → 4)-2-*O*-acetyl-3-*O*-benzyl-*β*-L-rhamnopyranoside **28** (40 mg, 0.045 mmol), D-galactose derived C-3 alcohol **5** (17 mg, 0.037 mmol), molecular sieves (40 mg) were added in CH_2Cl_2 (0.4 mL) and the reaction mixture was cooled to -20 ℃ and stirred for 10 min. *N*-Iodosuccinimide (NIS) (20 mg, 0.089 mmol) and Triflic acid (TfOH) (0.58 μL, 6.66 µmol added at -20 ℃. After stirring at -20 ℃ for 5 min. the reaction mixture was placed in an ice bath (0 ℃) and stirred for 1 h. Temperature of the reaction mixture was increased to room temperature and stirred for another 1 h. The progress of the reaction was monitored by TLC (Hexanes:EtOAc =2:1) and after the 1 h, it was completed. The reaction mixture was quenched with Et_3N (0.18 eq.) and filtered. The organic layer was washed with saturated $Na_2S_2O_3$ (2×5 mL), water (2×5 mL), brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude residue was purified by preparative thin layer chromatography (Hexanes/EtOAc = 2/1), to afford the compound methyl 2,3,4,6-tetra-*O*-benzyl- *β* -D-mannopyranosyl-(1→4)-2-*O*-acetyl-3-*O*-benzyl-β-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside **29** (42 mg, 0.033 mmol, 90%) as a colorless oil. The *α* configuration of the rhamnosidic linkage in **29** was assigned by measuring the $J_{(C1\text{-}H1)}$ of anomeric carbon of the rhamnose moiety (170.80 Hz). **^{1}H NMR (600 MHz, Chloroform-*d*) δ** 7.40 – 7.23 (m, 32H, Ar-*H*), 7.21 – 7.18 (m, 2H, Ar-*H*), 7.17 – 7.09 (m,5H, Ar-*H*), 7.07 – 7.03 (m, 1H, Ar-*H*), 5.57 (dd, *J* = 3.3, 1.8 Hz, 1H, *H4fuco*), 5.25 (d, *J* = 1.9 Hz, 1H, *H1Gal*), 4.89 (d, *J* = 11.0 Hz, 1H, R-*CH*$_2$-Ph), 4.85 (d, *J* = 10.9 Hz, 1H, R-*CH*$_2$-Ph), 4.76 (t, *J* = 12.3 Hz, 2H, R-*CH*$_2$-Ph), 4.70 – 4.66 (m, 2H, H1mann, R-*CH*$_2$-Ph), 4.65 – 4.61 (m, 3H, R-*CH*$_2$-Ph), 4.58 (d, *J* = 4.2 Hz, 1H, *H1fuco*), 4.55 (d, *J* = 3.2 Hz, 1H, R-*CH*$_2$-Ph), 4.53 (d, *J* = 5.3 Hz, 1H, R-*CH*$_2$-Ph), 4.50 (d, *J* = 6.3 Hz, 1H, R-*CH*$_2$-Ph), 4.43 (d, *J* = 11.9 Hz, 1H, R-*CH*$_2$-Ph), 4.31 – 4.23 (m, 2H, *H6Gal*, R-*CH*$_2$-Ph), 4.19 (dd, *J* = 10.1, 3.0 Hz, 1H, R-*CH*$_2$-Ph), 4.07 (d, *J* = 10.9 Hz, 1H, *H2mann*), 4.03 (dd, *J* = 10.1, 3.5 Hz, 1H, *H3Gal*), 3.97 (t, *J* = 6.6 Hz, 1H, R-*CH*$_2$-Ph), 3.91 (dd, *J* = 9.5, 6.2 Hz, 1H, *H5Fuco*), 3.88 – 3.86 (m, 1H, *H5Gal*), 3.83 (t, *J* = 9.5 Hz, 1H, *H5mann*), 3.78 (d, *J* = 3.4 Hz, 1H, *H3fuco*), 3.76 (d, *J* = 3.7 Hz, 2H, *H4mann*, R-*CH*$_2$-Ph), 3.65 (d, *J* = 3.0 Hz, 1H, *H6Gal*), 3.62 (t, *J* = 9.5 Hz, 1H, *H6Gal*), 3.55 – 3.49 (m, 2H, *H2Gal*, *H3mann*), 3.39 (s, 1H, *H2fuco*), 3.35 (s, 3H, R-*OMe*), 3.26 (dd, *J* = 9.5, 2.9 Hz, 1H, *H4Gal*), 2.11 (s, 3H, R-*OAc*), 1.46 (d, *J* = 6.2 Hz, 3H, *H6fuco*). **^{13}C NMR (151 MHz, Chloroform-*d*) δ** 170.15, 138.92, 138.64, 138.49, 138.43, 138.30, 138.03, 137.86, 137.80, 128.48, 128.44, 128.33, 128.31, 128.03, 127.99, 127.97, 127.94, 127.88, 127.85, 127.83, 127.71, 127.59, 127.53, 127.43, 127.26, 102.74, 99.27, 98.07, 82.65, 79.14, 78.15, 77.55, 75.80, 75.37, 75.18, 75.05, 74.64, 74.15, 73.78, 73.59, 73.56, 72.92, 71.62, 71.43, 69.79, 69.18, 68.71, 68.50, 68.21, 55.41, 21.11, 18.19. $[\alpha]_D^{22}$ = +23.1° (c=1.0, $CHCl_3$). **ESIHRMS:** Calculated for $[C_{77}H_{84}O_{16}Na]^+$ 1287.5759, found 1287.5735.

Methyl *β*-D-mannopyranosyl-(1→4)-β-L-rhamnopyranosyl-(1→ 3)-α-D-galactopyranoside (2): To a solution of trisaccharide **29** (24 mg, 0.023 mmol) in 0.25 mL of methanol:THF (1/1, v/v) was added NaOMe (4 µL, 0.023 mmol). The resulting mixture was heated at 50 ℃ for 3 h before the solvent was removed under reduced pressure. The residue was dried under high vacuum. A 100 mL three-necked round-bottom flask containing a glass stir bar was equipped with a "U" shape condenser (for cooling ammonia gas) and cooled at −78 °C under argon. After acetone and dry ice were added into the "U" shape condenser, liquid ammonia (∼5 mL) was collected in the three-necked flask. A piece of sodium metal (10 mg, 0.34 mmol) was added to the flask and stirred for 15 min. Extra sodium was added until the solution remained dark blue in color. A solution of

above-mentioned residue (deacetylated trisaccharide) (24 mg, 0.02 mmol) in 1 mL of THF was added and the resulting mixture was stirred at −78 °C for 30 min before being quenched with solid NH_4Cl. The reaction mixture was slowly warmed to room temperature, and liquid ammonia and THF were removed by air flow. The residue was desalted using size-exclusion chromatography (Bio-Gel P-2 Media, eluted with water) to furnish 5 mg (0.008 mmol, 42%) of desired compound. **^{1}H NMR (600 MHz, Deuterium Oxide) δ** 4.88 (d, *J* = 2.4 Hz, 1H), 4.78 – 4.74 (m, 1H), 3.97 – 3.92 (m, 3H), 3.86 (ddd, *J* = 9.5, 3.4, 2.1 Hz, 1H), 3.82 (dq, *J* = 9.1, 2.4 Hz, 3H), 3.78 – 3.73 (m, 2H), 3.61 (dddd, *J* = 26.2, 19.1, 8.2, 3.0 Hz, 5H), 3.55 – 3.51 (m, 1H), 3.46 (td, *J* = 9.7, 2.1 Hz, 1H), 3.31 (s, 3H), 3.27 – 3.23 (m, 1H), 1.22 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (151 MHz, Deuterium Oxide) δ** 102.27, 100.60, 99.30, 79.46, 77.62, 76.16, 72.98, 70.74, 70.54, 70.30, 70.12, 69.00, 67.84, 67.37, 66.73, 61.08, 60.95, 54.97, 36.87, 31.33, 16.89. **ESILRMS:** $[M-H]^-$ Calculated for $[C_{19}H_{33}O_{15}]^-$ 501.19; found 501.18.

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Keywords: Anomeric *O*-Alkylation • Carbohydrates • Glycosylation • *β*-Mannosylation • Microbial Glycans

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