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Practical heavy fluorous tag for carbohydrate synthesis with minimal chromatographic purification

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ABSTRACT

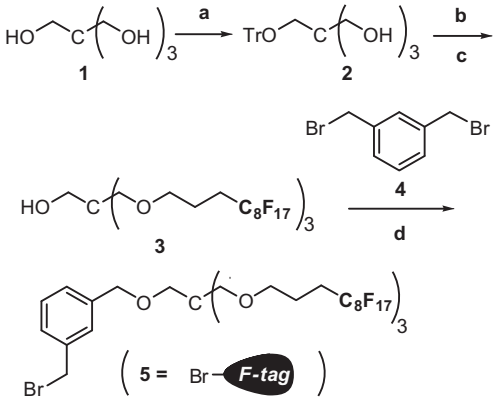
A practical heavy fluorous tag **5** bound to a benzylic linker was prepared and applied to carbohydrate synthesis. The fluorous tag **5** was readily introduced to the desired hydroxyl group and carboxyl group by using various methods. Synthesis of the oligosaccharide, which included the terminal structure of class III mucin, was achieved with single-column chromatographic purification. In addition, because of the symmetrical structure of **5**, each fluorous synthetic intermediate could be analyzed much easier by NMR spectroscopy than in the case of the fluorous compounds connecting our previous fluorous tags.

Since the seminal articles of fluorous biphasic catalyst techniques in 1994[1] and the heavy fluorous tag method in 1997[2], fluorous chemistry has found a wide range of applications[3], such as in catalytic chemistry and synthetic chemistry. A major advantage of the heavy fluorous tag method is that a non-column chromatographic purification system can be used owing to the easy separation of the fluorous compounds from the general non-fluorous compounds. This separation can be readily achieved in a straightforward manner with fluorous–organic partitioning. We have also reported the synthesis of oligosaccharides and peptides by using the heavy fluorous tag method with 'polyamide-type' fluorous tags[4] and the more useful 'polyether-type' fluorous tag.[5] The desired properties of fluorous tags are (1) high introduction yields and cleavage yields; (2) easily recyclable; (3) simple analysis of the NMR spectrum; (4) introducing to desired positions; and (5) stability under various reaction conditions. However, even with our previous polyether-type tag[5] it was difficult to analyze the NMR spectra of these fluorous compounds, because the peaks of the fluorous tags frequently overlap with those of the sugar ring protons. Furthermore, in oligosaccharide synthesis, the introduction of these heavy fluorous tags is virtually limited to the anomeric position of the carbohydrate. A more user-friendly fluorous tag, which would resolve these intractable problems, is essential for practical application of the heavy fluorous tag method. Herein, we describe the synthesis of carbohydrates by using more a practical fluorous tag bound to a benzylic linker.

The benzyl group is one of the most important and useful protecting groups in oligosaccharides synthesis, and some benzyl-type fluorous tags have already been exploited in oligosaccharide synthesis.[6] However, these benzyl type tags have some problems that need to be resolved, such as low introduction yields and glycosylation yields, complexity of the NMR spectra, and difficulty in recycling the fluorous tag after the reaction. In order to overcome these problems, we designed and synthesized a novel fluorous tag **5** (Scheme 1).

A triphenylmethyl group was introduced to a primary alcohol of pentaerythritol[7] (**1**) to give triol **2**[8], which was coupled with fluorous tosylate[9]; subsequent removal of the triphenylmethyl group afforded fluorous alcohol **3** connecting three fluorous chains in 78% yield. Finally, α,α′-*m*-dibromoxylene (**4**) was introduced as a benzylic linker to give a fluorous tag **5**[10] in 83% yield.

Next, we investigated the conditions of introduction of the fluorous tag **5** to compounds **6**, **8,** and **10**, which are commercially available (Scheme 2). *Method 1* is Williamson ether synthesis, a conventional and commonly used method of forming ether bonds.



Scheme 1. Preparation of benzyl-type fluorous tag **5**. Reaction conditions: (a) TrCl, DMAP, Pyr-DMF, 100 °C, 3 h, 59%; (b) $TsO(CH_2)_3C_8F_{17}$, NaH, 15-Crown-5, THF, rt, 17 h; (c) CSA, MeOH–$CHCl_3$, rt, 19 h, two steps 78%; (d) NaH, 15-Crown-5, $PhCF_3$, 10 °C, 24 h, 83%.

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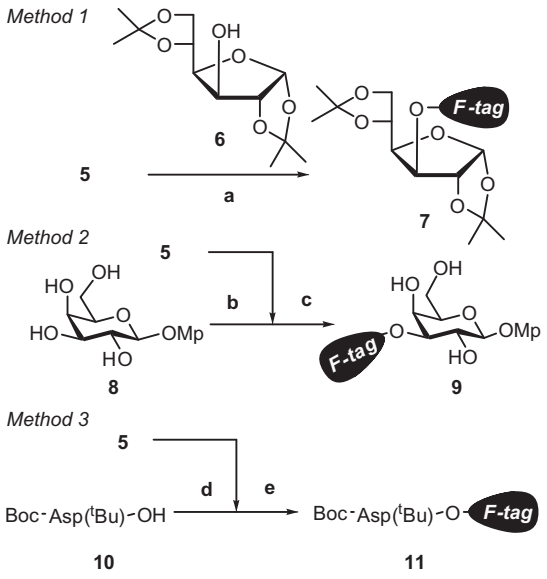
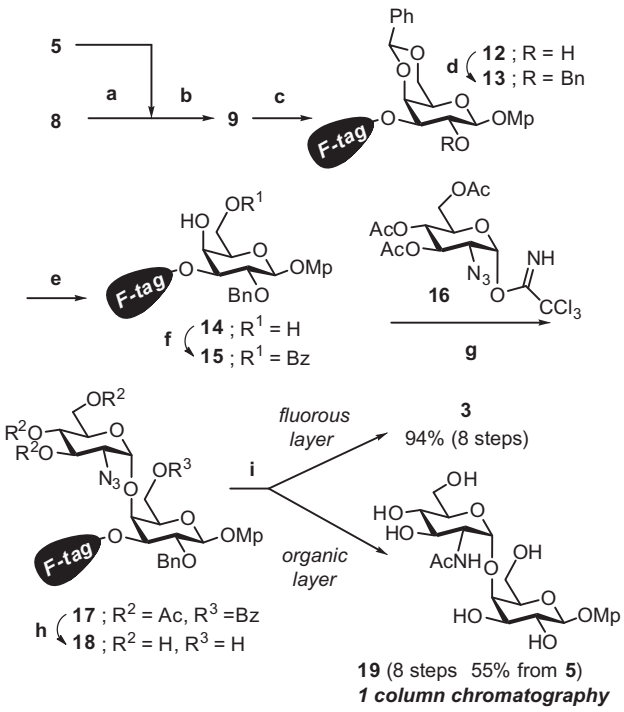


Scheme 2. Introduction conditions. Reagent and conditions: (a) NaH, 15-Crown-5, THF, rt, 22 h, quant; (b) *n*-Bu_2SnO, MeOH, reflux, 4 h; (c) TBAB, THF, reflux, 16 h 90%; (d) Cs_2CO_3, EtOH-H_2O, rt, 10 min; (e) THF–DMF, rt, 16 h, quant.



Scheme 3. Disaccharide synthesis by using a fluorous tag **5**. Reagent and conditions: (a) *n*-Bu_2SnO, MeOH, reflux, 4 h; (b) TBAB, THF, reflux, 16 h; (c) $PhCH(OMe)_2$, CSA, MeCN–HFE7100[12], rt, 1 h; (d) BnBr, NaH, 15-Crown-5, THF, rt, 1 h; (e) CSA, MeOH–HFE7100, rt, 7 h; (f) BzCl, Et_3N, THF, −20 °C, 14 h; (g) TMSOTf, CH_2Cl_2–ether, rt, 2 h; (h) NaOMe, MeOH-HFE7100, rt, 2 h; (i) H_2 gas, $Pd(OH)_2$, Ac_2O, AcOH, EtOH–HFE7100, rt, 20 h.

In this case, 15-Crown-5 is essential for constructing the ether bond smoothly.[5a] It seems that 15-Crown-5 can dramatically enhance the reactivity between the corresponding alkoxide and the fluorous compound. *Method 2* is the selective introduction by using *n*-Bu_2SnO, and *Method 3* is the introduction to the amino acid derivative **10** with Cs_2CO_3.[11] The results showed that this fluorous tag **5** could be easily introduced not only to the desired hydroxyl group, but also to the carboxyl group, in excellent yields.

This fluorous tag **5** was then applied to the synthesis of disaccharide **19**, which included the terminal structure of a class III mucin[13] (Scheme 3). The introduction of fluorous tag **5** to compound **8** at *O*-3 position was conducted as in Scheme 2 to give **9**. The formation of benzaldehyde dimethylacetal produced **12** and subsequent benzylation afforded **13**. Cleavage of the benzylidene acetal of **13** gave a *O*-4,6 diol **14**. Selective benzoylation of **14** to primary alcohol then

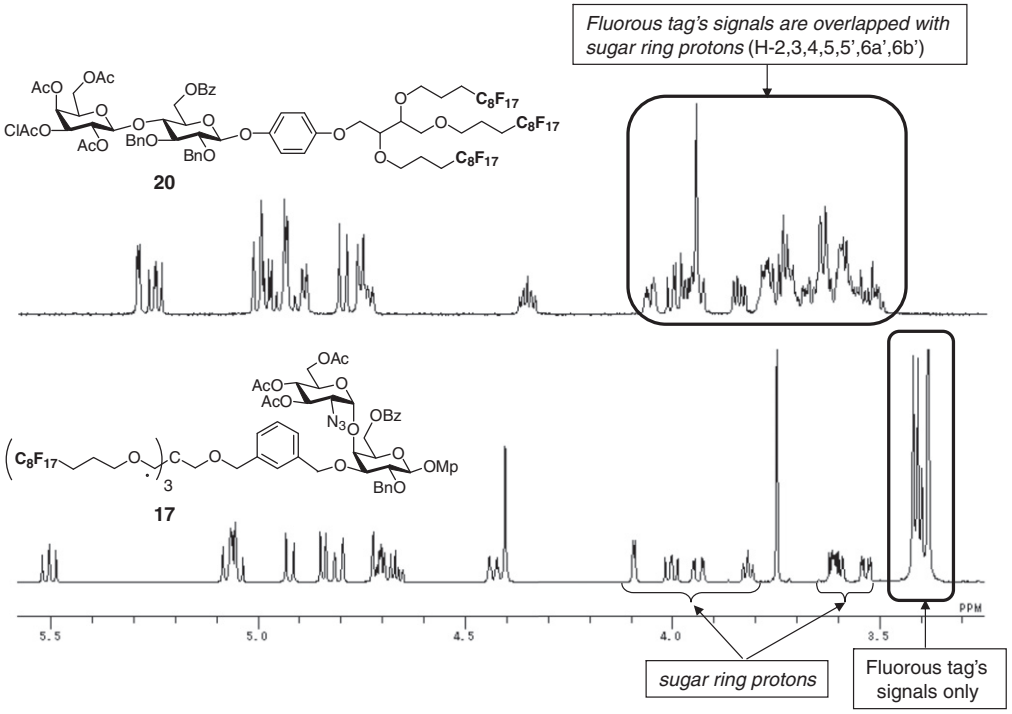


Figure 1. NMR spectra of compounds **17** and **20**.[5a]

produced glycosyl acceptor **15**. Compound **15** and glycosyl donor **16**[14] were coupled by the Schmidt method[15] with TMSOTf to give a fluorous disaccharide **17**.[16] All acyl groups of **17** were removed by NaOMe in MeOH–HFE7100 to afford **18**, this was followed by hydrogenation in the presence of $Pd(OH)_2$ to give the crude product of the desired disaccharide **19**. In this synthesis, each compound bound to the fluorous tag (**12**–**15**, **17**, and **18**) was partitioned into the fluorous layer,[17] and the desired compound **19** was partitioned into the organic layer.[18] No further purification (e.g., by silica-gel column chromatography) of the fluorous intermediates was conducted. After a single-column chromatographic purification of **19**, pure **19**[19] was obtained in 58% yield. The fluorous alcohol **3**[20] was recovered from the fluorous layer in 94% yield and was recyclable.

Finally, a comparison of ^{1}H NMR spectra with fluorous compound **17**, which has a pentaerythritol (**1**) scaffold, and a previously reported fluorous compound **20**[5a] bound to an old type of fluorous tag, which has a *meso*-erythritol scaffold, is shown in Figure 1. In the spectrum of **20** we observed complicated peaks around 3.5–4.0 ppm (Fig. 1, top panel). These peaks are overlapping signals of the fluorous tag moiety and some sugar ring protons. In general, many peaks of the sugar ring protons are also observed around the same range. This result indicates that the previous tags are not appropriate for efficient oligosaccharide synthesis because of the difficulty in analyzing their NMR spectra. In contrast, because of the more symmetrical structure of the fluorous part, the spectrum of **17** was much simpler than that of **20** and the signals of the fluorous moiety barely influenced the analysis of the sugar ring protons (Fig. 1, bottom panel).

In conclusion, we developed a more practical fluorous tag **5** that could be easily introduced not only to various hydroxyl groups of monosaccharides but also to carboxyl groups, in excellent yields. Effective application of **5** in oligosaccharide synthesis could be achieved by single-column chromatographic synthesis of **19** in good yields. Each fluorous synthetic intermediate could be obtained in a straightforward manner by a simple fluorous–organic solvent partitioning and easily analyzed via its NMR spectrum owing to its symmetrical structure. Furthermore, the fluorous alcohol **3** was easily recyclable from the fluorous layer, in excellent yields. We are currently investigating the possibility of the total synthesis of a wide variety of oligosaccharides and glycoconjugates by the fluorous tag method.

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10. Compound **5**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.79–1.87 (m, 6H), 2.06–2.18 (m, 6H), 3.40 (s, 6H), 3.44 (t, J = 6.2 Hz, 6H), 3.44 (s, 2H), 7.20–7.33 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 20.65 (br s, $-CH_2CH_2CH_2-C_8F_{17}$), 27.84 (t, $^2J_{CF}$ = 21.7 Hz, $-CH_2CH_2CH_2-C_8F_{17}$), 33.25, 45.46, 69.37, 69.52, 69.59, 69.66, 72.95, 106.13–120.65 (complex signals of $-CF_2-$ and $-CF_3$), 127.31, 127.89, 128.10, 128.73, 137.91, 139.52; (MALDI-TOF MS): calcd for $C_{46}H_{34}BrF_{51}O_4Na$ m/z $[M+Na]^+$: 1722.6, found: 1723.5.
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16. Compound **17**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.77–1.85 (m, 6H), 2.01 (s, 3H), 2.04 (s, 3H), 2.05–2.16 (m, 9H), 3.38 (s, 6H), 3.41 (t, J = 6.7 Hz, 6H), 3.42 (s, 2H), 3.44 (dd, J = 3.4, 10.3, Hz, 1H), 3.58–3.63 (m, 2H), 3.75 (s, 3H), 3.81 (t, J = 6.7 Hz, 1H), 3.94 (dd, J = 2.7, 12.4 Hz, 1H), 4.00 (dd, J = 7.6, 9.6 Hz, 1H), 4.09 (d, J = 2.7 Hz, 1H), 4.40(s, 2H), 4.43 (d, J = 10.3 Hz, 1H), 4.64–4.73 (m, 3H), 4.81 (d, J = 11.6 Hz, 1H), 4.84 (d, J = 7.6 Hz, 1H), 4.92 (d, J = 11.0 Hz, 1H), 5.03–5.10 (m, 3H), 5.51 (t, J = 9.6 Hz, 1H), 6.74 (d, J = 8.9 Hz, 2H), 7.02 (d, J = 8.9 Hz, 2H), 7.19 (s, 1H), 7.25–7.34 (m, 6H), 7.39 (d, J = 6.9 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 8.03 (d, J = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 20.67, 20.78, 27.83 (t, $^2J_{CF}$ = 21.6 Hz, $-CH_2CH_2CH_2-C_8F_{17}$), 45.46, 55.63, 61.07, 61.92, 62.58, 67.94, 68.23, 69.49, 69.56, 69.66, 71.42, 72.39, 73.17, 73.64, 75.15, 75.78, 78.52, 79.65, 98.95, 103.22, 106.02–120.68 (complex signals of $-CF_2-$ and $-CF_3$), 114.51, 118.55, 128.59, 126.83, 126.89, 127.81, 128.38, 128.45, 128.55, 128.59, 129.66, 129.79, 133.44, 137.81, 138.29, 139.21, 151.46, 155.40, 166.10, 169.83, 169.97, 170.47; (MALDI-TOF MS): calcd for $C_{85}H_{76}F_{51}O_{19}Na$ m/z $[M+Na]^+$: 2435.4, found: 2434.6.
17. Product mixtures containing the fluorous compounds **12**–**15**, **17**, and **18** were partitioned between fluorous mixed solvent (HFE7100: FC72[21] = 4:1) and 95% aq MeCN. None of the fluorous compounds was 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.
18. Compound **19** was partitioned between FC-72 and MeOH and extracted with the MeOH layer.
19. Compound **19**: ^{1}H NMR (600 MHz, CD_3OD) δ = 2.01 (s, 3H), 3.45 (t, J = 10.3 Hz, 1H), 3.67–3.62 (m, 2H), 3.84–3.70 (m, 8H), 3.82 (dd, J = 2.7, 11.7 Hz, 1H), 3.95 (dd, J = 4.1, 10.3 Hz, 1H), 4.03 (d, J = 2.7 Hz, 1H), 4.28 (ddd, J = 2.1, 2.7, 10.3 Hz, 1H), 4.82 (d, J = 7.6 Hz, 1H), 4.93 (d, J = 4.1 Hz, 1H), 6.85 (d, J = 8.9 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ = 22.67, 55.67, 56.07, 60.76, 62.33, 72.04, 72.45, 72.65, 73.69, 74.35, 76.86, 77.71, 100.32, 104.03, 115.55, 119.08, 153.00, 156.78, 173.74; HRMS(ESI-TOF MS): calcd for $C_{21}H_{32}NO_{12}$ m/z $[M+H]^+$: 490.1919, found: 490.1891. The correlation between anomeric protons of *N*-acetyl glucosamine residue and 4-position carbons of galactose residue was observed by HMQC and HMBC of NMR spectroscopic analysis.
20. Compound **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 1.83–1.90 (m, 6H), 2.08–2.20 (m, 6H), 2.58 (t, J = 6.2 Hz, 1H), 3.44 (s, 6H), 3.47 (t, J = 6.2 Hz, 6H), 3.68 (d, J = 5.5 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 20.70 (br s, $-CH_2CH_2CH_2-C_8F_{17}$), 27.85 (t, $^2J_{CF}$ = 21.6 Hz, $-CH_2CH_2CH_2-C_8F_{17}$), 45.09, 65.68, 69.99, 71.01, 105.84–120.79 (complex signals of $-CF_2-$ and $-CF_3$); (MALDI-TOF MS): calcd for $C_{38}H_{27}F_{51}O_4Na$ m/z $[M+Na]^+$: 1539.5, found: 1539.4.
21. FC72 is a commercially available fluorocarbon solvent, which consists of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.