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A novel benzoyl-type fluorous protecting group for use in fluorous synthesis

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Abstract—TfBz–OH, a novel benzoyl-type fluorous protecting reagent, has been easily prepared. It was found that the TfBz (trisfluorous chain-type benzoyl) group can be successfully introduced onto a hydroxyl function, removed in high yield, and recycled after deprotection. The use of the TfBz group makes it possible to synthesize an oligosaccharide by minimal column chromatography purification, because each synthetic intermediate is easily purified simply by fluorous-organic solvent extraction.

1. Introduction

The fluorous tag method is an excellent methodology in which a highly fluorinated synthetic intermediate can be easily separated from non-fluorinated compounds.[1] It is expected to be a strategic alternative to solid-phase synthesis, because it removes some serious disadvantages of the usual solid phase method such as the difficulty of large-scale synthesis and the inability to monitor the reaction by TLC, NMR spectroscopic analysis, or mass spectrometry. The fluorous tag method is classified into a light fluorous technique and a heavy fluorous technique.[2] In particular, the heavy fluorous technique using a fluorous tag with a high fluorine content can easily separate fluorinated intermediates from non-fluorinated compounds through simple fluorous-organic solvent partitioning without tedious column chromatography. Effective fluorous tags are essential for the fluorous tag method: silyl-,[3] acetal-,[4] and benzyl-ether[5] type fluorous tags for a hydroxyl function have been reported as protecting groups. Different types of fluorous protecting groups for several other functions have also been reported.[6]

We have developed the synthesis of a simple natural oligosaccharide, such as the Gb3 oligosaccharide and galactose β(1–6) pentamer, involving the Bfp (bisfluorous chain-type propanoyl) group as an aliphatic acyl-type fluorous protecting group.[7] In addition, we have reported the synthesis of oligosaccharides and peptides using a fluorous support with a high fluorine content.[8] The use of the Bfp group made it possible to synthesize rapidly a simple oligosaccharide. However, it is difficult to synthesize a complex oligosaccharide using only the Bfp group as an aliphatic acyl-type fluorous protecting group. A multitude of hydroxyl groups in carbohydrates have a similar reactivity and the selective protection and deprotection of each hydroxyl function is needed for the synthesis of the desired oligosaccharide.

Several kinds of protecting groups are used in oligosaccharide synthesis. Aliphatic acyl-type protecting groups, such as the acetyl group, are easily rearranged onto the primary hydroxyl functions from the neighboring secondary hydroxyl function. It is difficult to form the 1–6 linkage of galactose using aliphatic acyl-type protecting groups, because an aliphatic acyl-type group at 4-position of galactose tends to rearrange to the hydroxyl function at the 6-position.[7c] The benzoyl group as another acyl-type protecting group can selectively protect the primary hydroxyl function of carbohydrates and resists the acyl rearrangement in contrast to the acetyl

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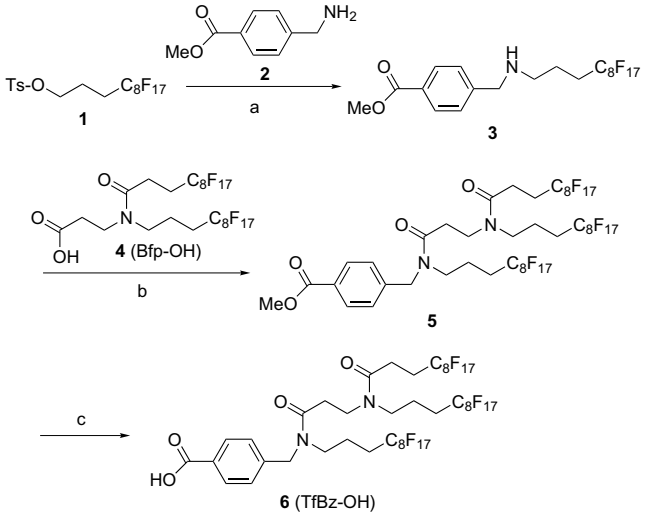
group.[9] The benzoyl group is very useful as a protecting group and essential for the synthesis of complex oligosaccharides. Therefore, a benzoyl-type fluorous protecting group is required for fluorous oligosaccharide synthesis. Herein we report the development of a novel fluorous benzoyl-type protective group and its application to the rapid synthesis of oligosaccharides.

2. Results and discussion

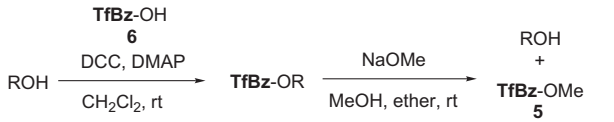
We designed and synthesized compound **6** (TfBz–OH) containing three fluorous chains as a novel fluorous benzoyl-type protecting reagent (Scheme 1). The reaction of the fluorous tosylate **1**[10] with methyl 4-aminomethylbenzoate (**2**, 4.0 equiv) in the presence of K_2CO_3 (30 equiv) in MeCN provided the monoalkylating product **3** in 78% yield. The amine **3** was coupled with Bfp-OH (**4**,[7] 1.1 equiv) in the presence of PyBOP (1.3 equiv), and Et_3N (3.0 equiv) in CH_2Cl_2 to afford the corresponding amide **5** in 94% yield. The treatment of **5** with aqueous sodium hydroxide in dioxane gave the desired fluorous benzoic acid **6** ($M_W = 1617$) in 99% yield. We named the acyl moiety of **6**, TfBz (trisfluorous chain-type benzoyl).

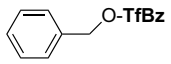
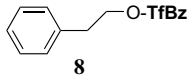
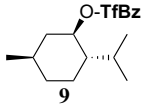
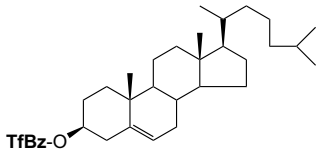


Scheme 1. Reagents and conditions: (a) K_2CO_3, MeCN, reflux, 22 h, 78%; (b) PyBOP, Et_3N, CH_2Cl_2, rt, 4 h, 94%; (c) 1 M NaOH, dioxane, 70 °C, 3 h, 99%.

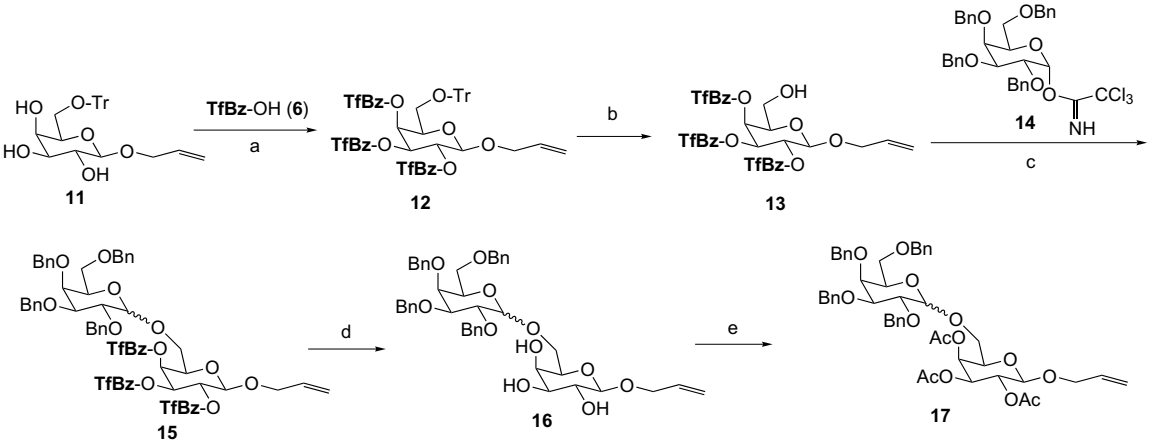
The TfBz group was easily introduced into both primary and secondary alcohols using DCC (2.5 equiv) and DMAP (1.5 equiv) in CH_2Cl_2 to afford the corresponding esters **7**, **8**, **9**, and **10** in good to excellent yields (Table 1). The TfBz–OH **6** did not react with 1-adamantanol having a tertiary hydroxyl function under similar reaction conditions. The fluorous compounds containing the TfBz group were separated from the non-fluorinated compounds by partitioning the product mixtures between FC-72 and MeOH. The TfBz groups of **7**, **8**, **9**, and **10** were easily removed by treatment with NaOMe in MeOH–ether (2/3) to afford the corresponding alcohols, which were extracted with MeOH by partitioning the mixture between FC-72[11] and MeOH. The methyl ester of TfBz (TfBz–OMe), **5** was recovered from the FC-72 layer in excellent yields. Compound **5** was treated with aqueous sodium hydroxide to give **6**, which can be recycled.

Table 1.



TfBz–OR	Introduced yield (%)	Removed yield (%)	
		ROH	TfBz–OMe
 **7**	81	88	99
 **8**	92	88	98
 **9**	71	93	92
 **10**	67	90	97

We next attempted to synthesize a disaccharide **16** as shown in Scheme 2. The TfBz group was also easily introduced into the three hydroxyl functions of a galactose derivative **11** using **6** (3.3 equiv), DCC (7.5 equiv), and DMAP (4.5 equiv) in CH_2Cl_2 to give the corresponding fluorous compound **12**. The trityl (Tr) group of **12** was removed by treatment with camphorsulfonic acid (CSA, 7.0 equiv) in MeOH–$CHCl_3$ (1/2) to afford the fluorous glycosyl acceptor **13**. The fluorous disaccharide **15** was obtained by the reaction of **13** with the excess glycosyl donor **14** (7.0 equiv) in the presence of trimethylsilyl trifluoromethanesulfonate (TMS–OTf, 2.0 equiv) in ether–$EtOC_4F_9$[12] (1/1). The fluorous intermediates **12**, **13**, and **15** were each extracted with the fluorous solvent FC-72 by partitioning the product mixtures between FC-72 and an organic solvent such as methanol or toluene. No further purification such as silica gel column chromatography was carried out. The TfBz group of **15** was easily removed by treatment with NaOMe in MeOH–ether–$EtOC_4F_9$ (2/4/1) to afford the crude **16**, which was extracted with MeOH by partitioning the mixture between FC-72 and MeOH. TfBz–OMe (**5**) was recovered from the FC-72 layer in 94% yield. Finally, the pure disaccharide **16** was obtained from a single silica gel column chromatographic purification in a 46% overall yield from **11** (four steps). The disac-



Scheme 2. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 24 h; (b) CSA, $CHCl_3$–MeOH, rt, 17 h; (c) TMSOTf, 4 Å molecular sieves, ether–$EtOC_4F_9$, 0 °C, 15 min; (d) NaOMe, ether–$EtOC_4F_9$–MeOH, rt, 3 h, then silica gel chromatography, 46% from **11** (in four steps); (e) Ac_2O, Py, rt, 19 h, 96%.

charide **16** was introduced to the acetate **17**[13] by treatment with acetic anhydride in pyridine. It is worth noting that no rearrangement of the TfBz group in **13** was observed at all, even if **13** was purified by silica gel column chromatography.

The partition coefficient information for fluorous compounds is very important for the successful performance of the heavy fluorous technique. We measured the liquid–liquid partition coefficients for the fluorous compounds **5**, **7**, **8**, **9**, **10**, **13**, and **15** between FC-72 and an organic solvent (methanol or toluene) as shown in Table 2. In the case of the fluorous compounds, the partition coefficients for separation by FC-72-methanol extraction are higher than those by FC-72-toluene extraction. Although the fluorine contents of the fluorous compounds **9**, **10**, and **15** are low (<55.2%), these partition coefficients are higher than those of the other fluorous compounds **7** and **8**.

Table 2. Partition coefficient of fluorous compounds

TfBz–OR	F content (wt%)	FC-72:MeOH	FC-72:toluene
TfBz–OMe **5**	59.4	86:14	58:42
7	56.8	70:30	6:94
8	56.3	53:47	6:94
9	55.2	80:20	11:89
10	48.8	91:9	13:87
13	58.0	97:3	96:4
15	52.5	>99:1	>99:1

In conclusion, the fluorous benzoyl-type protecting reagent **6** (TfBz–OH) could be easily prepared on a large scale. The TfBz group is readily introduced into several alcohols, removed in high yield by the usual procedure and is recyclable after deprotection. The use of the TfBz group as a fluorous protecting group makes it possible to synthesize rapidly a natural oligosaccharide with minimal column chromatography purification. Each fluorous synthetic intermediate could be obtained in a straightforward manner by simple FC-72-organic solvent extraction. The TfBz group is stable under acidic conditions and no acyl rearrangement occurred. Therefore, the galactose (1–6) linkage can be easily formed. The partition coefficients for some fluorous compounds were provided for the heavy fluorous technique. Further application to the synthesis of bioactive carbohydrates and glycoconjugates is now in progress.

Acknowledgements

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11. The fluorocarbon solvent (FC-72, bp 56 °C, formally called Fluorinert™ FC-72) is commercially available and consists of perfluorohexane isomers (C_6F_{14}).
12. The fluorocarbon solvent ($EtOC_4F_9$, Novec™ HFE-7200) is commercially available.
13. The α and β isomers (**17a** and **17b**) were separated by silica gel column chromatography and the anomeric ratio was determined to be α:β = 40:60. **17a** (α isomer): $[\alpha]_D^{25} = +7.7$ (*c* 0.96, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.98 (s, 3H), 2.05 (s, 3H), 2.06 (s, 3H), 3.47 (dd, *J* = 6.2, 9.6 Hz, 1H), 3.54 (dd, *J* = 6.2, 9.6 Hz, 1H), 3.62 (dd, *J* = 6.2, 10.3 Hz, 1H), 3.70 (dd, *J* = 6.2, 10.3 Hz, 1H), 3.89 (dd, *J* = 2.1, 9.6 Hz, 1H), 3.94 (m, 2H), 3.97 (t, *J* = 6.2 Hz, 1H), 4.01 (m, 2H), 4.28 (m, 1H), 4.40 (d, *J* = 8.2 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.77 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 4.1 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 4.92 (d, *J* = 11.7 Hz, 1H), 5.01 (dd, *J* = 3.4, 10.3 Hz, 1H), 5.14 (m, 1H), 5.20 (m, 1H), 5.42 (d, *J* = 3.4 Hz, 1H), 5.80 (m, 1H), 7.32 (m, 20H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.61, 20.67, 20.79, 67.07, 67.84, 69.13, 69.16, 69.80, 71.04, 71.79, 73.22, 73.36, 73.52, 74.72, 75.13, 76.43, 78.81, 98.79, 99.99, 117.20, 127.47, 127.57, 127.63, 127.72, 127.82, 128.09, 128.20, 128.36, 133.46, 138.01, 138.42, 138.57, 138.77, 169.49, 170.03, 170.31; HRMS (ESI-TOF): calcd for $C_{49}H_{56}O_{14}Na$ ($M+Na^+$): 891.3562. Found: 891.3522. **17b** (β isomer): $[\alpha]_D^{25} = -12.6$ (*c* 0.87, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.97 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 3.47 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.53 (m, 3H), 3.74 (m, 1H), 3.79 (t, *J* = 8.2 Hz, 1H), 3.87 (m, 3H), 3.93 (m, 1H), 4.24 (m, 1H), 4.38 (d, *J* = 8.2 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 8.2 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1 H), 4.93 (d, *J* = 11.7 Hz, 1H), 4.99 (dd, *J* = 3.4, 10.3 Hz, 1H), 5.10 (d, *J* = 10.3 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 5.21 (dd, *J* = 8.2, 11.0 Hz, 1H), 5.37 (d, *J* = 3.4 Hz, 1H), 5.71 (m, 1H), 7.31 (m, 20H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.61, 20.70, 20.80, 67.73, 68.04, 68.57, 69.05, 69.81, 71.03, 72.88, 72.95, 73.32, 73.53, 74.52, 75.14, 79.43, 81.98, 99.97, 103.89, 117.18, 127.52, 127.55, 127.57, 127.83, 127.93, 128.14, 128.18, 128.30, 128.35, 128.46, 133.33, 137.79, 138.41, 138.59, 138.74, 169.51, 170.07, 170.27; HRMS (ESI-TOF): Calcd for $C_{49}H_{56}O_{14}Na$ ($M+Na^+$): 891.3562. Found: 891.3550.