α,α-*gem*-Difluorination of α-(Alkylthio)acetophenone Derivatives with *N*-Fluoropyridinium Salts

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The α,α-*gem*-difluorination of 2′,4′-difluoro-α-(methylthio)acetophenone (1a) with *N*-fluoropyridinium salts gave 2′,4′,α,α-tetrafluoro-α-(methylthio)acetophenone (3a). This reaction was accelerated by the addition of zinc chloride, zinc bromide or anhydrous iron(III) chloride, and higher yields than the reaction without additives were obtained. The *gem*-difluorination reaction using FP-T300 in the presence of zinc bromide was applicable to other α-(alkylthio)acetophenone derivatives (1).

Key words *gem*-difluorination; *N*-fluoropyridinium; α-(alkylthio)-α,α-difluoroacetophenone; zinc chloride; zinc bromide; iron(III) chloride

The introduction of fluorine atoms into an organic molecule has been widely carried out in the fields of medicinal chemistry, because it causes a dramatic enhancement in biological activity.[1)] The change is mainly due to the high electronegativity of the fluorine atom, the strong carbon–fluorine bond and increased lipophilicity.[1a)] For example, peptides containing difluorostatine or difluorostatone inhibit the hydrolytic action of aspartyl protease renin.[2)]

We have studied a series of antifungal imidazoles[3)] and triazoles[4)] and found that triazole derivatives containing the $-CF_2S(O)_n-$ ($n=0, 1, 2$) moiety had potent antifungal activity against *Candida* and *Aspergillus* species.[5)] These derivatives were synthesized from α-(alkylthio)-α,α-difluoroacetophenones (**3**). Although α-(alkylthio)-α,α-difluoroacetophenone analogs have been prepared by the electrolytic fluorination[6)] of α-(phenylthio)acetophenone or oxidative desulfurization–fluorination[7)] of orthothioesters in the literature, the former method is limited to laboratory scale, and the latter lacks wide applicability.

On the other hand, electrophilic fluorinating agents[8)] have been widely used for the introduction of fluorine atoms into an organic compound such as aromatic compounds, 1,3-dicarbonyl compounds, enol silyl ethers and sulfides. However, there are no reports on the α,α-*gem*-difluorination of α-(alkylthio)acetophenones (**1**). In this paper, we describe the α,α-*gem*-difluorination of α-(alkylthio)acetophenone deriva-

Table 1. Physiological and Spectral Data of **1** Derivatives

1	bp (°C/mmHg)	^{1}H-NMR ($CDCl_3$, δ)	^{19}F-NMR ($CDCl_3$, δ)	IR (cm^{-1}) (neat)	HR-MS
1a	126/14	2.08 (3H, s), 3.73 (2H, d, J_{HF}=2.4 Hz), 686—6.91 (1H, m), 6.97—7.02 (1H, m), 7.98—8.04 (1H, m)	−25.5—−25.6 (1F, m), −27.4—−27.5 (1F, m)	1677	(M^+): Calcd for $C_9H_8F_2OS$: 202.0264. Found: 202.0249
1b	143/13	1.24 (3H, t, J=7.3 Hz), 2.52 (2H, q, J=7.3 Hz), 3.78 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.97—7.01 (1H, m), 7.96—8.02 (1H, m)	−25.5—−25.6 (1F, m), −27.4—−27.6 (1F, m)	1677	(M^+): Calcd for $C_{10}H_{10}F_2OS$: 216.0420. Found: 216.0427
1c	123/3	0.50—0.54 (2H, m), 0.83—0.88 (2H, m), 1.82—1.88 (1H, m), 3.86 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.97—7.02 (1H, m), 7.97—8.03 (1H, m)	−25.6—−25.7 (1F, m), −27.5—−27.6 (1F, m)	1681	(M^+): Calcd for $C_{11}H_{10}F_2OS$: 228.0421. Found: 228.0415
1d	125/5	1.32 (9H, s), 3.88 (2H, d, J_{HF}=2.4 Hz), 6.86—6.91 (1H, m), 6.96—7.01 (1H, m), 7.91—7.97 (1H, m)	−25.7—−25.8 (1F, m), −27.9—−28.0 (1F, m)	1682	(M^+): Calcd for $C_{12}H_{14}F_2OS$: 244.0734. Found: 244.0752
1e	—[a)]	2.37 (1H, br s), 2.73 (2H, t, J=5.9 Hz), 3.75 (2H, t, J=5.9 Hz), 3.84 (2H, d, J_{HF}=2.4 Hz), 6.87—6.93 (1H, m), 6.98—7.03 (1H, m), 7.98—8.04 (1H, m)	−24.7—−24.8 (1F, m), −27.3—−27.4 (1F, m)	3423, 1676	(M^+-H_2O)[d)]: Calcd for $C_{10}H_8F_2OS$: 214.0264. Found: 214.0258
1f	164/3	2.06 (3H, s), 2.76 (2H, t, J=6.4 Hz), 3.84 (2H, d, J_{HF}=2.4 Hz), 4.25 (2H, t, J=6.4 Hz), 6.87—6.92 (1H, m), 6.98—7.03 (1H, m), 7.98—8.04 (1H, m)	−24.9—−25.0 (1F, m), −27.4—−27.5 (1F, m)	1741 1677	(M^+): Calcd for $C_{12}H_{12}F_2O_3S$: 274.0476. Found: 274.0470
1g	110/3[b)]	2.14(3H, s), 3.77 (2H, s), 7.48 (2H, t, J=7.3 Hz), 7.58 (1H, dd, J=7.3, 1.5 Hz), 7.98 (2H, dd, J=7.3, 1.5 Hz)	—	1673	(M^+): Calcd for $C_9H_{10}OS$: 166.0452. Found: 166.0440
1h	—[a)]	2.21 (3H, s), 3.86 (2H, s), 7.43 (1H, dd, J=8.3, 2.0 Hz), 7.55 (1H, d, J=2.0 Hz), 7.63 (1H, d, J=8.3 Hz)	—	1691	(M^+): Calcd for $C_9H_8Cl_2OS$: 233.9673. Found: 233.9669
1i	175/10[c)]	2.14 (3H, s), 3.73 (2H, s), 3.88 (3H, s), 6.95 (2H, d, J=8.8 Hz), 7.97 (2H, d, J=8.8 Hz)	—	1666	(M^+): Calcd for $C_{10}H_{12}O_2s$: 196.0558. Found: 196.0548
1j	107/5	2.13 (3H, s), 3.77 (2H, s), 7.75 (2H, d, J=7.8 Hz), 8.09 (2H, d, J=7.8 Hz)	12.6 (3F, s)	1682	(M^+): Calcd for $C_{10}H_9F_3OS$: 234.0326. Found: 234.0350

a) Decomposition was occurred at 210 °C (3 mmHg). *b*) lit.[9)] 94—96 °C (0.3 mmHg). *c*) lit.[10)] 132—136 °C (1 torr). *d*) FAB-MS *m/z*: 233 (MH^+).

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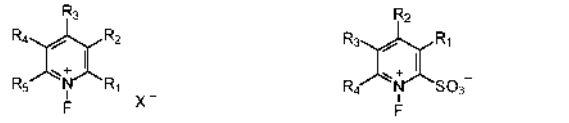


Chart 1

tives (**1**) using commercially available *N*-fluoropyridinium salts and the catalytic effect of the additives on this reaction.

Results and Discussion

The α-(alkylthio)acetophenone derivatives (**1**) were prepared from the corresponding phenacyl halides and alkylmercaptans. The hydroxyethyl derivative (**1e**) was acetylated to the acetoxyethyl derivative (**1f**). The physical and spectral data and ^{13}C-NMR spectral data of α-(alkylthio)acetophenone derivatives (**1**) are listed in Tables 1 and 2.

The fluorinating reagents (F-reagents) used in this experiment were the FP-T series (FP-T300, FP-T500, FP-T700) and the MEC series (MEC-01, MEC-02, MEC-03) (Chart 1).

Initially, we examined the fluorination of 2′,4′-difluoro-α-(methylthio)acetophenone (**1a**) using various F-reagents (Table 3). The reaction with FP-T300 in 1,2-dichloroethane (DCE) at room temperature gave the monofluorinated product, 2′,4′,α-trifluoro-α-(methylthio)acetophenone (**2**), in good yield (run 1). Whereas that with FP-T300, FP-T500, MEC-01 and MEC-02 in 1,1,2-trichloroethane (TCE) at 105 °C[11] afforded a *gem*-difluorinated product, 2′,4′,α,α-tetrafluoro-α-(methylthio)acetophenone (**3a**), in moderate yield (runs 3, 4, 6, 8, 9). More powerful reagents such as FP-T700 or MEC-03 caused the decomposition of **1a** (run 7) or a low yield of **3a** (run 10), respectively.

The ^{1}H-, ^{19}F- and ^{13}C-NMR spectra of **2** showed the introduction of one fluorine atom at Cα [δ_H 6.67 (1H, d, J_{HF}=49 Hz), δ_F −97.2 (1F, d, J_{HF}=49 Hz) and δ_C 95.6 (dd, J_{CF}=230, 11 Hz)]. The presence of *gem*-difluorine atoms at Cα in **3a** was assigned based on the ^{19}F- [δ_F 9.4 (2F, d, J_{FF}=15 Hz)] and ^{13}C-NMR spectra [δ_C 123.2 (t, J_{CF}=289 Hz)] in addition to the absence of a signal due to Cα-protons in the ^{1}H-NMR spectrum.

We next examined the catalytic effect of additives on this difluorination reaction (Table 4). Umemoto and co-workers[8c] have reported that zinc chloride or aluminum chloride catalyzes the difluorination of 1,3-dicarbonyl compounds with FP-T300. As a result, we also found that zinc chloride (runs 1, 7), zinc bromide (runs 2, 3, 6, 8) and anhydrous iron(III) chloride (runs 5, 9) were effective catalysts for the difluorination of **1a** with FP-T300 or FP-T500 but not with MEC-01, when higher yields than the reaction without additives were obtained. Other additives (aluminum fluoride, zinc fluoride, zinc iodide, zinc sulfate, tin(IV) chloride, aluminum chloride, boron trifluoride, copper(II) chloride and titanium(IV) chloride) were not fruitful. The best combination of an F-reagent and an additive for the difluorination of **1a** was 3.0 eq of FP-T300 and 0.5 eq of zinc bromide in TCE (run 3).

The combination of FP-T300 and zinc bromide in TCE was applicable to the difluorination reaction of various types of α-(alkylthio)acetophenones (**1b**—**1d**, **1f**—**1j**) (Table 5). Thus, satisfactory results were obtained except in substrates

Table 2. ^{13}C-NMR Spectral Data of **1** Derivatives[a]

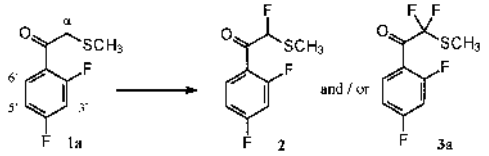
C	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j
Ar<u>C</u>=O	190.2 (d, 6)	190.8 (d, 6)	191.5 (d, 3.7)	193.6 (d, 6)	191.2 (d, 6)	190.5 (d,4)	194.0 (s)	195.3 (s)	192.9 (s)	184.3 (t, 29)
Cα	43.6 (d, 7)	41.2 (d, 7)	43.9 (d, 9)	40.1 (d, 7)	41.4 (d, 7)	41.5 (d, 7)	39.0 (s)	42.7 (s)	38.8 (s)	39.0 (s)
C1′	120.4 (d, 11)	120.5 (d, 11)	120.7 (d, 13)	121.1 (d, 13)	120.3 (d, 13)	119.5 (d, 11)	135.1 (s)	132.4 (s)	128.1 (s)	137.8 (s)
C2′	162.4 (dd, 257, 11)	163.3 (dd, 258, 13)	162.4 (dd, 257, 13)	162.3 (dd, 256, 13)	162.9 (dd, 257, 13)	162.5 (dd, 257, 13)	128.7 (s)	135.6 (s)	131.8 (s)	129.1 (s)
C3′	105.5 (t, 26)	104.8 (t, 28)	104.8 (t, 26)	104.8 (t, 28)	104.9 (t, 28)	104.9 (t, 26)	128.6 (s)	130.4 (s)	113.8 (s)	125.7 (d, 4)
C4′	166.1 (dd, 257, 13)	166.1 (dd, 258, 13)	166.0 (dd, 257, 13)	165.9 (dd, 257, 13)	166.2 (dd, 257, 13)	166.2 (dd, 257, 13)	133.3 (s)	137.7 (s)	163.7 (s)	134.5 (q, 31)
C5′	112.5 (dd, 22, 4)	112.5 (dd, 22, 4)	112.4 (dd, 22, 4)	112.4 (dd, 22, 4)	112.6 (dd, 22, 4)	112.6 (dd, 22, 4)	128.6 (s)	127.3 (s)	113.8 (s)	125.7 (d, 4)
C6′	133.4 (dd, 11, 4)	133.4 (dd, 11, 4)	133.3 (dd, 11, 4)	133.3 (dd, 11, 4)	133.4 (dd, 11, 4)	133.4 (dd, 11, 4)	128.7 (s)	131.0 (s)	131.8 (s)	129.1 (s)
CαS<u>C</u>	15.4 (s)	25.8 (s)	12.7 (s)	43.4 (s)	35.2 (s)	30.1 (s)	15.9 (s)	15.7 (s)	15.9 (s)	15.8 (s)
CαSC<u>C</u>	—	14.1 (s)	8.3 (s)×2	30.8 (s)×3	60.4 (s)	62.7 (s)	—	—	—	—
O<u>C</u>OCH$_3$	—	—	—	—	—	170.8 (s)	—	—	—	—
OCO<u>C</u>H$_3$	—	—	—	—	—	20.8 (s)	—	—	—	—
C4′O<u>C</u>H$_3$	—	—	—	—	—	—	—	—	55.5 (s)	—
C4′<u>C</u>F$_3$	—	—	—	—	—	—	—	—	—	123.5 (q, 274)

a) δ in CDCl$_3$ (J_{CF}).

containing acid-sensitive substituents (runs 3 and 4). The physical and spectral data and ^{13}C-NMR spectral data of the *gem*-difluorinated products (**3**) are listed in Tables 6 and 7.

In summary, the α,α-*gem*-difluorination of α-(alkylthio) acetophenones (**1**) were found to proceed smoothly by a combination of FP-T300 and zinc bromide to give the corresponding difluoro derivatives (**3**) in good yields except in the case of compounds with an acid-sensitive function.

Table 3. Fluorination of **1a** with F-Reagents under Various Conditions



Run	F-reagent[a)]	Solvent	Conditions	Results (yield, %)
1	FP-T300	DCE	r.t., 12 h	**2** (91.7)
2	FP-T300	DCE	refl., 3.0 h	**2** (17.0)+**3a** (31.5)
3	FP-T300	TCE	105 °C, 3.0 h	**3a** (47.6)
4	FP-T300	AcOBu	105 °C, 4.0 h	**3a** (42.8)
5	FP-T300	Toluene	105 °C, 4.0 h	Decomposition
6	FP-T500	TCE	105 °C, 1.0 h	**3a** (47.6)
7	FP-T700	TCE	105 °C, 0.5 h	Decomposition
8	MEC-01	TCE	105 °C, 1.5 h	**3a** (56.7)
9	MEC-02	TCE	105 °C, 0.5 h	**3a** (50.7)
10	MEC-03	TCE	105 °C, 5 min	**3a** (11.9)

a) Three molecular equivalents of an F-reagent were used.

Table 4. Difluorination of **1a** with F-Reagents in the Presence of Additives at 105 °C

Run	F-reagent[a)]	Solvent	Additive (eq)	Time (h)	Results (yield of **3a**, %)
1	FP-T300	TCE	$ZnCl_2$ (0.5)	2.5	72.2
2	FP-T300	TCE	$ZnBr_2$ (0.2)	2.5	72.8
3	FP-T300	TCE	$ZnBr_2$ (0.5)	2.5	82.2
4	FP-T300	TCE	$ZnBr_2$ (0.8)	0.5	Decomposition
5	FP-T300	TCE	$FeCl_3$ (0.5)	2.5	79.9
6	FP-T300	AcOBu	$ZnBr_2$ (0.5)	2.5	62.6
7	FP-T500	TCE	$ZnCl_2$ (0.5)	1.0	63.5
8	FP-T500	TCE	$ZnBr_2$ (0.5)	1.0	65.2
9	FP-T500	TCE	$FeCl_3$ (0.5)	1.0	72.8
10	MEC-01	TCE	$ZnBr_2$ (0.5)	1.0	58.1
11	MEC-01	TCE	$FeCl_3$ (0.5)	1.0	41.6

a) Three molecular equivalents of an F-reagent were used.

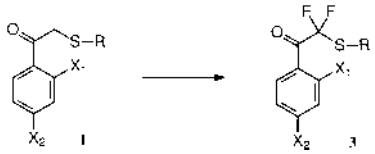
Experimental

IR spectra were measured with a Perkin-Elmer 1600 FT-IR spectrometer. The ^{1}H- and ^{13}C-NMR spectral data were recorded on a JOEL JNM-EX400 FT-NMR spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. The ^{19}F-NMR spectra were measured in $CDCl_3$ with trifluoroacetic acid as the external standard. The following abbreviations were used: s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet, br=broad. FAB-MS or high resolution (HR)-MS were obtained on a JEOL JMS-DX303 or JEOL JMS-AX500 mass spectrometer. TLC was performed on Silica gel $60F_{254}$ (Merck). Column chromatography was performed on Silica gel 60 (70—230 mesh) (Merck) with hexane–ethyl acetate (10 : 1) as the eluent. The organic layer was washed with water, brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography and/or distillation.

Fluorinating Reagent The FP-T series (FP-T300, FP-T500, FP-T700) or the MEC series (MEC-01, MEC-02, MEC-03) was purchased from F-Tech Co., Ltd., or Daikin Industries Co., Ltd., respectively.

Preparation of α-(Methylthio)acetophenones (1a, 1g—1j): 2′,4′-Difluoro-α-(methylthio)acetophenone (1a). General Procedure To a solution of 2′,4′-difluorophenacyl chloride (35.00 g, 0.18 mol) in methanol (700 ml) was dropwise added 10% aqueous methylmercaptan sodium salt (151 ml,

Table 5. Difluorination of **1** Derivatives with a Combination of FP-T300 (3.0 eq) and $ZnBr_2$ (0.5 eq) in TCE at 105 °C



Run	**1**	X_1	X_2	R	Time (h)	Product (**3**) (yield, %)
1	**1b**	F	F	CH_2CH_3	2.0	**3b** (84.3)
2	**1c**	F	F	Cyclopropyl	2.5	**3c** (72.3)
3	**1d**	F	F	*tert*-Butyl	0.5	Decomposition
4	**1f**	F	F	$(CH_2)_2OAc$	3.0	**3f** (45.4)
5	**1g**	H	H	CH_3	1.5	**3g** (75.9)
6	**1h**	Cl	Cl	CH_3	1.0	**3h** (72.3)
7	**1i**	H	OCH_3	CH_3	1.5	**3i** (63.9)
8	**1j**	H	CF_3	CH_3	2.0	**3j** (60.1)

Table 6. Physiological and Spectral Data of **2** and **3** Derivatives

2 or **3**	bp (°C/mmHg)	^{1}H-NMR ($CDCl_3$, δ)	^{19}F-NMR ($CDCl_3$, δ)	IR (cm^{-1}) (neat)	HR-MS
2	115/4	2.09 (3H, s), 6.67 (1H, d, J_{HF}=49 Hz), 6.88—6.93 (1H, m), 7.01—7.06 (1H, m), 8.04—8.10 (1H, m)	−23.7—−23.8 (1F, m), −25.2—−25.3 (1F, m), −97.2 (1F, d, J_{HF}=49 Hz)	1698	(M^+): Calcd for $C_9H_7F_3OS$: 220.0170 Found: 220.0174
3a	96/5	2.35 (3H, s), 6.91—7.02 (2H, m), 7.95—8.01 (1H, m)	−9.4 (2F, d, J_{FF}=15 Hz), −23.0—−23.1 (1F, m), −26.0—−26.1 (1F, m)	1713	(M^+): Calcd for $C_9H_6F_4OS$: 238.0076. Found: 238.0079
3b	105/7	1.37 (3H, t, *J*=7.8 Hz), 2.92 (2H, q, *J*=7.8 Hz), 6.90—7.02 (2H, m), 7.95—8.01 (1H, m)	−6.4 (2F, d, J_{FF}=14 Hz), −23.0—−23.1 (1F, m), −26.1—−26.2 (1F, m)	1714	(M^+): Calcd for $C_{10}H_8F_4OS$: 252.0232. Found: 252.0229
3c	115/4	0.71—0.75 (2H, m), 0.99—1.04 (2H, m), 2.06—2.10 (1H, m), 6.91—7.02 (2H, m), 7.96—8.02 (1H, m)	−7.5 (2F, d, J_{FF}=12 Hz), −23.0—−23.1 (1F, m), −26.0—−26.1 (1F, m)	1713	(M^+): Calcd for $C_{11}H_8F_4OS$: 264.0232. Found: 264.0206
3f	151/3	2.07 (3H, s), 3.14 (2H, t, *J*=6.4 Hz), 4.31 (2H, t, *J*=6.4 Hz), 6.92—7.03 (2H, m), 7.94—7.99 (1H, m)	−5.4 (2F, d, J_{FF}=15 Hz), −22.4—−22.5 (1F, m), −25.5—−25.6 (1F, m)	1744, 1712	(M^+−AcOH)[b)]: Calcd for $C_{10}H_6F_4OS$: 250.0076. Found: 250.0032
3g	87/4	2.36 (3H, s), 7.50 (2H, t, *J*=7.8 Hz), 7.65 (1H, dd, *J*=7.8, 1.5 Hz), 8.14 (2H, dd, *J*=7.8, 1.5 Hz)	−3.3 (2F, s)	1703	(M^+): Calcd for $C_9H_8F_2OS$: 202.0264. Found: 202.0256
3h	—[a)]	2.35 (3H, s), 7.34 (1H, dd, *J*=8.3, 2.0 Hz), 7.53 (1H, d, *J*=2.0 Hz), 7.69 (1H, d, *J*=8.3 Hz)	−10.1 (2F, s)	1723	(M^+): Calcd for $C_9H_8Cl_2F_2OS$: 269.9485. Found: 269.9459
3i	140/4	2.36 (3H, s), 3.90 (3H, s), 6.97 (2H, d, *J*=8.8 Hz), 8.14 (2H, d, *J*=8.8 Hz)	−5.2 (2F, s)	1692	(M^+): Calcd for $C_{10}H_{10}F_2O_2S$: 232.0369. Found: 232.0359
3j	91/5	2.38 (3H, s), 7.77 (2H, d, *J*=8.3 Hz), 8.25 (2H, d, *J*=8.3 Hz)	12.3 (3F, s), −6.8 (2F, s)	1714	(M^+): Calcd for $C_{10}H_7F_5OS$: 270.0138. Found: 270.0093

a) Decomposition was occured at 210 °C/3 mmHg. *b*) FAB-MS *m/z*: 311 (MH^+).

Table 7. ^{13}C-NMR Spectral Data of **2** and **3** Derivatives[a)]

C	**2**	**3a**	**3b**	**3c**	**3f**	**3g**	**3h**	**3i**	**3j**
Ar<u>C</u>=O	185.5 (dd, 24, 6)	182.6 (t, 31)	183.0 (t, 31)	183.2 (t, 31)	182.8 (t, 31)	185.2 (t, 29)	185.5 (t, 31)	183.7 (t, 28)	184.3 (t, 29)
Cα	95.6 (dd, 230, 11)	123.2 (t, 289)	123.6 (t, 291)	123.7 (t, 289)	123.6 (t, 291)	124.4 (t, 289)	122.9 (t, 290)	124.7 (t, 287)	124.0 (t, 287)
C1′	118.6 (d, 11)	117.4 (d, 11)	117.6 (d, 13)	117.6 (d, 11)	117.3 (d, 11)	131.0 (s)	127.7 (s)	123.1 (s)	133.8 (s)
C2′	162.2 (dd, 257, 13)	162.7 (dd, 265, 13)	162.9 (dd, 265, 13)	162.9 (dd, 265, 13)	162.9 (dd, 265, 13)	130.5 (s)	134.5 (s)	133.1 (s)	130.8 (s)
C3′	105.0 (t, 28)	105.5 (t, 26)	105.6 (t, 26)	105.6 (t, 26)	105.6 (t, 26)	128.7 (s)	130.6 (s)	114.0 (s)	125.7 (d, 4)
C4′	166.6 (dd, 259, 13)	166.3 (dd, 259, 13)	166.4 (dd, 259, 13)	166.4 (dd, 259, 13)	166.6 (dd, 259, 13)	134.7 (s)	138.8 (s)	164.8 (s)	135.7 (q, 33)
C5′	113.0 (dd, 22, 4)	111.8 (dd, 22, 4)	111.9 (dd, 22, 4)	111.9 (dd, 22, 4)	112.1 (dd, 4)	128.7 (s)	126.9 (s)	114.0 (s)	125.7 (d, 4)
C6′	133.3 (dd, 9, 4)	133.4 (dd, 11, 4)	133.6 (dd, 11, 4)	133.5 (dd, 11, 4)	133.6 (dd, 11, 4)	130.5 (s)	131.0 (s)	133.1 (s)	130.8 (s)
CαS<u>C</u>	10.9 (s)	10.8 (s)	27.4 (s)	8.6 (s)	27.4 (s)	27.4 (s)	11.2 (s)	10.8 (s)	10.9 (s)
CαS<u>C</u><u>C</u>	—	—	15.0 (s)	7.6 (s)×2	63.0 (s)	—	—	—	—
O<u>C</u>OCH$_3$	—	—	—	—	170.6 (s)	—	—	—	—
OCO<u>C</u>H$_3$	—	—	—	—	20.8 (s)	—	—	—	—
C4′O<u>C</u>H$_3$	—	—	—	—	—	—	—	55.6 (s)	—
C4′<u>C</u>F$_3$	—	—	—	—	—	—	—	—	123.3 (q, 274)

a) δ in $CDCl_3$ (J_{CF}).

0.22 mol) at 0 °C. The mixture was stirred at room temperature for 1.0 h and evaporated under reduced pressure. The residue was poured into water and extracted with chloroform. Distillation gave **1a** as a pale yellow oil (23.90 g, 64.4%).

Preparation of α-(Alkylylthio)acetophenones (1b—1e): 2′,4′-Difluoro-α-(ethylthio)acetophenone (1b). General Procedure Potassium carbonate (3.92 g, 28.4 mmol) was added to a solution of 2′,4′-difluorophenacyl chloride (4.50 g, 23.6 mmol) and ethylmercaptan (1.61 g, 25.9 mol) in methanol (48 ml) at 0 °C. The mixture was stirred at room temperature for 2.0 h. After filtration, most of the solvent was removed under reduced pressure. The residue was poured into water and extracted with chloroform. Distillation gave **1b** as a pale yellow oil (4.53 g, 88.6%).

α-[(β'-Acetoxyethyl)thio]-2′,4′-difluoroacetophenone (1f) Acetic anhydride (0.60 g, 5.9 mmol) was added to a solution of 2′,4′-difluoro-2-[(2-hydroxyethyl)thio]acetophenone (**1e**) (1.14 g, 4.9 mmol) in pyridine (10 ml). The mixture was stirred at 50 °C for 3.0 h. The reaction mixture was evaporated under reduced pressure. The residue was poured into water and extracted with ether. Distillation gave **1f** as a pale yellow oil (1.31 g, 97.0%).

2′,4′,α-Trifluoro-α-(methylthio)acetophenone (2): The Monofluorination of 1a with FP-T300 A solution of **1a** (3.00 g, 14.8 mmol) in DCE (10 ml) was dropwise added to a suspension of FP-T300 (12.80 g, 44.3 mmol) in DCE (100 ml) at room temperature for 10 min. The mixture was stirred at room temperature for 12 h. Column chromatography and distillation gave **2** as a pale yellow oil (3.00 g, 91.7%).

2′,4′,α,α-Tetrafluoro-α-(methylthio)acetophenone (3a): The *gem*-Difluorination of 1a with Fluorinating Reagent in the Presence of Zinc Bromide. General Procedure A solution of **1a** (3.00 g, 14.8 mmol) in TCE (10 ml) was dropwise added to a suspension of FP-T300 (12.80 g, 44.3 mmol) and zinc bromide (1.67 g, 7.4 mmol) in TCE (100 ml) at 80 °C[12] for 10 min. The mixture was stirred at 105 °C for 2.5 h. Column chromatography and distillation gave **3a** as a pale yellow oil (2.90 g, 82.2%).

References and Notes

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11) Difluorination of α-(alkylthio)acetophenones (**1**) with F-reagent in TCE at reflux condition occurred vigorously.
12) The internal temperature of the reaction mixture rose to *ca.* 100 °C.