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Gram-Scale Synthesis of an Armed Colitose Thioglycoside

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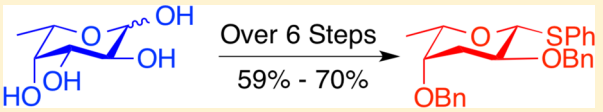
Supporting Information

ABSTRACT: A concise gram-scale synthesis of protected colitose thioglycosides for use in bacterial carbohydrate antigen synthesis is described. The synthesis proceeds in six steps and 59−70% overall yield from commercially available L-fucose, making it the most efficient route reported to date. Key steps include regioselective installation of a thiocarbonate using catalytic dioctyltin dichloride (10 mol%) and a tris(trimethylsilyl)silane-mediated radical deoxygenation.



The unique carbohydrate structures found on many pathogenic bacteria has led to increased interest in developing carbohydrate-based antimicrobial vaccines.[1,2] Such vaccine approaches are viewed as particularly attractive because many bacterial polysaccharides not only possess glycosidic linkages that are not found in mammalian systems but also contain unusual monosaccharides, such as deoxy sugars, that are not found in eukaryotic species.[3] This leads to a challenge in vaccine development, however, as many of these sugars are not readily available and must be constructed through multistep synthesis. An example of such a sugar is the 3,6-dideoxyhexose colitose, which is found in a number of pathogens, including *Escherichia coli*, *Salmonella adelaide*, *Salmonella greenside*, *Yersinia pseudotuberculosis*, and *Vibrio cholera*.[3−7] As part of a program directed at applying our recently developed reagent controlled 1,2-*cis*-α-selective thioglycoside activation to the construction of the *E. coli* O111 antigen minimum repeat unit,[8] we had need of a large quantity of protected colitose thioglycoside **1**. Approaches to various colitose-based glycosyl donors had been reported in the past; however, they all suffer from low overall yields, lengthy synthetic routes, and/or the requirement of stoichiometric amounts of toxic reagents.[6,9−15] Here we report a short and highly efficient approach to protected colitose thioglycosides from commercially available L-fucose **2**.

Retrosynthetically, we envisioned that **1** would arise from fucose derivative **3**, which possesses a handle for radical deoxygenation (Scheme 1). While the use of stoichiometric tributyltin hydride-mediated deoxygenation has been reported in the past, we were interested in avoiding such toxic reagents.[6,10,12,13] Accordingly, we envisioned that this transformation could be achieved using the tris(trimethylsilyl)silane-mediated radical deoxygenation reported by Nishiyama.[16,17] Returning to the retrosynthesis, **3** was envisioned to arise from thioglycoside **4** through Muramatsu's catalytic tin-mediated regioselective installation of the thiocarbonate.[18] Finally, compound **4** could arise from fucose **1** using straightforward chemistry.

In the synthetic direction, **2** was peracetylated using acetic anhydride in pyridine to afford tetraacetate **5** (Scheme 2). A mixture of this compound and thiophenol in dichloromethane was subjected to slow addition of $BF_3{\cdot}Et_2O$ to afford thioglycoside **6**[19] in excellent yield and selectivity (98%, two steps from **2**, 12:1 β:α). Finally, deacetylation under Zemplén conditions[20] afforded **4**, which would be used for regioselective installation of the deoxygenation handle, in near-quantitative yield.

With **4** in hand, we next explored its transformation to the corresponding C-3 thiocarbonate **3**, (Table 1). To this end, we chose to examine regioselective thiocarbonylation of C-3 using dioctyltin chloride as described by Muramatsu.[17,18] Importantly, the Muramatsu conditions[18] are catalytic in tin, which provides a distinct advantage over previously reported approaches that required the use of stoichiometric tin reagents.[6,10−13] In order to assess the most efficient method for obtaining the desired target structure, we chose to examine three different thiocarbonylating agents: *O*-phenyl chlorothionoformate, 1,1′-thiocarbonyldiimidazole (TCDI), and phenyl isothiocyanate (PITC) (Table 1). Under these conditions, we found that *O*-phenyl chlorothionoformate was superior to both PITC and TDCI, providing the product **3b** in good yield and regioselectivity on both small (Table 1, entry 2) and gram scale (Table 1, entry 3). Due to the ease of preparation of **3b** on gram scale, this compound was carried on to the critical deoxygenation step.

In the deoxygenation step, we chose to first examine the use of tris(trimethylsilyl)silane (TTMSS) as a nontoxic alternative to the use of stoichiometric toxic trialkylstannane derivatives.[16,17,21−24] This reagent proved to be effective with **3b** (Table 2, entry 1), providing the product in excellent yield. Notably, TTMSS-mediated deoxygenation provided the desired product in much higher yield than tributyltin hydride (Table 2, entry 2). Based on these results, we next examined the ability of TTMSS to deoxygenate **3b** on gram scale. Pleasingly, increasing the scale of the reaction did not have a significant impact on the efficiency of the reaction and we were able to obtain thioglycoside **7** in 90% yield (Table 1, entry 3).

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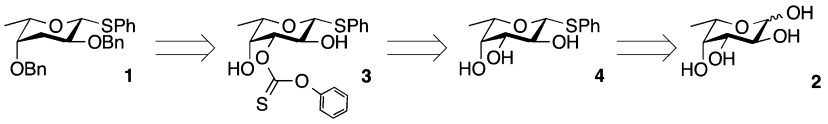
Scheme 1. Retrosynthesis of Colitose Thioglycoside



Scheme 2. Synthesis of Fucose Thioglycoside 4

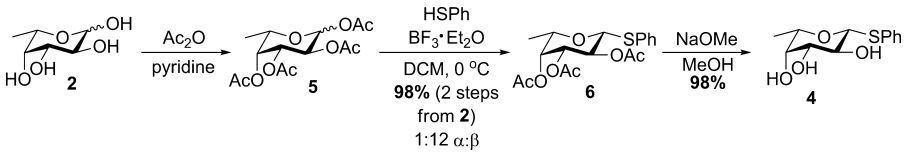
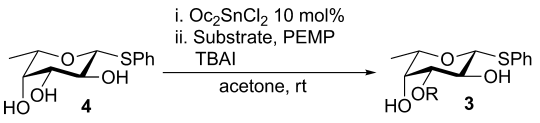
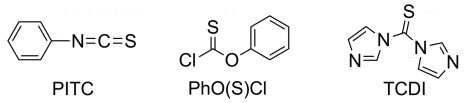


Table 1. Thiocarbonylation Reactions[a]



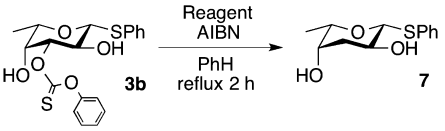
3a R = C(S)NPh
3b R = C(S)OPh
3c R = C(S)Im

entry	substrate	product	time	yield (%)
1	PITC	**3a**	57.5 h	43
2	PhO(S)Cl	**3b**	3 h	90
3[b]	PhO(S)Cl	**3b**	6 h	83
4	TCDI	**3c**	--	decomp



[a]Reactions conditions: **4** (0.39 mmol), Oc_2SnCl_2 (0.039 mmol), substrate (0.5 mmol), PEMP (0.58 mmol), and TBAI (0.039 mmol) in acetone (8 mL) at 25 °C. PEMP = 1,2,2,6,6-pentamethylpiperidine; Oc_2SnCl_2 = dioctyltin dichloride; TBAI = tetrabutylammonium iodide; PITC = phenyl isothiocyanate; PhO(S)Cl = *O*-phenyl chlorothionoformate; TCDI = 1,1′-thiocarbonyldiimidazole. [b]1 g scale reaction in acetone (80 mL).

Table 2. Barton–McCombie Deoxygenation Reaction Comparison of Tris(trimethylsilyl)silane and Tributyltin Hydride[a]

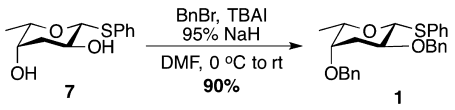


entry	substrate	reagent	yield (%)
1	**3b**	TTMSS	98
2	**3b**	Bu_3SnH	84
3[b]	**3b**	TTMSS	90

[a]Reactions conditions: TTMSS or Bu_3SnH (2 equiv), AIBN (20 mol %), refluxed at 80 °C in benzene (5 mL) for 2 h. [b]1 g scale reaction in benzene (100 mL). AIBN = 2,2′-azobis(2-methylpropionitrile); TTMSS = tris(trimethylsilyl)silane Bu_3SnH = tributyltin hydride

With the dideoxy thioglycoside **7** in hand, we next completed the synthesis of **1**. To this end, benzylation of **7** with benzyl bromide in the presence of tetrabutylammonium iodide (TBAI) afforded **1** in 90% yield (Scheme 3). Depending on the scale, the overall synthesis proceeded in 59 to 70% yield from commercially available L-fucose.

Scheme 3. Synthesis of Armed Colitose Thioglycoside 1



In summary, we have developed a highly selective and efficient route to armed colitose thioglycoside **1**. Starting from L-fucose, the synthesis was completed on gram scale in six steps and 59% overall yield. This represents the most concise route to a colitose donor reported to date. Based on its efficiency, we anticipate that this approach will be extremely valuable for the construction of bacterial O-antigens, and find broad application in the construction of antimicrobial vaccines.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed under inert argon atmosphere, unless otherwise noted. Flash column chromatography was performed on P-60 silica gel, 230–400 mesh. Analytical and preparative thin-layer chromatography was carried out on silica gel 60 F-254 plates. Products were visualized using UV or by staining with 5% aqueous sulfuric acid or ceric ammonium molybdate. NMR spectra were acquired at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR. Chemical shifts are reported in ppm relative to TMS (for ^{1}H NMR in $CDCl_3$) or $CDCl_3$ (for ^{13}C NMR in $CDCl_3$). For ^{1}H NMR spectra, data are reported as follows: δ shift, multiplicity (s = singlet, m = multiplet, t = triplet, d = doublet, dd = doublet of doublets, td = triplet of doublets, q = quartet, brs = broad singlet), coupling constants are reported in Hz. Proton assignments were made using ^{1}H–^{1}H homonuclear correlation spectroscopy (COSY) at 500 MHz. Low-resolution mass spectra (LRMS) were recorded using ESI-MS. High-resolution mass spectra (HRMS) were obtained on a Fourier transform ion cyclotron resonance mass spectrometer. Optical rotations were measured at 589 nm in a 5 cm cell at 24 °C.

Materials. Solvents for reactions were dried immediately prior to use. All other chemicals were purchased at the highest possible quality and used as received. Compounds **4**–**6** were prepared according to literature methods.[19,20]

Phenyl 3-*O*-(*N*-Phenylthiocarbamoyl)-1-thiol-β-L-fucopyranoside (3a). In a foil-covered flask phenyl 1-thio β-L-fucopyranoside (**4**) (100 mg, 0.39 mmol) and dioctyltin dichloride (16 mg, 0.039 mmol) were suspended in dry acetone (8 mL), and stirred for 10 min. To this suspension were added tetrabutylammonium iodide (14 mg, 0.039 mmol), phenyl isothiocyanate (0.05 mL, 0.5 mmol), and 1,2,2,6,6-pentamethylpiperidine (0.06 mL, 0.5 mmol). The reaction was stirred for 57.5 h, at which point it was quenched with saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude product was purified with column chromatography (25% ethyl acetate in hexanes) to give **3a** (65 mg, 43%): $[\alpha]^{24}_D$ = −0.075° (*c* 1.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.79 (brs, 1H), 8.58 (brs, 1H), 7.55–7.53 (m,

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3H), 7.34−7.26 (m, 6H), 7.17 (brs, 1H), 5.63 (dd, J = 6.5, 3, 1H, H3), 4.65 (d, J = 9.5, 1H, H1), 4.12 (m, 1H, H4), 3.98 (brs, 1H, H2), 3.79 (q, J = 6, 1H, H5), 2.97 (brs, 1H), 1.33 (d, J = 5, 3H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 187.3, 137.4, 132.5, 129.1, 128.9, 128.2, 126.2, 123.7, 121.9, 89.3, 84.6, 81.3, 74.6, 70.4, 70.0, 67.7, 16.6; LRMS (ESI, pos. ion) m/z calcd for $C_{19}H_{21}NO_4S_2$ (M + Na) 414.08, found 414.18; HRMS (ESI, pos ion) m/z calcd for $C_{19}H_{21}NO_4S_2$ (M + Na) 414.0810, found 414.0811.

Phenyl 3-*O*-Phenoxythiocarbonyl-1-thiol-β-L-fucopyranoside (3b). In a foil-covered flask, phenyl 1-thio β-L-fucopyranoside (**4**) (100 mg, 0.39 mmol) and dioctyltin dichloride (16 mg, 0.039 mmol) were suspended in dry acetone (8 mL) at 25 °C for 10 min. Then, reaction was treated with tetrabutylammonium iodide (14 mg, 0.039 mmol), *O*-phenyl chlorothionoformate (0.07 mL, 0.5 mmol), and 1,2,2,6,6-pentamethylpiperidine (0.06 mL, 0.5 mmol). After 3 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted three times with ethyl acetate. The organic layer was washed with water and brine, dried over Na_2SO_4, filtrated, and concentrated in vacuo. The crude sample was purified by column chromatography on silica gel (20% ethyl acetate in hexanes) to give **3** (138 mg, 90%).

Phenyl 3-*O*-Phenoxythiocarbonyl-1-thiol-β-L-fucopyranoside 3b (1 g scale). The title compound was prepared according to the above procedure using phenyl 1-thio β-L-fucopyranoside (**4**) (1.0 g, 3.9 mmol), dioctyltin dichloride (162 mg, 0.39 mmol), tetrabutylammonium iodide (144 mg, 0.39 mmol), *O*-phenyl chlorothionoformate (0.7 mL, 5 mmol), 1,2,2,6,6-pentamethylpiperidine (0.6 mL, 5 mmol), and acetone (80 mL). After 6 h, the crude product was purified with column chromatography (20% ethyl acetate in hexanes) to give **3b** (1.25 g, 83%): $[\alpha]^{24}_D$ = +0.033° (c 1.06, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (m, 2H), 7.43−7.28 (m, 6H), 7.13 (d, J = 7.5 Hz, 2H), 5.39 (d, J = 9.5 Hz, 1H, H1), 4.62 (d, J = 10 Hz, 1H, H3), 4.20 (s, 1H, H2), 4.00 (t, J = 9.7 Hz, 1H, H4), 3.82 (q, J = 6.5 Hz, 1H, H5), 2.56 (brs, 1H), 1.96 (brs, 1H), 1.39 (d, J = 6.5 Hz, 3H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.4, 153.3, 133.1, 133.1, 131.4, 129.6, 129.2, 128.5, 126.8, 121.9, 88.7, 86.0, 74.7, 69.2, 67.0, 16.6; LRMS (ESI, pos ion) m/z calcd for $C_{19}H_{20}O_5S_2$ (M + Na) 414.06, found 415.18; HRMS (ESI, pos ion) m/z calcd for $C_{19}H_{20}O_5S_2$ (M + NH_4) 410.1096, found 410.1072.

General Procedure for the Synthesis of Phenyl 3,6-Dideoxy-1-thio-β-L-*xylo*-hexopyranoside (7). Thiocarbonylate **3** (0.25 mmol), tris(trimethylsilyl)silane (TTMSS) (method A) or tributyltin hydride (Bu_3SnH) (method B) (2 equiv), and 2,2′-azobis(isobutyronitrile) (20 mol %) were refluxed at 82 °C for 2 h in benzene (5 mL). When the reaction was complete according to TLC, it was concentrated in vacuo. The crude sample was purified by column chromatography on silica gel (40% ethyl acetate in hexanes followed by 70% ethyl acetate in hexanes) to afford pure 1-phenyl 3,6-dideoxy-1-thio-β-L-*xylo*-hexopyranoside **7**.

Method A. The title compound was prepared according to the general procedure using tris(trimethylsilyl)silane (0.07 mL, 0.25 mmol), phenyl 3-*O*-phenoxythiocarbonyl-1-thio-β-L-fucopyranoside **3b** (47 mg, 0.12 mmol) and 2,2′-azobis(isobutyronitrile) (4 mg, 0.02 mmol), and benzene (5 mL) were used. The product was obtained as a white powder **7** (27 mg, 98%): $[\alpha]^{24}_D$ = +0.438° (c 1.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56 (dd, J = 2.5, 2 Hz, 2H), 7.35−7.30 (m, 3H), 4.52 (d, J = 10 Hz, 1H, H1), 3.79−3.69 (m, 3H, H2, H4, H5), 2.45−2.39 (m, 2H, H3), 1.78 (d, J = 8 Hz, 1H), 1.65 (td, J = 8.5, 3 Hz, 2H, H3), 1.30 (d, J = 6.5 Hz, 3H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.6, 132.5, 129.1, 128,1, 92.1, 77.2, 69.3, 64.2, 39.0, 17.0; LRMS (ESI, pos ion) m/z calcd for $C_{12}H_{16}O_3S$ (M + Na) 263.07, found 263.09; HRMS (ESI, pos ion) m/z calcd for $C_{12}H_{16}O_3S$ (M + NH_4) 258.1164, found 258.1139.

Method A (Gram Scale). According to the general procedure, tris(trimethylsilyl)silane (1.5 mL, 5 mmol), phenyl 3-*O*-phenoxythiocarbonyl-1-thio-β-L-fucopyranoside **3b** (1 g, 2.5 mmol), 2,2′- azobis(isobutyronitrile) (82 mg, 0.5 mmol), and benzene (100 mL) were used. The product was obtained as a white powder **7** (550 mg, 90%).

Method B. According to the general procedure, tributyltin hydride (0.06 mL, 0.24 mmol), phenyl 3-*O*-phenoxythiocarbonyl-1-thio-β-L-fucopyranoside **3b** (47 mg, 0.12 mmol), 2,2′- azobis(isobutyronitrile) (4 mg, 0.02 mmol), and benzene (5 mL) were used. The product was obtained as a white powder **7** (24 mg, 82%).

1-Phenyl 2,4-Di-*O*-benzyl-3,6-dideoxy-1-thio-β-L-*xylo*-hexopyranoside (1). Sodium hydride (95%, 460 mg, 18 mmol) and tetrabutylammonium iodide (10 mg, 0.04 mmol) were suspended in DMF (15 mL). The suspension was cooled to 0 °C and treated with a solution of **7** (1 g, 4.1 mmol) in DMF (2 mL), while additional DMF (20 mL) was simultaneously added. After the mixture was stirred for 10 min at 0 °C, benzyl bromide (2.1 mL, 18 mmol) was added dropwise to the mixture and the reaction was then allowed to warm to room temperature. After being stirred for 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted three times with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$, water, and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexanes) to give 1-phenyl 2,4-di-*O*-benzyl-3,6-dideoxy-1-thio-β-L-*xylo*-hexopyranoside **1** (1.5 g, 90%): $[\alpha]^{24}_D$ = +0.283° (c 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58 (d, J = 6.5 Hz, 2H), 7.31−7.23 (m, 14H), 4.68 (t, J = 14 Hz, 2H, H1, OCH_2), 4.49 (t, J = 14 Hz, 2H, OCH_2), 4.37 (d, J = 12 Hz, 1H, OCH_2), 3.69 (t, J = 10 Hz, 1H, H2), 3.61 (brs, 1H, H5), 3.40 (s, 1H, H4), 2.42 (d, J = 12 Hz, 1H, H3), 1.49 (t, J = 12.5 Hz, 1H, H3), 1.27 (d, J = 5 Hz, 3H, H6); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.6, 138.3, 134.7, 131.7, 128.8, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.0, 89.4, 76.7, 75.2, 72.7, 71.6, 71.2, 34.5, 17.2; LRMS (ESI, pos ion) m/z calcd for $C_{26}H_{28}O_3S$ (M + Na) 443.21, found 443.27; HRMS (ESI, pos ion) m/z calcd for $C_{26}H_{28}O_3S$ (M + NH_4) 438.2103, found 438.2075.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for **1**, **3a**, **3b**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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