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A practical fluorous benzylidene acetal protecting group for a quick synthesis of disaccharides

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Abstract—A new fluorous benzylidene acetal protecting group was regioselectively introduced into carbohydrates, deprotected under acidic conditions, and reused. Oligosaccharides were synthesized via regioselective conversion of the fluorous acetal group to the benzyl group by traditional reaction conditions. The fluorous compounds were easily separated from non-fluorous by-products by fluorous solid phase extraction.

Fluorous protecting groups have become increasingly popular in organic synthesis because they not only fulfill all the requirements for traditional protecting groups[1] but they are also readily separated from non-fluorous by-products by solid phase extraction with a fluorous reverse-phase silica gel column (Fluorous solid phase extraction; FSPE).[2] In order to apply the technologies to total, parallel and combinatorial syntheses of complex molecules, various fluorous protecting groups for alcohols,[3] amines,[4] carboxylic acids[5] and aldehydes or ketones[6] have been synthesized so far, and some of them are commercially available. Utilizing these protecting groups, many researchers have accomplished quick and efficient synthesis of natural products including oligosaccharides, oligonucleotides, peptides[7] and chemoenzymatic synthesis of sialidase inhibitor.[8] Recently, we have also reported a synthesis and utilization of fluorous dimethylthiocarbamate (^{F}DMTC) groups as a new fluorous protecting group for alcohols.[9] The ^{F}DMTC groups were easily introduced into simple alcohols and carbohydrates, and selectively removed with *m*-CPBA.

Regioselective protection of hydroxyl groups of polyhydroxy compounds plays a crucial role in syntheses of natural products. The benzylidene acetal group is often used for protection of 1,3-diol compounds,[10] because it can also be transformed into the benzoyl or benzyl group by ring opening oxidation[11] or reduction,[12] respectively. Especially regioselective reduction of 4,6-*O*-benzylidene acetal group of hexopyranosides is useful for syntheses of biologically potent oligosaccharides and glycoconjugates. Therefore, development of a new fluorous acetal protecting group[13] for 1,2 and 1,3-diols is still a challenging target. We describe herein a synthesis of fluorous benzaldehydes as a reagent for 4,6-*O*-protection of hexopyranosides and its application to an oligosaccharide synthesis via the regioselective ring opening reaction of the fluorous cyclic acetal groups.

Fluorous protecting reagents, 4-(3-perfluoroalkyl) propyl benzaldehydes **4a**–**c**, were prepared by the route shown in Scheme 1. We chose the Wittig reaction for introducing perfluoroalkyl chains onto aromatic rings, because the reaction conditions are very mild and suitable for large-scale synthesis. Fluorous phosphonium salts **1a**–**c** (Fig. 1) were synthesized according to Gladyz's method[14] from the corresponding C_nF_{2n+1}-CH_2CH_2I ($n = 6, 8, 10$). Salts **1a**–**c** were reacted with methyl 4-formylbenzoate in the presence of potassium carbonate to give the corresponding alkenes **2a**–**c**. Compounds **2a**–**c** were hydrogenated with 10% Pd–C in EtOAc to give fluorous benzoates **3a**–**c**. The benzoates **3a**–**c** were converted into fluorous benzaldehydes **4a**–**c** in high yields with a pyrrolidine-modified aluminum hydride reagent according to Abe's procedure.[15]

We next examined introduction of ^{F}benzylidene acetal groups into 4,6-hydroxyl groups of hexopyranosides using fluorous benzaldehydes **4a**–**c** (Table 1).

Keywords: Benzylidene acetal group; Regioselective reduction; Oligosacchrides; Fluorous solid phase extraction.
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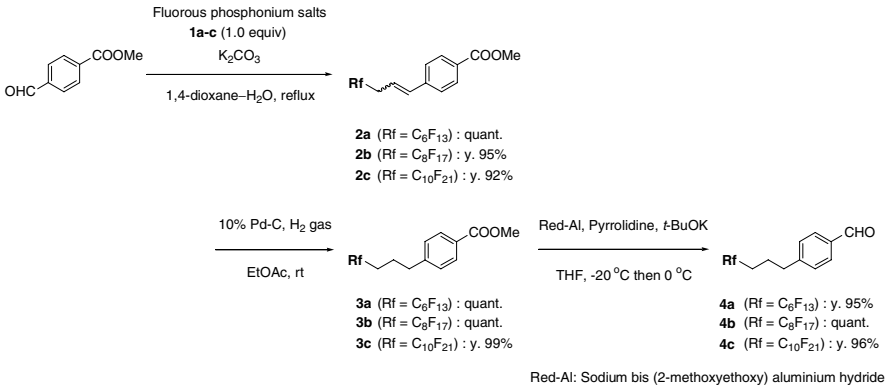


Scheme 1. Preparation of ^{F}benzaldehydes **4a**–**c**.

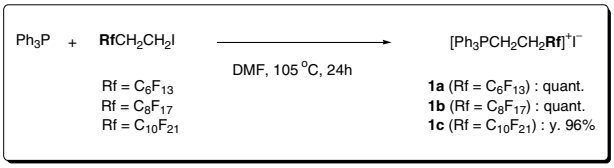
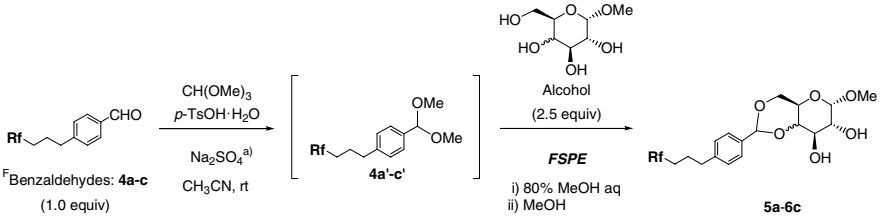


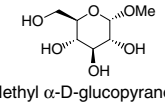
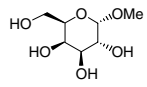
Figure 1. Preparation of fluorous phosphonium salts **1a**–**c**.

Benzaldehyde **4a** (1.0 equiv) was reacted with trimethyl orthoformate (2.0 equiv) in the presence of *p*-TsOH·H_2O (0.2 equiv) at room temperature. After monitoring the complete conversion of ^{F}benzaldehyde **4a** into the corresponding ^{F}dimethyl acetal **4a′** on TLC, methyl α-D-glucopyranoside (2.5 equiv) was added to the reaction mixture. After the reaction was completed, the reaction was quenched with Et_3N. The reaction mixture was filtered off and then the filtrate was concentrated. To separate the fluorous product from non-fluorous by-products, the crude product was loaded onto a fluorous reverse-phase silica gel (Fluoro*Flash*®)[16] column and then the column was eluted successively with 80% aq MeOH and MeOH. The MeOH fraction was concentrated to give ^{F}benzylidene acetal compound **5a** in 87% yield (entry 1). Similarly, ^{F}benzaldehydes **4a**–**c** were reacted with hexopyranosides. After purification of the crude products by FSPE, ^{F}benzylidene acetal compounds **5b**, **5c** and **6a**–**c** were obtained in good yields (Table 1).

Since ^{F}benzylidene acetal groups were successfully introduced into 4,6-hydroxyl group of hexopyranosides, we next tried to deprotect the fluorous acetal groups (Table 2). 4,6-*O*-^{F}Benzylidene acetal derivatives **7a**–**c** obtained by acetylation of **5a**–**c** were hydrolyzed in 90% aq AcOH at room temperature. After the reaction was completed, the aq AcOH solvent was removed and then the residue was treated with FSPE as described above. The 80% aq MeOH fraction gave the corresponding alcohol **9** in quantitative yield in each case. ^{F}Benzaldehydes **4a**–**c** were quantitatively recovered from the MeOH fraction (entries 1–3), and the recovered compound **4b** was reused as the protecting agent (Table 1, entry 3). Another method of deprotection was carried out by hydrogenation of ^{F}benzylidene acetal groups with 10% Pd–C. After purification of the crude products by FSPE,

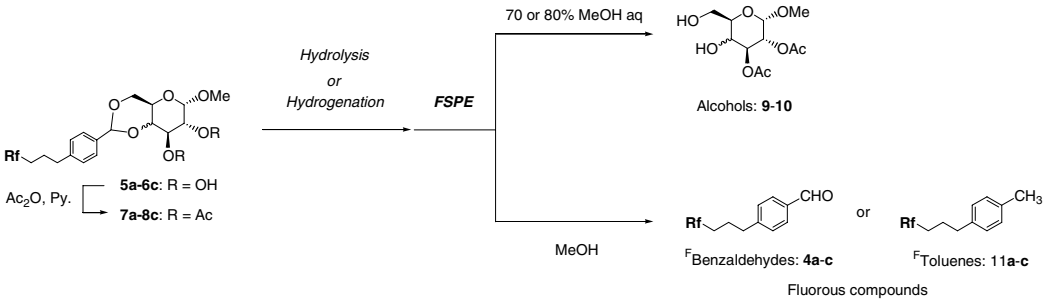
Table 1. Introduction of ^{F}benzylidene acetal groups into hexopyranosides

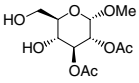
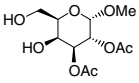


Entry	^{F}Protecting reagent	Alcohol	Yield (%)
1	**4a**		**5a** (Rf = C_6F_{13}): 87
2	**4b**		**5b** (Rf = C_8F_{17}): 85
3	**4b**		**5b** (Rf = C_8F_{17}): 85[b]
4	**4c**	Methyl α-D-glucopyranoside	**5c** (Rf = $C_{10}F_{21}$): 94
5	**4a**		**6a** (Rf = C_6F_{13}): 95
6	**4b**		**6b** (Rf = C_8F_{17}): 88
7	**4c**	Methyl α-D-galactopyranoside	**6c** (Rf = $C_{10}F_{21}$): 67

[a] Na_2SO_4 (200 mg) as a dehydrating reagent was added to ^{F}benzaldehydes **4a**–**c** (200 mg).
[b] Recovered ^{F17}benzaldehyde **4b** of entry 2 in Table 2 was used.

Table 2. Deprotection of ^{F}benzylidene acetal groups



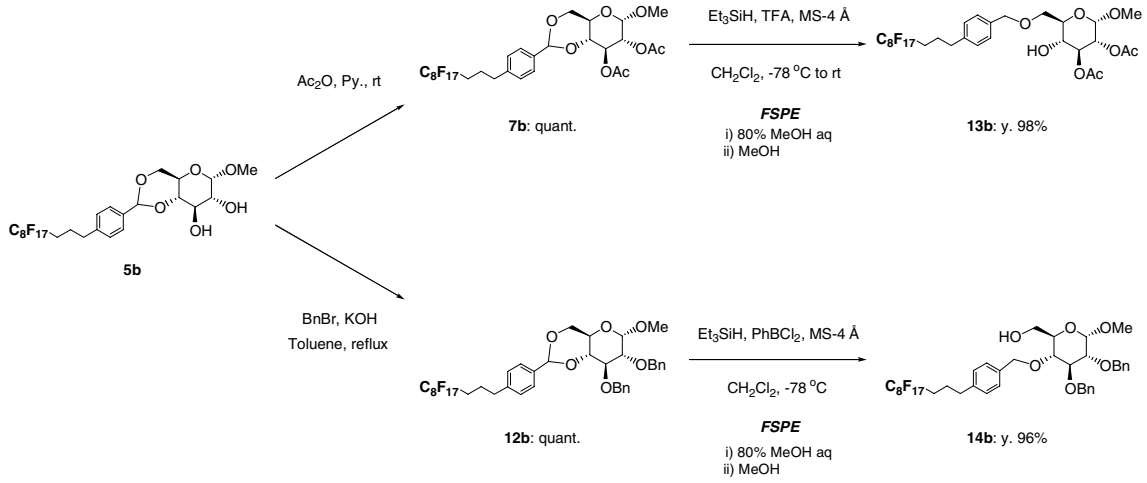
Entry	Substrate	Reaction condition	Yield (%)		
			Alcohol		Fluorous compound
1	**7a** (D-Gluco)	90% aq AcOH, rt	**9**: quant.[a]		**4a** (Rf = C_6F_{13}): quant.[a]
2	**7b** (D-Gluco)	90% aq AcOH, rt	**9**: quant.	**9**	**4b** (Rf = C_8F_{17}): quant.
3	**7c** (D-Gluco)	90% aq AcOH, rt	**9**: quant.		**4c** (Rf = $C_{10}F_{21}$): quant.
4	**8a** (D-Galacto)	10% Pd–C, H_2 gas/EtOAc, rt	**10**: 99[a]		**11a** (Rf = C_6F_{13}): 88[a]
5	**8b** (D-Galacto)	10% Pd–C, H_2 gas/EtOAc, rt	**10**: 91	**10**	**11b** (Rf = C_8F_{17}): 87
6	**8c** (D-Galacto)	10% Pd–C, H_2 gas/EtOAc, rt	**10**: 94		**11c** (Rf = $C_{10}F_{21}$): 88

[a] The crude product was loaded onto a fluorous reverse-phase silica gel column and then the column was eluted successively with 70% aq MeOH and MeOH.

deprotected alcohol **10** was obtained in high yields from the 80% aq MeOH fraction, and fluorous toluenes **11a–c** were obtained from the MeOH fraction in 88%, 87% and 88% yields, respectively (entries 4–6). The lower boiling point of **11a–c** must have resulted in the lower recoveries compared to those of **4a–c**.[17] The conversion of ^{F}toluenes **11a–c** into ^{F}benzaldehydes **4a–c** for reuse is now in progress.

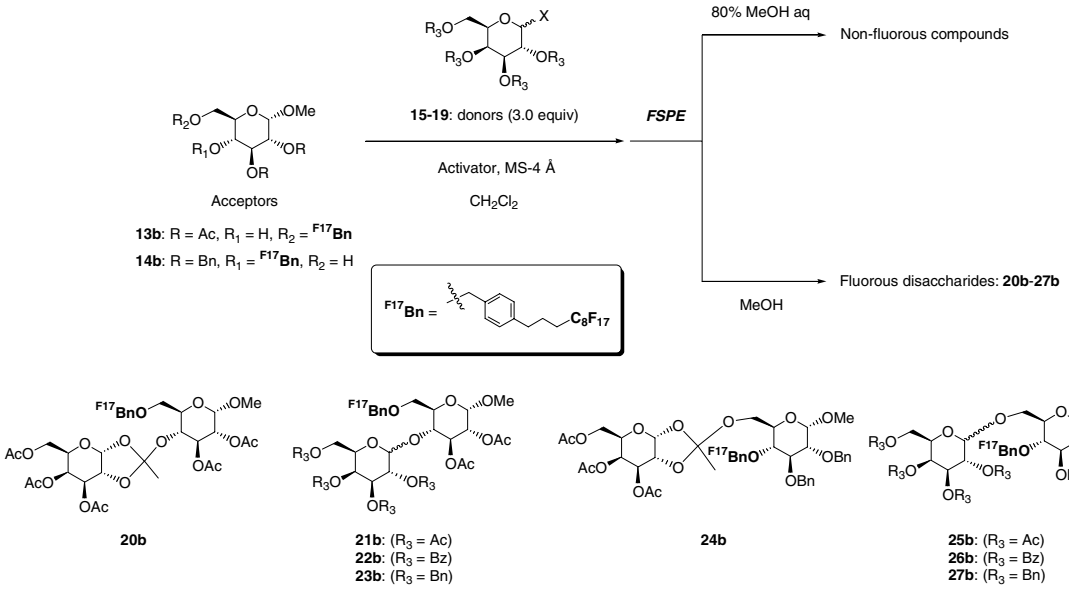
As mentioned above, the regioselective ring opening of the benzylidene acetal group is very useful in carbohydrate chemistry. Therefore, we examined the reductive cleavage of 4,6-*O*-^{F17}benzylidene acetal group into the ^{F17}benzyl group using Et_3SiH-TFA[12a] or $PhBCl_2$[12b] (Scheme 2). When TFA was used as an acid, compound **7b** was converted into the corresponding 6-*O*-^{F17}benzyl-4-*O*-hydroxyl derivative **13b** in 98% yield. On the other hand, using $PhBCl_2$ as an acid, the corresponding 4-*O*-^{F17}benzyl-6-*O*-hydroxyl derivative **14b** was obtained in 96% yield. The isolation of these ^{F17}Bn-protected products (**13b** and **14b**) by FSPE was very easy and quick.

Using **13b** and **14b** as acceptors, we tried to synthesize disaccharides by Schmidt's trichloroacetoimidate[18] and thioglycoside[19] methods. The results of the 4-*O*-glycosidation are shown in Table 3 (entries 1–6). Unexpectedly, the glycosidation of **13b** with galactosyl trichloroacetoimidate **15**[20] in the presence of a catalytic amount of TMSOTf (0.1 equiv) in anhydrous CH_2Cl_2 gave sugar–sugar orthoester **20b**[21] in 92% yield (entry 1). However, the desired disaccharide **21b** was obtained in 75% yield (β only) when 0.25 equiv of TMSOTf was used (entry 2). To avoid the formation of the orthoester,



Scheme 2. Regioselective ring opening reaction of the ^{F17}benzylidene acetal group with Et_3SiH-TFA or $PhBCl_2$.

Table 3. Glycosidation of acceptors **13**–**14b** with various donors **15**–**19**



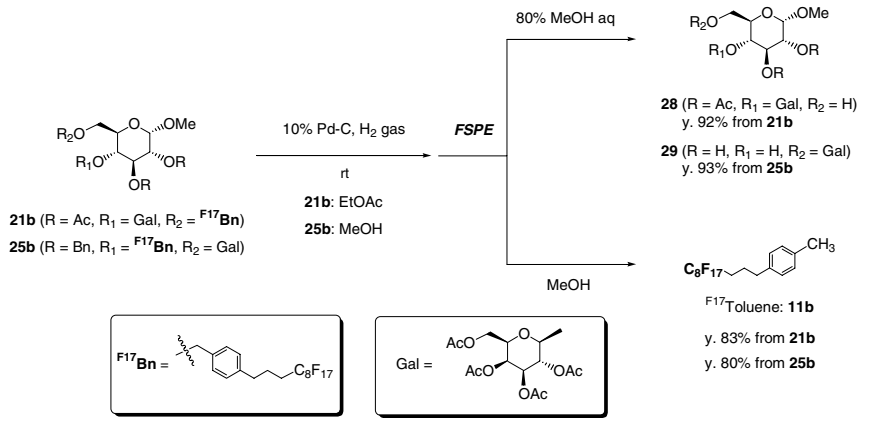
Entry	Acceptor	Donor		Activator	Reaction temperature	Yield (%)
		X	R_3			
1	**13b**	**15**: $OC(NH)CCl_3$	Ac	TMSOTf (0.1 equiv)	−20 °C	**20b**: 92
2		**15**: $OC(NH)CCl_3$	Ac	TMSOTf (0.25 equiv)	−40 °C then 0 °C	**21b**: 75 (β only)[a,b]
3		**16**: $OC(NH)CCl_3$	Bz	TMSOTf (0.25 equiv)	−40 °C then rt	**22b**: 73 (β only)[a]
4		**17**: $OC(NH)CCl_3$	Bn	TMSOTf (0.1 equiv)	−40 °C	**23b**: 86 (α/β = 10:1)[c]
5		**18**: SPh	Ac	TfOH (0.3 equiv)/NIS (4.0 equiv)	−20 °C	**21b**: 64 (β only)[a,b]
6		**19**: SPh	Bz	TfOH (0.3 equiv)/NIS (4.0 equiv)	−20 °C	**22b**: 75 (β only)[a]
7	**14b**	**15**: $OC(NH)CCl_3$	Ac	TMSOTf (0.1 equiv)	−20 °C	**24b/25b**: 94 (4:1)[c]
8		**15**: $OC(NH)CCl_3$	Ac	TMSOTf (0.25 equiv)	−40 °C then 0 °C	**25b**: 50 (β only)[c,d]
9		**16**: $OC(NH)CCl_3$	Bz	TMSOTf (0.25 equiv)	−40 °C then rt	**26b**: 70 (β only)[c]
10		**17**: $OC(NH)CCl_3$	Bn	TMSOTf (0.1 equiv)	−40 °C	**27b**: quant. α/β = 1:1[c]
11		**17**: $OC(NH)CCl_3$	Bn	TMSOTf (0.1 equiv)	−40 °C	**27b**: quant. α/β = 1:10[c,d]
12		**18**: SPh	Ac	TfOH (0.3 equiv)/NIS (4.0 equiv)	−20 °C	**25b**: 36 (β only)[a,e]
13		**19**: SPh	Bz	TfOH (0.3 equiv)/NIS (4.0 equiv)	−20 °C	**26b**: quant. (98)[f] (β only)[c]

[a] After separated by FSPE, purified by flash column chromatography.
[b] Acceptor **13b** resulting from rearrangement of sugar–sugar orthoester intermediate was isolated.[21b–d]
[c] Determined by ^1H NMR spectrum.
[d] CH_3CN was used instead of CH_2Cl_2.
[e] 6-*O*-Acetylated derivative of acceptor **14b** resulting from rearrangement of sugar–sugar orthoester was isolated.[21b–d]
[f] Isolated yield.

perbenzoylated galactosyl imidate **16**[22] was reacted with acceptor **13b** under similar reaction conditions to give the corresponding disaccharide **22b** (β only) in 73% yield (entry 3). In order to improve the yield of the disaccharide, perbenzylated galactosyl imidate **17**[23] was reacted with acceptor **13b** in the presence of catalytic amounts of TMSOTf (0.1 equiv) to give disaccharide **23b** (α/β = 10:1) in 86% yield (entry 4). Glycosidation of **13b** with thioglycoside **18**[24] and **19**[25] in the presence of *N*-iodosuccinimide (NIS, 4.0 equiv) and trifluoromethansulfonic acid (TfOH, 0.3 equiv) in CH_2Cl_2 at −20 °C smoothly gave the corresponding disaccharides **21b** and **22b** in 64% and 75% yields, respectively (entries 5 and 6). Similarly, the results of the 6-*O*-glycosidation are shown in Table 3 (entries 7–13). The glycosidations of **14b** with perbenzylated imidate **17** and thiogalactoside **19** gave disaccharides **27b** (α/β = 1:1) and **26b** (β only), respectively, in excellent yields (entries 10 and 13). When CH_3CN was used instead of CH_2Cl_2, the anomeric stereoselectivity was dramatically changed to α/β = 1:10 (entry 11).[26] The glycosidation of peracetylated imidate **15** and thioglycoside **18** gave the corresponding disaccharide **25b** in 50% and 36% yields, respectively, together with 6-*O*-acetylated derivative of acceptor **14b** resulting from a rearrangement of sugar–sugar orthoester **24b** (entries 8 and 12).[21b–d]

Finally, we examined deprotection of the ^{F17}Bn group of disaccharide **21b** and **25b** (Scheme 3). Compounds **21b** and **25b** were hydrogenated with 10% Pd–C in EtOAc and MeOH, respectively. After purification of the crude products by FSPE, disaccharides **28** and **29** were obtained in excellent yields from 80% aq MeOH fractions and fluorous toluene **11b** was recovered in 83% and 80% yields, respectively, from MeOH fractions.

In conclusion, we have developed a new fluorous benzylidene acetal protecting group of polyhydroxy com-



Scheme 3. Deprotection of ^{F17}benzyl group with 10% Pd–C.

pounds. It was attached and detached under common reaction conditions for a non-fluorous benzylidene acetal group. Using the fluorous acceptors, disaccharides were synthesized under traditional reaction conditions. The isolation of the fluorous intermediates by FSPE was very easy and quick, although the fluorine atom content was just about 21% at the final stage. The fluorous compounds were also purified by standard silica gel column chromatography, if necessary. Considering these attributes, the ^{F}benzylidene acetal groups may find valuable and versatile use in carbohydrate synthesis. Optimization of the glycosidation conditions and further application to syntheses of several bioactive carbohydrates are now in progress.

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