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Effective Application of Heavy Fluorous Thioglycoside for Oligosaccharide Synthesis

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A novel heavy fluorous thioglycoside **6** was developed and applied to oligosaccharide synthesis. The fluorous thioglycoside **6** was readily prepared via the corresponding fluorous thiol. Synthesis of the LacdiNPhth derivative was briefly achieved with a single-column chromatographic purification by using a heavy fluorous tag method. Additionally, the fluorous tag was recovered as fluorous alcohol **1** in high yield.

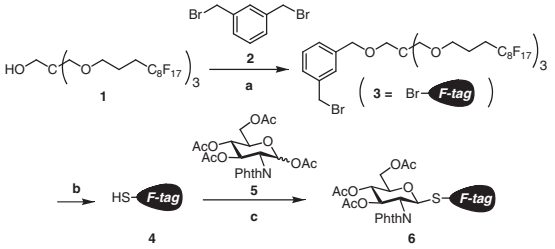
The use of fluorous techniques[1] has spread across various fields,[2] including those of synthetic, catalytic, and analytical chemistry. In synthetic chemistry, Curran et al. described the "fluorous tag method"[1b] in 1997 as a novel strategy that does not inevitably resort to chromatography. Currently this nonchromatographic purification system consists of two methodologies. One, the "heavy" fluorous tag method, is employed in fluorous–organic partitioning, and the other, the "light" fluorous tag method, is used in fluorous solid-phase extraction. Both the heavy and light method can achieve easy separation of the fluorous compounds from general nonfluorous compounds. We have also used heavy fluorous tags to synthesize oligosaccharides and peptides by using various fluorous tags that have included polyamide[3] or polyether[4] bonds within their structures.

Thioglycosides[5] are among the most useful derivatives of oligosaccharide synthesis. The principal features of the general thioglycosides are high stability against various reaction conditions and high reactivity under specific glycosylation conditions. In addition, unlike other glycosyl donors such as glycosyl halide and imidate, because of its stability thioglycoside can be exploited not only as a glycosyl donor but also as a glycosyl acceptor. Although a light fluorous thioglycoside has been reported,[6] application of this fluorous thioglycoside is confined to its use as only a glycosyl donor. Here, we describe oligosaccharide synthesis by using heavy fluorous thioglycoside as not only a glycosyl donor but also a glycosyl acceptor.

First, we designed and synthesized thioglycoside **6** (Scheme 1). A fluorous alcohol **1**[4d] having three fluorous chains was coupled with α,α-dibromoxylene[7] (**2**) as a suitable linker to give a fluorous benzyl bromide **3**, which was subsequently treated with thiourea to yield fluorous thiol **4**. Finally, the thiol **4** and a glucosamine derivative **5**[7] was reacted to give the desired fluorous thioglycoside **6**[8] in the presence of $BF_3 \cdot OEt_2$, with 82% yield.

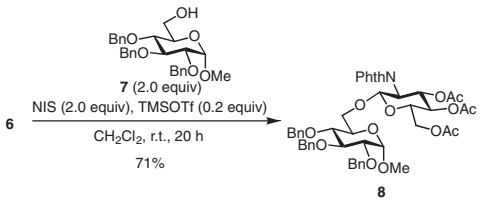
Next, we examined the function of this fluorous thioglycoside **6** as a glycosyl donor. The coupling reaction between **6** and **7**[7] in the presence of *N*-iodosuccinimide (NIS)/trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter system[9] gave a good yield of disaccharide **8** (Scheme 2).

Finally, in order to investigate other functions of this heavy fluorous thioglycoside, such as its stability under various reaction conditions and its potential as a glycosyl acceptor, we attempted the synthesis of disaccharide **15**, including



Reagent and conditions: (a) NaH, 15-Crown-5, $PhCF_3$, 10 °C, 24 h, 83%; (b) $SC(NH_2)_2$, EtOH, reflux, 4 h, then NaOH(aq), reflux, 2 h; (c) $BF_3 \cdot OEt_2$, $PhCF_3$, r.t., 18 h, 82% from **3**.

Scheme 1. Preparation of fluorous thioglycoside **6**.

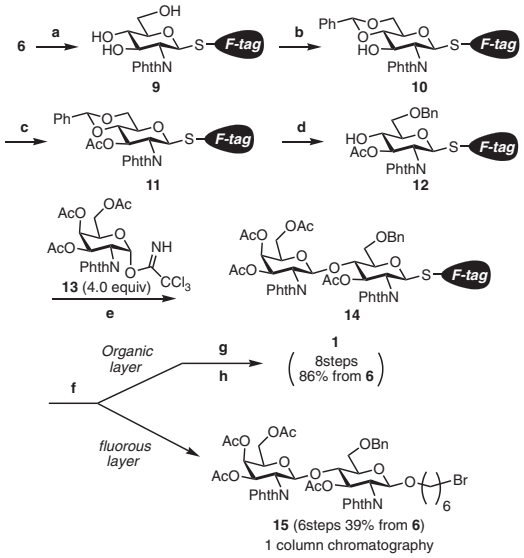


Scheme 2. Glycosylation.

LacdiNPhth residue, which might be a cancer-specific carbohydrate marker.[10] First, all acetyl groups of **6** were cleaved with NaOMe to yield **9**. Reaction with benzaldehyde dimethylacetal then produced **10**. The C-3 hydroxy group of **10** was protected by an acetyl group; the subsequent reductive opening of benzylidene acetal gave **12**. Compounds **12** and **13**[11] were coupled by using the Schmidt method[12] with $Cu(OTf)_2$ to give a fluorous disaccharide **14**. In this glycosylation step, aglycon-transfer[13] was observed as a side reaction (≈30%). The crude **14** was glycosylated again with $Br(CH_2)_6OH$[7] under NIS–TMSOTf conditions to give the crude product of the desired disaccharide **15** (Scheme 3). In this synthesis, each compound bound to the fluorous tag (compounds **10** to **12** and **14**) was partitioned into the fluorous layer,[14] and the crude **15** was partitioned into the organic layer.[15] No further purifications (e.g., silica gel column chromatography) of the fluorous intermediates were performed. After single-column chromatographic purification of **15**, pure **15**[16] was obtained, with a yield of 39%. These results indicate that these fluorous thioglycosides were useful not only as glycosyl donors but also as glycosyl acceptors.

In contrast, owing to some side reactions of the linker moiety bound to the fluorous tag under NIS–TMSOTf conditions, the fluorous layer was observed as a complex mixture on thin-layer chromatography. Therefore, acetolysis with Ac_2O–$BF_3 \cdot OEt_2$ was conducted for the mixture to cleave the linker moiety; this was followed by deacetylation. This achieved recovery of the fluorous tag as the fluorous alcohol **1**, with an excellent yield.

In conclusion, we developed the novel heavy fluorous thioglycoside **6**, which was readily prepared via the correspond-



Reagent and conditions: (a) NaOMe, MeOH-HFE7100-THF, r.t., 1 h; (b) $PhCH(OMe)_2$, CSA, MeCN-HFE7100, r.t., 1 h; (c) Ac_2O, Et_3N, DMAP, THF, r.t., 4 h; (d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2-HFE7100, –10 °C, 20 h; (e) $Cu(OTf)_2$ (0.2 equiv), CH_2Cl_2, 0 °C, 2 h; (f) $Br(CH_2)_6OH$ (4.0 equiv), NIS (4.0 equiv), TMSOTf (0.4 equiv), CH_2Cl_2, 0 °C, 1 h, (g) Ac_2O, $BF_3{\cdot}OEt_2$, $PhCF_3$, 50 °C, 3 h; (h) NaOMe, MeOH-HFE7100-THF, r.t., 20 h.

Scheme 3. Synthesis of the LacdiNPhth derivative **15** by using the heavy fluorous tag method.

ing fluorous thiol **4**. Moreover, through heavy fluorous synthesis of the LacdiNPhth derivative **15**, we confirmed that our thioglycosides are useful not only as glycosyl donors but also as glycosyl acceptors, and that they have high stability under various reaction conditions. In addition, the fluorous tag was briefly recovered with a good yield as the fluorous alcohol **1**. The synthesis of various glycoconjugates by using the heavy fluorous tag method is still in progress.

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8 Comound **6**; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.78–1.86 (m, 9H), 2.02 (s, 3H), 2.06–2.17 (m, 9H), 3.39 (s, 6H), 3.41 (s, 2H), 3.42 (t, $J = 6.2$ Hz, 6H), 3.79 (ddd, $J = 2.1$, 4.8, 10.3 Hz, 1H), 3.85 (d, $J = 12.4$ Hz, 1H), 3.89 (d, $J = 12.4$ Hz, 1H), 4.13 (dd, $J = 2.1$, 12.4 Hz, 1H), 4.31 (dd, $J = 4.8$, 12.4 Hz, 1H), 4.37 (d, $J = 12.4$ Hz, 1H), 4.40 (d, $J = 12.4$ Hz, 1H), 4.43 (t, $J = 10.3$ Hz, 1H), 5.18 (t, $J = 10.3$ Hz, 1H), 5.34 (d, $J = 10.3$ Hz, 1H), 5.79 (d, $J = 10.3$ Hz, 1H), 7.11–7.23 (m, 4H), 7.71–7.76 (m, 2H), 7.78–7.87 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.50, 20.65, 20.75 (brs, $-CH_2\boldsymbol{C}H_2CH_2-C_8F_{17}$), 20.80, 27.93 (t, $^2J_{CF} = 21.7$ Hz, $-CH_2CH_2\boldsymbol{C}H_2-C_8F_{17}$), 34.29, 45.54, 53.72, 62.32, 69.02, 69.43, 69.63, 69.75, 71.59, 73.21, 76.12, 80.66, 106.17–120.71 (complex signals of $-\boldsymbol{C}F_2-$ and $-\boldsymbol{C}F_3$), 123.75, 123.82, 126.43, 128.02, 128.27, 128.59, 131.36, 131.75, 134.36, 134.49, 136.89, 139.31, 167.26, 167.60, 169.58, 170.19, 170.77. MALDI-TOF-MS m/z: $[M + Na]^+$ calcd for $C_{66}H_{54}F_{51}NO_{13}SNa$ 2092.2, found: 2093.1.

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14 Product mixtures containing the fluorous compounds **10**–**12** and **14** were partitioned between fluorous mixed solvent (HFE7100:^{17}FC72^{18} = 2:1) and 95% aq. MeCN. None of the fluorous compounds were detected by TLC of the organic layer after three extractions with fluorous mixed solvent; this shows that these compounds were quantitatively extracted with the fluorous layer.

15 **15** was partitioned between FC-72 and MeCN and extracted with the MeCN layer.

16 Compound **15**; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.00–1.11 (m, 2H), 1.11–1.22 (m, 2H), 1.30–1.55 (m, 4H), 1.81 (s, 3H), 1.97 (s, 3H), 2.05 (s, 3H), 2.16 (s, 3H), 3.15 (t, $J = 6.9$ Hz, 2H), 3.28–3.36 (m, 1H), 3.45 (dd, $J = 3.4$, 11.0 Hz, 1H), 3.48–3.58 (m, 2H), 3.69–3.76 (m, 1H), 3.83 (t, $J = 7.6$ Hz, 1H), 4.02–4.19 (m, 4H), 4.33 (d, $J = 11.7$ Hz, 1H), 4.35 (d, $J = 11.7$ Hz, 1H), 4.43 (t, $J = 8.9$ Hz, 1H), 5.21 (d, $J = 8.2$ Hz, 1H), 5.38 (d, $J = 3.4$ Hz, 1H), 5.47 (d, $J = 8.9$ Hz, 1H), 5.66–5.76 (m, 2H), 7.16–7.37 (m, 5H), 7.64–7.91 (m, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.46, 20.64, 20.68, 25.01, 27.66, 29.02, 32.57, 33.48, 51.74, 55.06, 60.70, 66.33, 67.61, 67.85, 69.45, 70.48, 71.72, 72.76, 74.34, 74.73, 97.58, 97.96, 123.47, 127.31, 127.36, 127.42, 128.22, 131.41, 134.25, 134.32, 138.19, 167.31, 167.59, 167.99, 168.35, 169.77, 169.94, 170.19, 170.31. MALDI-TOF-MS m/z: $[M + Na]^+$ calcd for $C_{49}H_{53}BrN_2O_{17}Na$ 1043.2, found: 1043.3.

17 HFE7100 is a commercially available fluorocarbon solvent (3M, Tokyo), which consists of perfluorobutyl methyl ether (C_4F_9OMe) isomers. It is called Novec™ HFE7100 and is miscible in common organic solvents and fluorous solvents.

18 FC72 is a commercially available fluorocarbon solvent, which consists of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.

