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<td>Author(s)</td>
<td>Kobayashi, Shingo; Yoneda, Atushi; Fukuhara, Tsuyoshi; Hara, Shoji</td>
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Deoxyfluorination of alcohols using
N,N-diethyl-α,α-difluoro-(m-methylbenzyl)amine

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Abstract: Deoxyfluorination of alcohols was carried out using
N,N-diethyl-α,α-difluoro-(m-methylbenzyl)amine (DFMBA). Primary alcohols were
effectively converted to fluorides under microwave irradiation or conventional heating.
Deoxyfluorination of an anomeric hydroxy group in sugars by DFMBA proceeded at
below room temperature and glycosyl fluorides could be obtained in good yields. The
deoxyfluorination reaction chemoselectively proceeded and various protecting groups
on the sugar can survive under the reaction conditions.

1. Introduction

Deoxyfluorination reaction of alcohols is useful for the synthesis of organo fluorine
compounds, and diethylaminosulfur trifluoride (DAST) has been the most frequently
used.1 Recently, α-fluoroamines, such as 2,2-difluoro-1,3-dimethylimidazolidine
(DFI),2 have been reevaluated as thermally stable deoxyfluorination reagents.
N,N-Dimethyl-α,α-difluorobenzylamine was also used for the deoxyfluorination
reaction of simple alcohols.3 However, due to the mild reactivity of the reagent,
relatively high reaction temperature was required to convert butanol to butyl fluoride.
In order to apply the reagent for the deoxyfluorination of more complex alcohols, higher
reaction temperature would be required and its thermal stability was problematic.4
Quite recently, a similar fluoroamine, N,N-diethyl-α,α-difluoro(m-methylbenzyl)amine
(DFMBA, 1), was reported to have high thermal stability (ARC 180 °C)6 and we
successfully used DFMBA for the deoxyfluorination reaction of sugars.7 We wish to
report here details of the deoxyfluorination reaction of various alcohols using DFMBA.

Keywords: Deoxyfluorination; DFMBA; Fluoro sugars; Microwave.
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2. Result and discussion

2.1. Fluorination of alcohols using DFMBA

DFMBA is a colorless liquid and can be conveniently prepared from the corresponding amide in two steps through a chloroiminium salt.\(^6\) It slowly reacted with 1-dodecanol (2a) at room temperature to give 1-dodecyl fluoride (3a) in 12% yield after 17 h and most of 2a remained as an ester (4a) (Eq 1). Under reflux in heptane, the fluorination reaction was completed in 1 h to give 3a in good yield. Recently, microwave irradiation is reported to be effective to complete the thermal reaction in short time, and we applied the microwave irradiation to the reaction.\(^8\) The reaction was carried out using a modified household microwave oven. In an acetonitrile or without a solvent, the reaction mixture was refluxed vigorously under the irradiation of microwave and the reaction was completed in 10 min to give 3a in good yields. However, a dark tarry material was also formed. Both DFMBA and acetonitrile can absorb microwave energy very well and the reaction mixture could reach a high temperature. As it is difficult to control the reaction temperature in the household oven, we used a hydrocarbon solvent which does not absorb microwave energy well.\(^8\) Though the reaction mixture was refluxed vigorously even in heptane under microwave irradiation, the formation of the tarry material was not observed and 3a was obtained in good yield in 10 min (Table 1).

\[
\text{C}_{12}\text{H}_{25}-\text{OH} \quad + \quad \text{NEt}_2 \quad \text{FF} \quad \text{C}_{12}\text{H}_{25}-\text{OH} \quad \longrightarrow \quad \text{C}_{12}\text{H}_{25}-\text{F} \quad + \quad \text{COOC}_{12}\text{H}_{25} (1)
\]
<table>
<thead>
<tr>
<th>React. temp.</th>
<th>React. Time</th>
<th>Solvent</th>
<th>Yield of 3a (%)\textsuperscript{b}</th>
<th>Yield of 4a (%)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 °C</td>
<td>17 h</td>
<td>Heptane</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>98 °C</td>
<td>10 min</td>
<td>Heptane</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>98 °C</td>
<td>1 h</td>
<td>Heptane</td>
<td>86</td>
<td>trace</td>
</tr>
<tr>
<td>MW</td>
<td>10 min</td>
<td>CH\textsubscript{3}CN</td>
<td>83</td>
<td>trace</td>
</tr>
<tr>
<td>MW</td>
<td>10 min</td>
<td>Heptane</td>
<td>85</td>
<td>trace</td>
</tr>
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</table>

\textsuperscript{a) The reaction was carried out using 1.2 eqv. of 1 to 2a.}\n\textsuperscript{b) Isolated yield based on 2a.}\n\textsuperscript{c) GC yield.}

The deoxyfluorination reaction of various alcohols was carried out using 1 as shown in Table 2. Under the microwave irradiation, primary alcohols 2b, c, d, h, i could be converted to the corresponding fluorides 3b, c, d, h, i in good yields without the formation of olefinic by-products or the esters 4, and the functional groups, such as the double bond 2b, ether 2c and ester group 2i, remained unchanged. On the other hand, secondary alcohols 2e, f, g were converted to the corresponding fluorides in moderate yields and olefinic by-products were also formed (8 - 40%). A benzylic alcohol 2j is more reactive than the others, and it could be converted to the fluoride 3j in high yield without the microwave irradiation.
The proposed reaction mechanism is as follows. The alcohol 2 reacts with DFMBA 1 to give an adduct. This step is fast even at room temperature and hydrolysis at this stage gives ester 4. A fluoride attacks the alkyl group of the alcohol to give alkyl fluoride 3 and an amide. This step is slow, and heating or the microwave irradiation is required to complete the reaction (Scheme 1).
2.2. Deoxyfluorination of sugars using DFMBA

Fluorinated carbohydrates have recently received much attention because of their important role in the study of enzyme-carbohydrate interactions as well as their interesting biological activities, and we applied DAST to the fluorinated carbohydrate synthesis. The reaction of methyl 2,3-O-isopropylidene-β-D-ribofuranose (5b) with DAST was previously reported to cause migration of a methoxy group from 1- to 5-position, and an unexpected 5-O-methyl-2,3-O-isopropylidene-β-D-ribofuranosyl fluoride (7) was obtained instead of the desired 5-deoxy-5-fluoro derivative (6b). In the reaction of 5b with DAST under the microwave irradiation, the desired 6b could be obtained in 51% yield but 7 was also formed in 20% yield. Under the microwave irradiation conditions, it was difficult to control the reaction temperature and selectivity, and we examined the reaction under conventional thermal heating conditions. The fluorination reaction was slow under the thermal conditions, and 6a was obtained only in 28% yield at 98 °C in 3 h. Moreover, migration of the methoxy group also took place under the thermal conditions. In order to accelerate the fluorination at the 5-position of 5b, we added spray dry KF as a fluoride source and used a polar solvent, dioxane, to dissolve the KF. By carrying out the reaction at 100 °C for 16 h, migration of the methoxy group could be prevented and 6b could be selectively obtained in 67% yield (Eq. 2).
Similarly, an α-isomer (6e) could be stereospecifically obtained in 63% yield from an α-ribofuranose derivative (5c) (Table 3). Under the same conditions, 1,2,3,4-tetra-\(O\)-acetyl-\(\alpha\)-D-glucopyranose (5d) could be converted to 1,2,3,4-tetra-\(O\)-acetyl-6-deoxy-6-fluoro-\(\alpha\)-D-glucopyranose (6d) in 68 % yield. The conversion of 1,2;3,4-di-\(O\)-isopropylidene-\(\alpha\)-D-galactopyranose (5a) to the corresponding fluoride (6a) could be achieved in 20 min under the microwave irradiation without affecting an acetonide protecting group. DFMBA 1 can be also used for the deoxyfluorination of nucleosides, and 2',3'-\(O\)-isopropylideneuridine (5e) could be converted to a 5'-deoxy-5'-fluorouridine derivative (6e) in 55% yield without migration of an uracil ring under the microwave irradiation.11
### Table 3. Deoxyfluorination of hydroxy groups in sugars and a nucleoside using DFMBA $^{1a}$

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield, %$^b$</th>
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<tr>
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<td>MW 20 min heptane</td>
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<td>70</td>
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<tr>
<td><img src="image" alt="Structure 5b" /></td>
<td>100 °C 16 h dioxane</td>
<td><img src="image" alt="Structure 6b" /></td>
<td>67$^c$</td>
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<tr>
<td><img src="image" alt="Structure 5c" /></td>
<td>100 °C 24 h dioxane</td>
<td><img src="image" alt="Structure 6c" /></td>
<td>63$^c$</td>
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<tr>
<td><img src="image" alt="Structure 5d" /></td>
<td>100 °C 6 h dioxane</td>
<td><img src="image" alt="Structure 6d" /></td>
<td>68$^c$</td>
</tr>
<tr>
<td><img src="image" alt="Structure 5e" /></td>
<td>MW 10 min heptane</td>
<td><img src="image" alt="Structure 6e" /></td>
<td>55</td>
</tr>
</tbody>
</table>

a) If otherwise not mentioned, 2 eqiv. of 1 to substrate was used. b) Isolated yield based on substrate used. c) 4 eq of KF and 2.5 eqiv. of 1 to substrate were used.

### 2.3. Glycosyl fluorides synthesis using DFMBA

Glycosyl fluorides have been used as a key compound for polysaccharides synthesis and many reagents have been developed for their synthesis from the corresponding sugars.$^{12}$
The hydroxy group of the sugars at the 1-position is highly reactive and even HF can be used for the conversion of the sugars to glucosyl fluorides. However, some protecting groups of sugars are sensitive to acidic reagents, and mild reagents for the synthesis of glycosyl fluorides have been desired. Various sugars having protecting groups such as acetonide (8a, d, e), benzyl ether (8b), acetate (8c) and, silyl ether (8d) reacted with 1 at below room temperature quickly without affecting the protecting groups to give the corresponding glycosyl fluorides in good yields as shown in Table 4. Moreover, the hydroxy groups at other than the 1-position were not converted to the fluoride by 1 at below room temperature, and, therefore, the glycosyl fluoride synthesis can be carried out without protection of the hydroxy groups. For instance, 2,3-O-isopropylidene-D-ribofuranose (8e) reacted with 2.4 eq of 1 at 0 °C to give 2,3-O-isopropylidene-5-O-methylbenzoyl-D-ribofuranosyl fluoride (9e) in 70% yield. Under the reaction conditions, only the hydroxy group at the 1-position was selectively deoxyfluorinated and the hydroxy group at the 5-position was only acylated. Furthermore, D-xylopyranose (8f), having four free hydroxy groups, can be directly converted to 2,3,4-tri-O-methylbenzoyl-D-xylopyranosyl fluoride (9f) in 60% yield by the reaction with 8 eq of 1. In most of the cases, selectivity for α- or β-isomers was not observed and a mixture of both isomers was obtained regardless of the stereochemistry of the starting materials. Therefore, the reaction proceeds not via an S_N2 mechanism but through an oxonium intermediate. In the cases of a glucose (8c) and a xylose derivative (8f), the β-isomers (9c and 9f) were selectively formed by the neighboring-group participation of the acyloxy groups at the 2-position.
Table 4. Deoxyfluorination of hydroxy groups at 1-position in sugars using DFMBA 1

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield, %b</th>
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<tr>
<td><img src="image" alt="Diagram 8a" /></td>
<td><img src="image" alt="Diagram 9a" /></td>
<td>α : β = 43 : 57</td>
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<tr>
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<td><img src="image" alt="Diagram 9b" /></td>
<td>α : β = 40 : 60</td>
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<tr>
<td><img src="image" alt="Diagram 8c" /></td>
<td><img src="image" alt="Diagram 9c" /></td>
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</tr>
<tr>
<td><img src="image" alt="Diagram 8d" /></td>
<td><img src="image" alt="Diagram 9d" /></td>
<td>α : β = 75:25</td>
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<tr>
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<td><img src="image" alt="Diagram 9e" /></td>
<td>α : β = 70:30</td>
</tr>
<tr>
<td><img src="image" alt="Diagram 8f" /></td>
<td><img src="image" alt="Diagram 9f" /></td>
<td>β only</td>
</tr>
</tbody>
</table>

a) If otherwise not mentioned, the reaction was carried out in CH2Cl2 at room temperature for 1 h with 1.2 eqiv. of 1. b) Isolated yield based on sugar used. c) The reaction was carried out without solvent. d) The reaction was carried out at 0 °C. e) 2.4 eqiv. of 1 to sugar was used. f) The reaction was carried out for 12 h using 8 eqiv. of 1.

3. Experimental

3.1. General
The IR spectra were recorded using a JASCO FT/IR-410. The \(^1\)H NMR (400MHz), \(^{19}\)F NMR (376MHz), and \(^{13}\)C NMR (100 MHz) spectra were recorded in CDCl\(_3\) on a JEOL JNM-A400II FT NMR and the chemical shift, \(\delta\), are referred to TMS (\(^1\)H, \(^{13}\)C) and CFCl\(_3\) (\(^{19}\)F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. A commercially available GoldStar microwave oven (500W, MW-JIK96H5) was modified to accept a port for connecting a reactor to a reflux condenser located outside the oven.\(^{15}\) A hole of 10 mm diameter was drilled in the oven top and an 80 mm length of Teflon™ PFA tube was snugly fitted into the hole. A reflux condenser located outside was connected to the port tightly and another side of the port in the oven was used to connect to a reactor which is a Teflon™ PFA tube with a diameter of 10 mm and a length of 80 mm sealed at one end. DFMBA 1 was obtained from Mitsubishi Gas Chemical Company Inc. and used without further purification. Though handling 1 with glassware is possible, it is recommended to use equipment made of Teflon™. As 1 is slightly moisture-sensitive, it should be handled as quickly as possible in air and kept in a Teflon™ bottle with a tight screw cap. Alcohols 2d, 2e were prepared from 1,2-dodecene oxide by the reaction with Et\(_3\)N-3HF.\(^{16}\) Sugar derivatives 5a, 5d, 8a were purchased from Sigma-Aldrich Co. and 8b, 8f were obtained from Junsei Chemical Co. Ltd. Other derivatives 5b,\(^ {17}\) 5c,\(^ {17}\) 5e,\(^ {18}\) 8c,\(^ {19}\) 8d,\(^ {20}\) 8e\(^ {21}\) were prepared from the corresponding sugars or nucleocide according to the literature. The spray dry KF was obtained from Morita Chemical Industries Co. Ltd. and dried before use under the condition of 100 °C / 0.01 mHg for 1 h.

3.2. Fluorination of alcohols using DFMBA

3.2.1. Preparation of 1-fluorododecane (3a).\(^ {22}\) Into a reactor consisting of a Teflon™ PFA tube with a diameter of 10 mm sealed at one end, were introduced heptane (1 ml), 1 (256 mg, 1.2 mmol), and 2a (186 mg, 1.0 mmol). The open end of the reactor was connected to a port in a microwave oven and the port was connected to a reflux condenser located outside the oven. Then, the reaction mixture was submitted to microwave irradiation for 10 min. During the irradiation, the reaction mixture was refluxed vigorously. After the reaction, the reaction mixture was poured into aq
NaHCO₃ and extracted with ether three times. The combined ethereal layers were dried over MgSO₄, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane) gave 1-fluorododecane 3a (165 mg, 0.88 mmol) in 88% yield.

IR (neat): 2925, 2855, 1466, 1389, 1050, 1010 cm⁻¹. ¹H NMR δ = 4.44 (2H, dt, J = 47.3, 6.3 Hz), 1.74 - 1.64 (2H, m), 1.39 - 1.26 (18H, m), 0.88 (3H, t, J = 6.7 Hz). ¹³C NMR δ = 14.07 (1C, s), 22.71 (1C, s), 25.19 (1C, d, J = 5.0 Hz), 29.29 (1C, s), 29.39 (1C, s), 29.56 (1C, s), 29.60 (1C, s), 29.67 (1C, s), 29.69 (1C, s), 30.46 (1C, d, J = 19.0 Hz), 31.96 (1C, s), 84.11 (1C, d, J = 163.8 Hz). ¹⁹F NMR δ = -218.36 - -218.75 (1F, m). HRMS (EI) Calcd for C₁₂H₂₅F (M⁺) 188.1940. Found 188.1942.

3.2.2. 1-Fluoro-10-undecene (3b).²³ IR (neat): 2927, 2855, 1641, 1465 cm⁻¹. ¹H NMR δ = 5.86 - 5.76 (1H, m), 5.02 - 4.91 (2H, m), 4.44 (2H, dt, J = 47.3, 6.1 Hz), 2.07 - 2.01 (2H, m), 1.75 - 1.63 (2H, m), 1.39 - 1.29 (12H, m). ¹³C NMR δ = 25.13 (1C, d, J = 4.9 Hz), 28.90 (1C, s), 29.08 (1C, s), 29.21 (1C, s), 29.37 (1C, s), 29.45 (1C, s), 30.40 (1C, d, J = 19.0 Hz), 33.78 (1C, s), 84.15 (1C, d, J = 164.6 Hz), 114.09 (1C, s), 139.13 (1C, s). ¹⁹F NMR δ = -218.37 - -218.75 (1F, m). HRMS (EI) Calcd for C₁₁H₂₁F (M⁺) 172.1627. Found 172.1631.

3.2.3. 2-Benzyl oxyethyl fluoride (3c).²³ IR (neat): 3031, 2952, 2862, 1496, 1454, 1358 cm⁻¹. ¹H NMR δ = 7.36 - 7.28 (5H, m), 4.60 (2H, s), 4.59 (2H, dt, J = 47.6, 4.2 Hz), 3.72 (2H, dt, J = 29.3, 4.2 Hz). ¹³C NMR δ = 69.12 (1C, d, J = 19.8 Hz), 73.31 (1C, s), 83.09 (1C, d, J = 168.7 Hz), 127.71 (2C, s), 127.73 (1C, s), 128.41 (2C, s), 137.77 (1C, s). ¹⁹F NMR δ = -223.43 - -223.84 (1F, m). HRMS (EI) Calcd for C₉H₁₁OF (M⁺) 154.0794. Found 154.0786.

3.2.4. 1,2-Difluorododecane (3d).²⁴ IR (neat) 2926, 2855, 1467, 1042 cm⁻¹. ¹H NMR δ = 4.79 - 4.34 (3H, m), 1.74 - 1.26 (18H, m), 0.88 (3H, t, J = 6.8 Hz). ¹³C NMR δ = 14.09 (1C, s), 15.26 (1C, s), 22.67 (1C, s), 24.74 (1C, d, J = 5.0 Hz), 29.31 (1C, s), 29.39 (1C, s), 29.53 (1C, d, J = 5.8 Hz), 30.02 (1C, dd, J = 20.7, 6.6 Hz), 31.88 (1C, s), 65.84 (1C, s), 84.16 (1C, dd, J = 173.7, 23.2 Hz), 91.85 (1C, dd, J = 172.0, 19.0 Hz). ¹⁹F NMR δ = -189.18 - -189.60 (1F, m), -230.19 - -230.54 (1F, m).
3.2.5. 2-Fluorododecane (3f). $^{25}$ IR (neat) 2926, 2855, 1466, 1384, 1130 cm$^{-1}$. $^1$H NMR $\delta = 4.65$ (dm, 1H, $J = 50.5$ Hz), 1.71 - 1.26 (20H, m), 0.88 (3H, t, $J = 6.8$ Hz). $^{13}$C NMR $\delta = 14.10$ (1C, s), 20.99 (1C, d, $J = 23.2$ Hz), 22.69 (1C, s), 25.09 (1C, d, $J = 5.0$ Hz), 29.57 (1C, s), 29.33(1C, s), 29.47(1C, s), 29.55 (1C, s), 29.60 (1C, s), 31.91 (1C, s), 36.95 (1C, d, $J = 20.7$ Hz), 91.06 (1C, d, $J = 164.6$ Hz). $^{19}$F NMR $\delta = -172.45$ - -172.89 (1F, m).

3.2.6. 7-Fluorotridecane (3g). IR (neat) 2932, 2859, 1467 cm$^{-1}$. $^1$H NMR $\delta = 4.46$ (1H, dm, $J = 49.3$ Hz), 1.29 - 1.67 (20H, m), 0.89 (6H, t, $J = 6.7$ Hz). $^{13}$C NMR $\delta = 14.05$ (2C, s), 22.60 (2C, s), 25.13 (2C, d, $J = 5.0$ Hz), 29.22 (2C, s), 31.78 (2C, s), 35.22 (2C, d, $J = 20.7$ Hz), 94.53 (1C, d, $J = 167.1$ Hz). $^{19}$F NMR $\delta = -180.76$ - -180.38 (m, 1F). HRMS (EI) Calcd for C$_{13}$H$_{26}$ (M$^+$-HF) 182.2035. Found 182.2027.

3.2.7. 1, 12-Difluorododecane (3h). $^{23}$ IR (neat) 2928, 2855, 1467, 1390 cm$^{-1}$. $^1$H NMR $\delta = 4.49$ (4H, dt, $J = 47.3$, 6.3 Hz), 1.75 - 1.62 (4H, m), 1.55 - 1.28 (16 H, m). $^{13}$C NMR $\delta = 25.13$ (2C, d, $J = 5.0$ Hz), 29.22 (2C, s), 29.48 (4C, s), 30.39 (2C, d, $J = 19.9$ Hz), 84.17 (2C, d, $J = 163.8$ Hz). $^{19}$F NMR $\delta = -218.38$ - -218.77 (m, 2 F). HRMS (EI) Calcd for C$_{12}$H$_{24}$F$_2$ (M$^+$) 206.1846. Found 206.1843.

3.2.8. Butyl 5-fluoropentanoate (3i). IR (neat) 2962, 1736, 1172 cm$^{-1}$. $^1$H NMR $\delta = 4.46$ (2H, dt, $J = 47.6$, 5.6 Hz), 4.08 (2H, t, $J = 6.6$ Hz), 2.36 (2H, t, $J = 6.3$ Hz), 1.80 - 1.71 (4H, m), 1.65 - 1.56 (2H, m), 1.43 - 1.33 (2H, m), 0.94 (3H, t, $J = 7.4$ Hz). $^{13}$C NMR $\delta = 13.58$ (1C, s), 19.04 (1C, s), 20.77 (1C, d, $J = 5.0$ Hz), 29.69 (1C, d, $J = 19.9$ Hz), 30.58 (1C, s), 33.64 (1C, s) 64.14 (1C, s) 83.47 (1C, d, $J = 165.4$ Hz), 173.25 (1C, s). $^{19}$F NMR $\delta = -219.25$ - -219.66 (m, 1F). HRMS (EI) Calcd for C$_9$H$_{17}$O$_2$F (M$^+$) 176.1213. Found 176.1216.

3.2.9. Preparation of $p$-bromobenzyl fluoride (3j). $^{26}$ DFMBA (256 mg, 1.5 mmol), $p$-bromobenzyl alcohol (187 mg, 1.0 mmol), and CHCl$_3$ (2 ml) were introduced into a reaction vessel made of Teflon™ PFA with a tight screw cap and kept at 50 °C for 2 h in an oil bath. The mixture was poured into aq NaHCO$_3$ and extracted with ether three times. The combined ethereal layers were dried over MgSO$_4$, concentrated under
reduced pressure. Purification by column chromatography (silica gel/hexane-Et2O) gave 3j in 95% yield; IR (neat) 2961, 1593, 1487, 1374, 1213, 1071, 1011 cm⁻¹. ¹H NMR δ = 7.52 (2H, d, J = 7.3 Hz), 7.24 (2H, d, J = 7.3 Hz), 5.33 (2H, d, J = 47.6 Hz). ¹³C NMR δ = 83.71 (1C, d, J = 167.1 Hz), 122.75 (2C, d, J = 3.3 Hz), 129.0 (2C, d, J = 5.8 Hz), 131.73 (1C, s), 135.13 (1C, d, J = 18.2 Hz). ¹⁹F NMR δ = -208.64 (1F, t, J = 47.6 Hz).

3.3. Deoxyfluorination of sugars using DFMBA

3.3.1. 6-Fluoro-1,2;3,4-di-O-isopropylidene-6-deoxy-α-D-galactopyranose (6a). IR (neat) 2990, 1384, 1256, 1213, 1072 cm⁻¹. ¹H NMR δ = 5.56 (1H, d, J = 4.9 Hz), 4.65-4.48 (3H, m), 4.35 (1H, dd, J = 5.1, 2.4 Hz), 4.27 (1H, dd, J = 8.1, 2.0 Hz), 4.10-4.07 (1H, m), 1.55 (3H, s), 1.45 (3H, s), 1.34 (6H, s). ¹³C NMR δ = 24.39 (1C, s), 24.88 (1C, s), 25.9 (1C, s), 26.00 (1C, s), 66.60 (1C, d, J = 22.3 Hz), 70.39 (1C, s), 70.47 (1C, s), 70.55 (1C, s), 82.04 (1C, d, J = 167.9 Hz), 96.15 (1C, s), 108.78 (1C, s), 109.63 (1C, s). ¹⁹F NMR δ = -231.73 (1F, dt, J = 47.6, 14.0 Hz). HRMS (EI) Calcd for C₁₂H₁₉O₅F (M⁺) 262.1216. Found 262.1215.

3.3.2. Preparation of methyl 5-fluoro-2,3-O-isopropylidene-5-deoxy-β-D-ribofuranoside (6b). DFMBA (533 mg, 2.5 mmol), KF (232 mg, 4.0 mmol), 5b (204 mg, 1.0 mmol), and 1,4-dioxane (1 ml) were introduced into a reaction vessel made of Teflon™ PFA with a tight screw cap and kept at 100 °C for 16 h in an oil bath. After the reaction, the mixture was poured into aq NaHCO₃ and extracted with ether three times. The combined ethereal layers were dried over MgSO₄, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et₂O) gave 6b in 67% yield; IR (neat) 2941, 2837, 1458, 1383, 1212, 1090, 871 cm⁻¹. ¹H NMR δ = 4.99 (1H, d, J = 2.4 Hz), 4.71 (1H, d, J = 6.1 Hz), 4.60 (1H, d, J = 5.9 Hz), 4.39 (3H, dm, J = 37.8 Hz), 3.33 (3H, s), 1.50 (3H, s), 1.33 (3H, s). ¹³C NMR δ = 24.87 (1C, s), 26.37 (1C, s), 54.85 (1C, s), 81.00 (1C, d, J = 4.1 Hz), 82.91 (1C, d, J = 172.9 Hz), 84.36 (1C, s), 84.59 (1C, s), 85.05 (1C, s), 109.21 (1C, s). ¹⁹F NMR δ = -225.39 - -225.68 (1F, m). HRMS (EI) Calcd for C₉H₁₄O₄F (M⁺-H) 205.0876. Found 205.0869.
3.3.3. Methyl 5-fluoro-2,3-O-isopropylidene-5-deoxy-α-D-ribofuranoside (6c).\textsuperscript{28} IR (neat) 2939, 1371, 1215, 1098 cm\textsuperscript{-1}. $\text{^1}H$ NMR $\delta = 4.96$ (1H, s), 4.67 - 4.62 (2H, m), 4.58 (2H, dm, $J = 47.8$ Hz), 4.25 (1H, dm, $J = 30.7$ Hz), 3.51 (3H, s), 1.58 (3H, s), 1.37 (3H, s). $\text{^{13}}C$ NMR $\delta = 25.56$ (1C, s), 25.89 (1C, s), 56.14 (1C, s), 79.71 (1C, d, $J = 26.5$ Hz), 79.66 (1C, s), 80.46 (1C, s), 83.18 (1C, d, $J = 172.0$ Hz), 103.17 (1C, s), 115.26 (1C, s). $\text{^{19}}F$ NMR $\delta = -232.72$ (1F, dt, $J = 47.8, 30.7$ Hz).

3.3.4. 1,2,3,4-Tetra-O-acetyl-6-deoxy-6-fluoro-α-D-glucopyranose (6d).\textsuperscript{29} Mp 122-125 °C (lit\textsuperscript{26} 128-129 °C). IR (KBr) 2959, 1757, 1370, 1217, 1079, 1038 cm\textsuperscript{-1}. $\text{^1}H$ NMR $\delta = 5.74$ (1H, d, $J = 8.1$ Hz), 5.32 - 5.11 (3H, m), 4.60 - 4.37 (2H, m), 3.89 - 3.79 (1H, m), 2.12 (3H, s), 2.06 (3H, s), 2.04 (3H, s), 2.03 (3H, s). $\text{^{13}}C$ NMR $\delta = 25.55$ (1C, s), 20.76 (1C, s), 67.46 (1C, d, $J = 6.6$ Hz), 70.11 (1C, s), 72.70 (1C, s), 73.20 (1C, s), 80.61 (1C, s), 91.55 (1C, s), 168.95 (1C, s), 169.15 (1C, s), 169.28 (1C, s), 170.12 (1C, s). $\text{^{19}}F$ NMR $\delta = -232.73$ (1F, dt, $J = 47.0, 22.6$ Hz).

3.3.5. 5'-Fluoro-2',3'-O-isopropylidene-5'-deoxyuridine (6e).\textsuperscript{30} IR (neat) 2990, 1687, 1437, 1382, 1274, 1082 cm\textsuperscript{-1}. $\text{^1}H$ NMR $\delta = 9.18$ (1H, brs), 7.33 (1H, d, $J = 8.1$ Hz), 5.84 (1H, s), 5.76 (1H, d, $J = 8.1$ Hz), 4.94 - 4.88 (2H, m), 4.74 - 4.71 (1H, m), 4.62 - 4.59 (1H, m), 4.43 - 4.35 (1H, m), 1.60 (3H, s), 1.36 (3H, s). $\text{^{13}}C$ NMR $\delta = 25.15$ (1C, s), 27.02 (1C, s), 79.90 (1C, d, $J = 7.4$ Hz), 82.84 (1C, d, $J = 172.4$ Hz), 84.50 (1C, s), 85.62 (1C, d, $J = 18.2$ Hz), 93.73 (1C, s), 102.66 (1C, s), 114.57 (1C, s), 141.49 (1C, s), 150.19 (1C, s), 163.61 (1C, s). $\text{^{19}}F$ NMR $\delta = -229.973$ - -230.292 (1F, m). HRMS Calcd for C\textsubscript{12}H\textsubscript{15}N\textsubscript{2}O\textsubscript{5}F (M\textsuperscript{+}) 286.0965. Found 286.0965.

3.4. Glycosyl fluorides synthesis using DFMBA

3.4.1. Preparation of 2,3;5,6-di-O-isopropylidene-D-mannofuranosyl fluoride (9a).\textsuperscript{31} DFMBA (205 mg, 1.2 mmol), 8a (187 mg, 1.0 mmol), and CH\textsubscript{2}Cl\textsubscript{2} (2 ml) were introduced into a reaction vessel made of Teflon\textsuperscript{TM} PFA with a tight screw cap and the mixture was stirred at room temperature for 1 h. After the reaction, the mixture was poured into aq NaHCO\textsubscript{3} and extracted with ether three times. The combined ethereal layers were dried over MgSO\textsubscript{4}, concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane-Et\textsubscript{2}O) gave 9a in 90 % yield as a mixture of
α and β isomers in a ratio of 43:57.

(9a-α), IR (neat) 2989, 1374, 1212, 1130, 1070, 972, 849 cm⁻¹. ¹H NMR δ = 5.69 (1H, d, J = 59.5 Hz), 4.77 - 4.43 (2H, m), 4.43 - 4.38 (1H, m), 4.18 - 4.05 (3H, m), 1.46 (6H, s), 1.39 (3H, s), 1.35 (3H, s). ¹³C NMR δ = 24.49 (1C, s), 25.14 (1C, s), 25.80 (1C, s), 26.86 (1C, s), 66.64 (1C, s), 72.68 (1C, s), 78.56 (1C, s), 82.60 (1C, s), 84.72 (1C, d, J = 42.2 Hz), 109.39 (1C, s), 113.20 (1C, s), 113.64 (1C, d, J = 221.6 Hz). ¹⁹F NMR δ = -129.25 (1F, dd, J = 59.5, 6.7 Hz). HRMS (EI) Calcd for C₁₂H₁₉O₅F (M⁺+H) 263.1295. Found 263.1317.

(9a-β), Mp 113-114 °C (lit 31 114 - 115 °C). IR (neat) 2985, 1377, 1263, 1216, 1125, 1089, 1062, 1001, 846, 527 cm⁻¹. ¹H NMR δ = 5.51 (1H, dd, J = 3.7, 66.5 Hz), 4.87 - 4.84 (1H, m), 4.75 - 4.69 (1H, m), 4.50 - 4.46 (1H, m), 4.22 - 4.17 (1H, m), 4.11 (2H, d, J = 3.7 Hz), 1.57 (3H, s), 1.46 (3H, s), 1.41 (3H, s), 1.39 (3H, s). ¹³C NMR δ = 25.24 (2C, s), 25.67 (1C, s), 26.94 (1C, s), 66.45 (1C, s), 73.52 (1C, s), 77.55 (1C, s), 81.00 (1C, d, J = 1.7 Hz), 81.23 (1C, d, J = 19.8 Hz), 107.42 (1C, d, J = 234.9 Hz), 109.39 (1C, s), 115.74 (1C, s). ¹⁹F NMR δ = -125.13 (1F, ddd, J = 66.5, 15.3, 5.5 Hz). HRMS (EI) C₁₂H₂₀O₅F (M⁺+H) 263.1295. Found 263.1288

3.4.2. 2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl fluoride (9b-α). IR (neat) 2895, 1725, 1496, 1453, 1376, 1110, 872, 752, 699 cm⁻¹. ¹H NMR δ = 7.30 - 7.17 (15H, m), 5.55 (1H, d, J = 67.1 Hz), 4.63 - 4.47 (6H, m), 4.18 - 4.01 (3H, m), 3.56 - 3.47 (2H, m). ¹³C NMR δ = 69.32 (1C, s), 72.04 (1C, s), 72.09 (1C, s), 73.36 (1C, s), 82.45 (1C, s), 84.07 (1C, s), 86.82 (1C, d, J = 33.9 Hz), 113.50 (1C, d, J = 225.0 Hz), 127.66 - 128.50 (15C, s), 136.89 (1C, s), 137.41 (1C, s), 137.83 (1C, s). ¹⁹F NMR δ = -127.30 (1F, ddd, J = 65.3, 20.8, 5.5 Hz). HRMS (EI) Calcd for C₂₆H₂₇O₄F (M⁺) 422.1893. Found 422.1896.

(9b-β), Mp 78-79 °C (lit 13 77 - 78 °C). IR (neat) 3062, 3030, 2865, 1454, 1115, 1028, 738, 698 cm⁻¹. ¹H NMR δ = 7.30 - 7.17 (15H, m), 5.79 (5H, d, J = 61.5 Hz), 4.73 - 4.45 (7H, m), 4.17 (1H, dd, J = 9.3, 2.2 Hz), 3.96 (1H, dd, J = 5.1, 2.0 Hz), 3.64 - 3.57 (2H, m). ¹³C NMR δ = 71.52 (1C, s), 72.48 (1C, s), 72.63 (1C, s), 73.45 (1C, s), 81.53 (1C, s), 82.35 (1C, s), 84.52 (1C, d, J = 21.5 Hz), 108.32 (1C, d, J = 229.9 Hz), 127.66 -
128.51 (15C, s), 137.18 (1C, s), 137.73 (1C, s), 137.87 (1C, s). $^{19F}$ NMR $\delta = -121.23$ (1F, dd, $J = 61.6, 9.2$ Hz). HRMS (EI) Calcd for C$_{26}$H$_{27}$O$_4$F ($M^+$) 422.1893. Found 422.1882.

### 3.4.3. 2,3,4,5-Tetra-O-acetyl-α-D-glucopyranosyl fluoride (9c)$^{32}$

Mp 77-78 °C. IR (neat) 2942, 1761, 1439, 1378, 1227, 1109, 1042 cm$^{-1}$. $^1$H NMR $\delta = 5.37$ (1H, dd, $J = 52.0, 6.1$ Hz), 5.22 - 5.20 (2H, m), 5.18 -5.08 (1H, s), 4.29 - 4.20 (2H, m), 3.93 -3.88 (1H, s), 2.11 (6H, s), 2.05 (6H, s). $^{13C}$ NMR $\delta = 20.49 - 20.61$ (4C, s), 61.68 (1C, s), 67.36 (1C, s), 71.10 (1C, d, $J = 28.9$ Hz), 71.70 (1C, d, $J = 8.3$ Hz), 71.96 (1C, d, $J = 4.1$ Hz), 106.14 (1C, d, $J = 219.2$ Hz), 169.05 (1C, s), 169.23 (1C, s), 169.95 (1C, s), 170.49 (1C, s). $^{19F}$ NMR $\delta = -137.83$ (1F, dd, $J = 51.9, 10.4$ Hz). HRMS (EI) Calcd for C$_{14}$H$_{20}$O$_9$F ($M^{++}$) 351.1091. Found 351.1115.

### 3.4.4. 2,3-O-Isopropylidene-5-O-dimethylbutylsilyl-α-D-ribofuranosyl fluoride (9d-α)$^{3}$

IR (neat) 2932, 1858, 1472, 1381, 1258, 1215, 1108, 838 cm$^{-1}$. $^1$H NMR $\delta = 5.63$ (1 H, dd, $J = 66.5, 3.7$ Hz), 4.70 - 4.61 (2H, m), 4.47 (1H, brs), 3.75 (2H, d, $J = 2.6$ Hz), 1.57 (3H, s), 1.38 (3H, s), 0.89 (9H, s), 0.07 (3H, s), 0.05 (3H, s). $^{13C}$ NMR $\delta = -5.55$ (1C, s), -5.36 (1C, s), 18.25 (1C, s), 25.69 (1C, s), 25.71 (1C, s), 25.82 (3C, s), 63.23 (1C, s), 79.52 (1C, s), 81.10 (1C, d, $J = 19.9$ Hz), 84.26 (1C, d, $J = 2.5$ Hz), 114.84 (1C, s), 108.54 (1C, d, $J = 234.0$ Hz). $^{19F}$ NMR $\delta = -127.19$ (1F, dd, $J = 66.5, 14.6$ Hz). HRMS (EI) Calcd for C$_{14}$H$_{20}$O$_9$FSiNa ($M^{++}$+Na) 329.1561. Found 329.1567.

(9d-β). IR (neat) 2932, 1858, 1472, 1381, 1258, 1215, 1108, 838 cm$^{-1}$. $^1$H NMR $\delta = 5.74$ (1H, d, $J = 62.9$ Hz), 4.80 - 4.73 (2H, m), 4.39 - 4.35 (1H, m), 3.75 - 3.71 (1H, m), 3.56 - 3.35 (1H, m), 1.47 (3H, s), 1.34 (3H, s), 0.90 (9H, s), 0.07 (3H, s), 0.06 (3H, s). $^{13C}$ NMR $\delta = -5.32$ (1C, s), -5.30 (1C, s), 18.44 (1C, s), 25.08 (1C, s), 26.01 (3C, s), 26.51 (1C, s), 63.77 (1C, s), 81.19 (1C, s), 85.17 (1C, d, $J = 40.5$ Hz), 89.22 (1C, d, $J = 2.5$ Hz), 112.81 (1C, s), 115.61 (1C, d, $J = 222.5$ Hz). $^{19F}$ NMR $\delta = -114.94$ (1F, dm, $J = 62.9$ Hz).

### 3.4.5. 2,3-O-Isopropylidene-5-O-(m-methylbenzoyl)-α-D-ribofuranosyl fluoride (9e-α)$^{3}$

IR (neat) 2986, 1723, 1383, 1278, 1200, 1105, 745 cm$^{-1}$. $^1$H NMR $\delta = 7.80$ -
7.78 (2H, m), 7.38 - 7.23 (2H, m), 5.67 (1H, dd, $J = 64.9, 3.4$ Hz), 4.76 - 4.67 (3H, m), 4.53 - 4.34 (3H, m), 2.38 (3H, s), 1.56 (3H, s), 1.36 (3H, s). $^{13}$C NMR $\delta = 21.23$ (1C, s), 25.67 (1C, s), 25.71 (1C, s), 63.94 (1C, s), 79.41 (1C, s), 81.03 (1C, d, $J = 20.7$ Hz), 81.79 (1C, d, $J = 1.7$ Hz), 108.01 (1C, d, $J = 235.3$ Hz), 116.00 (1C, s), 126.64 (1C, s), 128.37 (1C, s), 129.30 (1C, s), 130.13 (1C, s), 133.11 (1C, s), 138.33 (1C, s), 166.12 (1C, s). $^{19}$F NMR $\delta = -130.22$ (1F, dd, $J = 14.6, 65.3$ Hz). HRMS (ESI) Calcd for C$_{16}$H$_{19}$O$_5$F (M$^+$) 310.1217. Found 310.1216.

(9e-$\beta$), IR (neat) 2990, 1724, 1383, 1278, 1200, 745 cm$^{-1}$. $^1$H NMR $\delta = 7.85 - 7.83$ (2H, m), 7.37 - 7.29 (2H, m), 5.80 (1H, d, $J = 61.7$ Hz), 4.85 - 4.81 (2H, m), 4.70 - 4.65 (1H, m), 4.39 - 4.36 (2H, m), 2.38 (3H, s), 1.47 (3H, s), 1.32 (3H, s). $^{13}$C NMR $\delta = 21.23$ (1C, s), 24.87 (1C, s), 26.29 (1C, s), 64.50 (1C, s), 80.94 (1C, s), 84.99 (1C, d, $J = 40.5$ Hz), 86.37 (1C, d, $J = 2.5$ Hz), 113.66 (1C, d, $J = 107.5$ Hz), 116.41 (1C, s), 126.87 (1C, s), 128.30 (1C, s), 129.42 (1C, s), 130.25 (1C, s), 134.02 (1C, s), 138.23 (1C, s), 166.20 (1C, s). $^{19}$F NMR $\delta = -116.39$ (1F, dt, $J = 61.7, 3.7$ Hz).

3.4.6. 2,3,4-Tri-O-(m-methylbenzoyl)-$\alpha$-D-xylopyranosyl fluoride (9f). IR (neat) 2957, 1733, 1590, 1185, 739, 681 cm$^{-1}$. $^1$H NMR $\delta = 7.89 - 7.80$ (6H, m), 7.41 - 7.33 (4H, m), 7.25 - 7.16 (2H, m), 5.80 (1H, d, $J = 48.8$ Hz), 5.67 (1H, s), 5.32 (1H, s), 5.23 (1H, s), 4.60 (1H, d, $J = 15.9$ Hz), 4.11 (1H, d, $J = 18.5$ Hz), 2.41 (3H, s), 2.26 (3H, s), 2.23 (3H, s). $^{13}$C NMR $\delta = 21.02$ (1C, s), 21.11 (1C, s), 21.25 (1C, s), 60.70 (1C, s), 68.99 (1C, s), 69.13 (1C, s), 71.23 (1C, d, $J = 24.8$ Hz), 104.26 (1C, d, $J = 229.9$ Hz), 126.86 - 138.28 (18C, s), 165.70 (1C, s), 165.77 (1C, s), 165.84 (1C, s). $^{19}$F NMR $\delta = -137.56$ (1F, dd, $J = 48.8, 4.9$ Hz). HRMS (ESI) Calcd for C$_{20}$H$_{27}$O$_7$F (M$^+$) 506.1741. Found 506.1744.

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References and Notes

4. DAST, was reported to explore at below 100 °C. Thermal stability of \( N,N\)-dimethyl-\( \alpha,\alpha \)-difluorobenzylamine was not shown.