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A Remarkably Simple Route to Versatile Difluoromethylated Molecules

Sadanori Kaneko, Takashi Yamazaki, and Tomoya Kitazume*

Department of Bioengineering, Tokyo Institute of Technology,
Nagatsuta, Midori-ku, Yokohama 227, Japan

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Difluoroacetaldehyde ethyl hemiacetal (1), prepared from ethyl difluoroacetate and lithium aluminum hydride in diethyl ether, was found to be a potential difluoroethylating reagent for the preparation of a wide variety of difluoromethylated compounds. Compound 1 shows promise for use in the synthesis of carbinols prepared by the reaction of 1 with metal reagents or enol silyl ethers, the synthesis of amino acid ketones and β-lactams via the nucleophilic reaction of imines, and the synthesis of sugar analogues.

Difluoromethyl substitution on an organic molecule often confers bioactivity on these compounds and can serve as a diagnostic handle for functionalized materials.[1-5] The difluoromethyl group is preferred due to its ability to act as a hydrogen donor, allowing the possibility for interaction with solvents and biological molecules.[6-11] Particularly, in *C*-glycoside chemistry, site-specific replacement of an oxygen atom possessing stereochemically significant lone pairs by the larger difluoromethylene unit would provide compounds which still retain hydrogen bonding potential.[2-4] Furthermore, difluoromethylated amino acids are also effective enzyme inhibitors; e.g., (1) difluoromethyl ornithine has been found to inhibit ornithine decarboxylase, and (2) difluoromethyl dopa exhibits selective peripheral activity.[2-4] To date, synthetic strategies for the preparation of difluoromethylated materials have been based on three methods: (1) The use of difluoromethylated compounds prepared from chlorodifluoromethane,[7] (2) the synthesis of difluoromethylated ketones and/or difluoroacetaldehyde by Grignard-type additions to ethyl difluoroacetate,[6] and (3) the ultrasound-promoted reduction of teminal fluoroolefins.[12] Clearly, selective and/or specific synthetic methods for introduction of the difluoromethyl group at a specific position in the molecule remain an important synthetic challenge.

Accordingly, we have devoted our attention to the development of simple synthetic methods for the preparation of a variety of functionalized compounds bearing the difluoromethyl group (Scheme I).

Results and Discussion

α-Difluoromethylated Carbinols from Nucleophilic Reactions. Fluorinated carbinols have been used as probes for enzymatic resolutions[13] and as building blocks for new fluorinated bioactive materials[2,14] and/or ferroelectric liquid crystals.[15] However, no general synthetic methods for α-difluoromethyl carbinols have been reported, with the possible exception of the reduction of α-difluoromethyl ketones derived from ethyl difluoroacetate.[6] We have found that difluoroacetaldehyde ethyl hemiacetal (1) is very susceptible to nucleophilic reaction with Grignard reagents or lithio acetylides, affording α-difluoromethylated carbinols in moderate to excellent chemical yield (Table I). Particularly, β-(difluoromethyl)-β-hydroxy carbonyl compounds have attracted considerable attention as versatile synthetic units, indicative of the increasing interest in the preparation of fluorinated sugars, amino acids, and/or fatty acids which often exhibit dramatic changes in biological activities.[1,2] Hemiacetal 1, a carbonyl equivalent in the Lewis acid mediated reaction of aldehyde enol silyl ethers, was subjected to reaction with a variety of enol silyl ethers. When the reaction was attempted in the presence of fluoride ion [tetra-*n*-butylammonium fluoride (TBAF)] or trimethylsilyl trifluoromethanesulfonate (TMSOTf), coordination did not occur. However, Lewis acids such as ZnI_2 and $ZnCl_2$ strongly promoted the desired reaction (Table II).

These results reveal some characteristic features of the reactivity of hemiacetal 1 with enol silyl ethers; i.e., (a) product was not formed with diastereoselectivity (entries 12, 13), and (b) the reaction with ketene silyl acetals (entry

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Scheme I

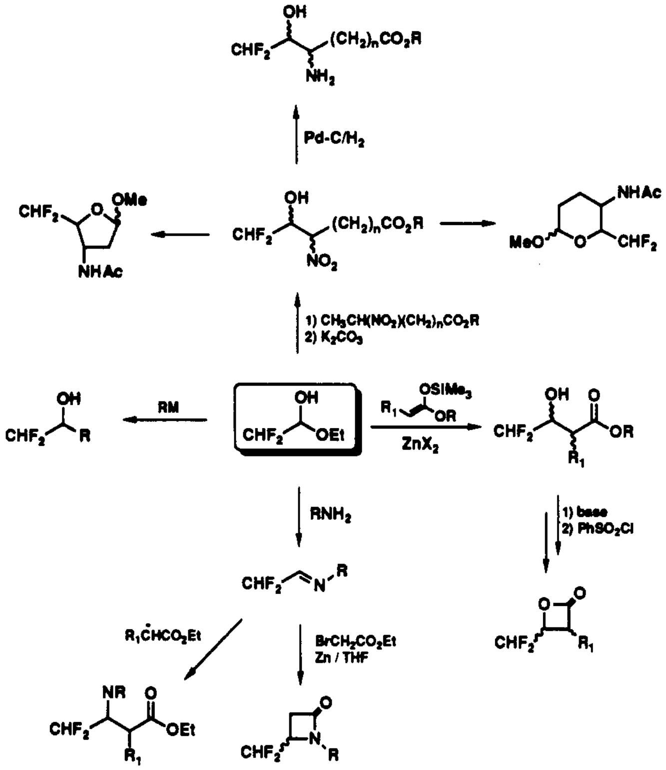
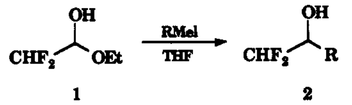


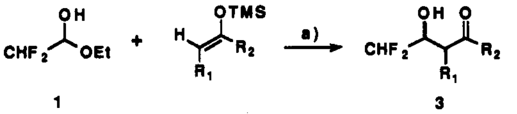
Table I. Reaction of Hemiacetal 1 with Metal Reagents



entry no.	compd no.	metal reagent	react. temp (°C)	react. time (h)	yield^a (%)
1	**2a**	PhMgBr	0 → rt	1	70
2	**2b**	p-MeC$_6$H$_4$MgBr	0 → rt	1	65
3	**2c**	o-MeC$_6$H$_4$MgBr	0 → rt	2	58
4	**2d**	PhCH$_2$CH$_2$MgBr	0 → rt	1.5	60
5	**2e**	n-C$_8$H$_{17}$MgBr	0 → rt	4	39
6	**2f**	PhC≡CLi	−78 → rt	1	70
7	**2g**	n-C$_6$H$_{13}$C≡CLi	−78 → rt	2	55
8	**2h**	n-C$_8$H$_{17}$C≡CLi	−78 → rt	2	67

^{a} Isolated yields based on hemiacetal 1.

Table II. Reaction of Hemiacetal 1 with Enol Silyl Ethers



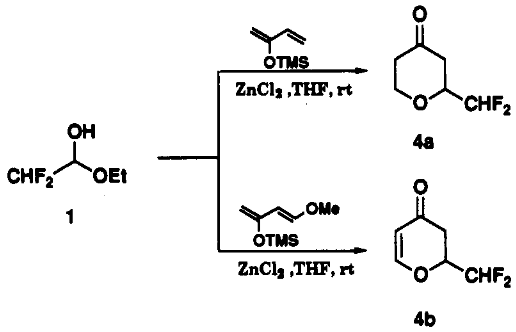
$^{a)}$ ZnCl$_2$ or ZnI$_2$, THF, refl.

entry no.	compd no.	R$_1$	R$_2$	react. time (h)	yield^a (%)	threo: erythro^b
9	**3a**	H	i-Bu	3	63	
10	**3b**	H	t-Bu	3	58	
11	**3c**	H	Ph	1	75	
12	**3d**	Me	Ph	1.5	74	1:2.5
13	**3e**	Cl	Ph	1.5	68	1:1
14	**3f**	H	OEt	24	25	

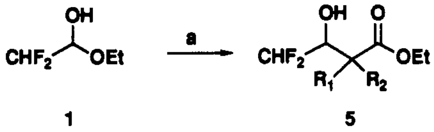
^{a} Isolated yields. ^{b} Determined by ^{19}F NMR.

14) could not be improved even under forcing conditions such as boron trifluoride etherate or TMSOTf. However, with enol silyl ethers generated from α,β-unsaturated ketones, cyclic compounds **4a** and/or **4b**, which are expected to be useful intermediates of difluoromethylated sugars, are obtained in good yields (Scheme II).

Scheme II

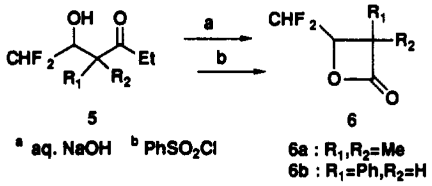


Scheme III



^{a} BrCH(R$_1$)(R$_2$)CO$_2$Et, Zn / THF, refl.

Table III. Reaction of Hemiacetal 1 with Reformatsky-Type Reagents



^{a} aq. NaOH ^{b} PhSO$_2$Cl

6a : R$_1$,R$_2$=Me
6b : R$_1$=Ph,R$_2$=H

entry no.	compd no.	R$_1$	R$_2$	react. time (h)	yield^a (%)	threo: erythro^b
15	**5a**	H	H	4	70	
16	**5b**	H	Me	2	70	53:47
17	**5c**	H	Et	2	73	58:42
18	**5d**	Me	Me	1.5	74	

^{a} Isolated yields. ^{b} Determined by ^{19}F NMR.

Hemiacetal 1 also acts as a difluoroacetaldehyde equivalent in Reformatsky-type reactions to form β-(difluoromethyl)-β-hydroxy esters **5**. After a survey of conditions, the reaction of hemiacetal 1 (1 equiv) with Reformatsky-type reagents (2.5 equiv) in THF was found to afford β-(difluoromethyl)-β-hydroxy esters **5** in the best yields (Table III).

β-(Difluoromethyl)-β-hydroxy ketones are useful precursors in the synthesis of difluoromethylated lactones. Following hydrolysis of β-hydroxy esters with aqueous sodium hydroxide, the cyclization with benzenesulfonic chloride[16] produced the corresponding lactones (Scheme III).

Synthesis and Synthetic Application of β-Nitro α-(Difluoromethyl)carbinols. β-Nitro α-(difluoromethyl)carbinols, readily obtained through the nitroaldol reaction of hemiacetal 1 with a nitroalkane or a nitro ester, are useful building blocks. Obviously, β-nitro α-(difluoromethyl)carbinols **7e**, **7f**, and **7g** may be key intermediates in the synthesis of amino acids or amino sugars possessing a difluoromethyl moiety. Compound **7e** was converted to ethyl 4,4-difluorothreonate and *allo*-ethyl 4,4-difluorothreonate (**8**),[17] which were easily separated by column chromatography. These materials are precursors to 4,4-difluorothreonine[6] and *allo*-4,4-difluorothreonine, novel

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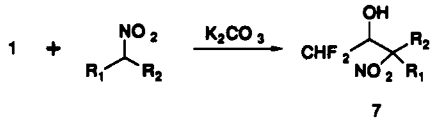
[16] Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000.

[17] In this text, nomenclature of the relative stereochemistry follows the method proposed by Noyori et al. See: Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

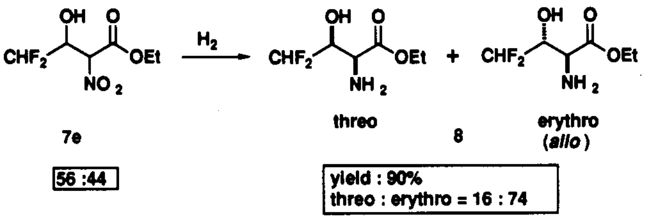
Table IV. Reaction of Hemiacetal 1 with Nitro Compounds



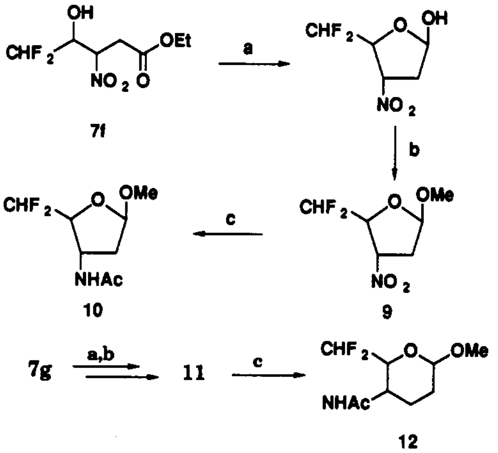
compd no.	R_1	R_2	yield[a] (%)	threo:erythro[b]
7a	H	H	65	
7b	H	Me	68	52:48
7c	H	Et	68	56:44
7d	Me	Me	82	
7e	H	CO_2Et	92	51:49
7f	H	CH_2CO_2Et	82	52:48
7g	H	$CH_2CH_2CO_2Me$	90	57:43

[a] Isolated yields. [b] Determined by ^{19}F NMR.

Scheme IV



Scheme V[a]



[a] Key: (a) DIBAL-H, Et_2O, −78 °C; (b) MeOH, p-$CH_3C_6H_4SO_3H$, refl., 24 h; (c) Pd–C, H_2, Et_2O.

potent antitumor agents. The present strategy permits isolation of *allo*-ethyl 4,4-difluorothreonate, which is not accessible by previously existing methods.[6] In the above procedure, epimerization probably occurs at this site to form the most stable configuration of the intermediate. Protonation occurs on the nitro group.

Conversion of **7f** and **7g** to the (deoxydifluoromethyl)-amino sugar precursor was achieved by the following procedures. Protection as the methyl glycoside by treatment with methanol in the presence of *p*-toluenesulfonic acid followed by treatment of **7f** and **7g** with diisobutylaluminum hydride in diethyl ether at −78 °C gave compounds **9** and **11**, and reduction of the nitro group by the Pd–C/H_2 system in diethyl ether formed the (deoxydifluoromethyl)amino sugars **10** and **12**.

These results clearly illustrate the reactivity of difluoroacetaldehyde ethyl hemiacetal **1**. Many nucleophiles, inactive with difluoroacetic acid and ethyl difluoroacetate, react with the hemiacetal to yield the corresponding difluoromethylated carbinols in a single step. With the exception of the nitro compounds, more than 2 equiv of the nucleophiles as well as, in some cases, 1 equiv of the Lewis acid per mole of the difluoroacetaldehyde ethyl hemiacetal (**1**) were required. Obviously, 1 equiv of nucleophile or Lewis acid was consumed by the hydroxy group in difluoroacetaldehyde ethyl hemiacetal (**1**), which generates the difluoroacetaldehyde in situ (Figure 1).

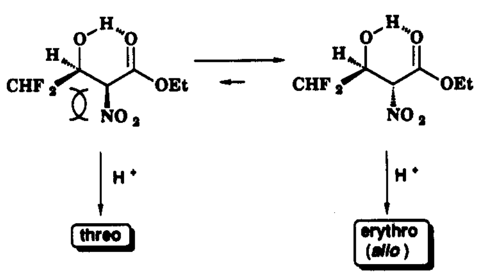


Figure 1.

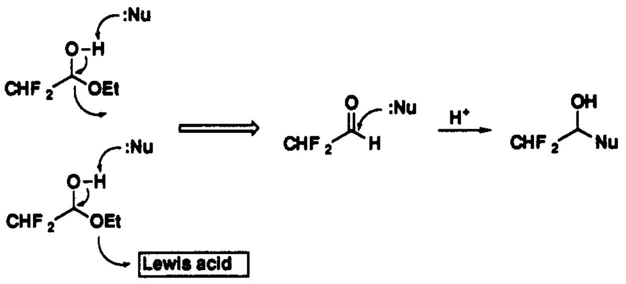


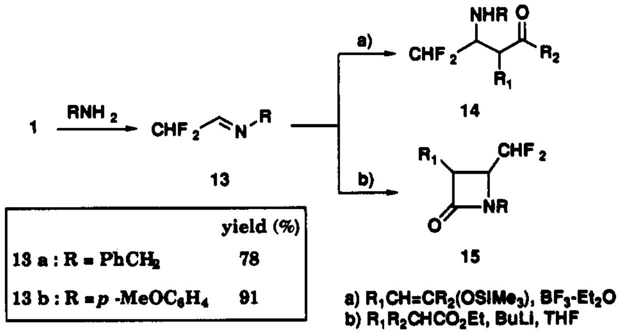
Figure 2.

In contrast, trifluoroacetaldehyde ethyl hemiacetal failed to undergo Grignard and/or Reformatsky reactions. The tetrahedral form was highly stable as a result of the strong electron-withdrawing effect of the trifluoromethyl group, so that transformation into the aldehyde form was not facile (Figure 2).

Unfortunately, the intermediacy of the aldehyde form could not be confirmed by spectral data.

Synthesis and Synthetic Application of Difluoromethylated Imines. Our synthetic route to difluoromethylated synthons led to a search for new uses for difluoroacetaldehyde ethyl hemiacetal (**1**). Compound **1** was smoothly transformed into difluoromethylated imines **13**, which were previously demonstrated to be useful synthetic tools in organic synthesis,[18] via the reaction of primary amines.

The synthesis of β-(difluoromethyl)-β-amino acids, which have been receiving increasing attention because of their properties as suicide inhibitors, has been explored via the reaction of difluoroethanimine **13** with enol silyl ethers. Particularly, β-(difluoromethyl)-β-alanine (3-



	yield (%)
13 a : R = $PhCH_2$	78
13 b : R = *p* -$MeOC_6H_4$	91

a) $R_1CH{=}CR_2(OSiMe_3)$, BF_3-Et_2O
b) $R_1R_2CHCO_2Et$, BuLi, THF

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[18] Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Applied Chem.* **1990**, *62*, 605.

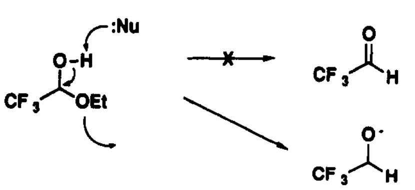
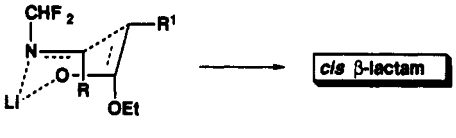


Figure 3.



A

Figure 4.

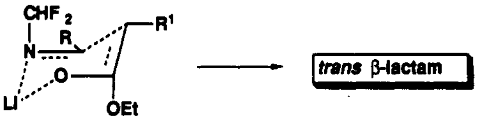


Figure 5.

amino-4,4-difluorobutanoic acid) is a potent in vitro and in vivo inhibitor of GABA-T;[1] however, its synthesis usually requires toxic reagents or multiple synthetic steps. The use of difluoroethanimine **13a** could overcome this problem. The reaction of **13a** with a silyl ketene acetal in the presence of TBAF gave a precursor of β-(difluoromethyl)-β-alanine in one step.

Furthermore, the synthesis of β-lactams (azetidin-2-one rings) **15**, which have been used in the total syntheses of nonclassical β-lactam antibiotics,[19-23] has been examined using cycloaddition-type reactions of imines with zinc or lithium enolates. Treatment of the imine with Reformatsky-type reagents in THF under reflux gave the racemic β-lactams. The diastereoselectivity of the process was very low, which might be due to the reaction occurring via an open-chain transition state (Figure 3). A better stereochemical outcome was obtained when lithium enolates were employed. The trans β-lactams were obtained exclusively, except from **15d**. It is obvious that the reaction mechanisms of these two types of reagents are quite different. In the former reaction, cyclic transition states are possible. The preference for the trans configuration of β-lactams is presumably dependent on the stereochemistry of **13a**.

As Figure 4 shows, if **13a** has the *E* configuration, the reaction with *Z*-enolates would proceed via transition state **A** to give the cis β-lactam. In the case of the *Z* isomer, the trans β-lactam was obtained, as shown in Figure 5. Results from Table VI suggest that the reaction proceeds as in Figure 4. In addition, the reaction of the *E*-enolate diminished the diastereomeric ratio of **15e** (trans:cis = 51:49).

On the basis of these results, the possibility of the *Z*-imine configuration cannot be ruled out. Further investigations are in progress.

Table V. Synthesis of β-Amino-γ-difluoro Ketones and Esters 14

compd no.	R_1	R_2	yield[a] (%)	threo:erythro[b]
14a	H	Ph	65	
14b	H	*t*-Bu	68	
14c	H	*i*-Bu	68	
14d	H	OEt	82	
14e	Me	OEt	92	68:32

[a] Isolated yields. [b] Determined by ^{19}F NMR.

Table VI. Synthesis of β-Lactams 15

compd no.	R_1	R	yield[a] (%)	trans:cis[b]
15a	H	$PhCH_2$	45	
15b	Me	$PhCH_2$	78	1:1
15c	Et	$PhCH_2$	71	1:1
15d	Me	$PhCH_2$	77	1:1
15e	Et	$PhCH_2$	82	88:12
15f	Pr	$PhCH_2$	75	86:14
15g	C_8H_{17}	$PhCH_2$	76	74:26
15h	Ph	$PhCH_2$	73	92:8

[a] Isolated yields. [b] Determined by ^{19}F NMR.

Experimental Section

General Procedures. All commercially available reagents were used without further purification. Infrared spectra were obtained using a JASCO A-102 or a JASCO FT/IR-5000 spectrometer and KBr pellets. Nuclear magnetic resonance (NMR) spectra were recorded at 200 or 500 MHz for ^{1}H NMR (internal Me_4Si), at 470 MHz for ^{19}F NMR (internal C_6F_6), and at 125 MHz for ^{13}C NMR in $CDCl_3$. Yields were those of isolated products.

Difluoroacetaldehyde Ethyl Hemiacetal (1). To a solution of ethyl difluoroacetate (20 mL, 200 mmol) in dry ether (30 mL) was added a solution of lithium aluminum hydride in tetrahydrofuran (1.0 M, 50 mL, 50 mmol) at -78 °C. After the solution was stirred at that temperature for 3 h, ethanol (95%, 5.0 mL) was added and the whole solution was allowed to warm to room temperature. The mixture was poured into a solution of crushed ice and concd H_2SO_4 (15 mL) and then extracted with ether. The extracts were dried over anhydrous $MgSO_4$. On removal of the solvent, the residual oil was purified by distillation to afford difluoroacetaldehyde ethyl hemiacetal (1) in 60% yield: bp 45–47 °C (27 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 3 H, $J_{H,H} = 7.1$ Hz), 3.2–3.4 (br, 1 H), 3.63 (dq, 1 H, $J_{H,H}$ 7.1, 9.6 Hz), 3.91 (dq, 1 H, $J_{H,H} = 7.1, 9.6$ Hz), 4.70 (ddd, 1 H, $J_{H,H} = 2.4, 5.7, 8.0$ Hz), 5.60 (ddd, 1 H, $J_{H,H} = 2.7$ Hz, $J_{H,F} = 54.9, 55.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 15.05, 64.55, 93.77 (dd, $J = 26.3, 29.2$ Hz), 113.40 (t, $J = 241$ Hz); ^{19}F NMR ($CDCl_3$) δ 25.15 (ddd, 1 F, $J_{F,H} = 7.6, 55.7$ Hz, $J_{F,F} = 291$ Hz), 30.11 (ddd, 1 F, $J_{F,H} = 6.1, 54.9$ Hz); IR (cm^{-1}) 3400 (OH). Anal. Calcd for $C_4H_8O_2F_2$: C, 38.10; H, 6.39. Found: C, 38.31; H, 6.24.

2,2-Difluoro-1-phenylethanol (2a). To a solution of phenylmagnesium bromide, which was prepared from bromobenzene (4.4 mmol) and magnesium turnings (0.12 g, 5.0 mmol) in tetrahydrofuran (5 mL), was added 1 (0.25 g, 2.0 mmol) at 0 °C. After 3 h of stirring at room temperature, the mixture was quenched with 1 N HCl (30 mL) and then extracted with ether. The extract was dried over anhydrous $MgSO_4$, and the solvent was removed. Flash chromatography (silica gel, 5:1 hexane–EtOAc) afforded compound **2a** in 70% yield: ^{1}H NMR ($CDCl_3$) δ 2.55 (br, 1 H), 4.81 (ddd, 1 H, $J_{H,H} = 4.8, 9.64, 10.5$ Hz), 5.76 (dt, 1 H, $J_{H,H} = 4.8$ Hz, $J_{H,F} = 55.5$ Hz), 7.3–7.6 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 74.03 (t, $J = 24.4$ Hz), 116.33 (t, $J = 246.3$ Hz), 127.72, 129.27, 129.63, 136.42 (t, $J = 3.1$ Hz); ^{19}F NMR ($CDCl_3$) δ 34.44 (ddd, 1 F, $J_{F,H}$ 11.1, 56.5 Hz, $J_{F,F} = 284.2$ Hz), 35.14 (ddd, 1 F, $J_{F,H} = 9.5, 55.7$, $J_{F,F} = 284.2$ Hz); IR (cm^{-1}) 3400 (OH); high-resolution mass calcd for $C_8H_8OF_2$ 158.0543, found 158.0554. Anal. Calcd for $C_8H_8OF_2$: C, 60.76; H, 5.10. Found: C, 60.39; H, 4.71.

2,2-Difluoro-1-(4-methylphenyl)ethanol (2b). In the above reaction, 1 (0.25 g, 2.0 mmol) and 4-bromotoluene (0.54 mL, 4.4 mmol) were used, and the reaction was worked up similarly, giving 2,2-difluoro-1-(4-methylphenyl)ethanol (**2b**) in 65% yield: ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 2.60–2.90 (br, 1 H), 4.69 (dt, 1 H,

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$J_{H,H}$ = 4.7, 10.2 Hz), 5.61 (dt, 1 H, $J_{H,H}$ = 4.7 Hz, $J_{F,H}$ = 56.0 Hz), 7.16–7.28 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 21.18, 73.51 (t, J = 23.4 Hz), 115.84 (J = 245 Hz), 127.04, 129.37, 130.02, 139.0; ^{19}F NMR ($CDCl_3$) δ 33.84 (ddd, 1 F, $J_{F,H}$ = 10.7, 56.5 Hz, $J_{F,F}$ = 284 Hz), 34.63 (ddd, 1 F, J = 9.9, 55.7 Hz, $J_{F,F}$ = 284 Hz); IR (cm^{-1}) 3400 (OH); high-resolution mass calcd for $C_9H_{10}OF_2$ 172.0700, found 172.0711. Anal. Calcd for $C_9H_{10}OF_2$: C, 62.79; H, 5.86. Found: C, 62.41; H, 5.63.

2,2-Difluoro-1-(2-methylphenyl)ethanol (2c). In the above reaction, 1 (0.25 g, 2.0 mmol) and 2-bromotoluene (0.54 mL, 4.4 mmol) were used, and the reaction was worked up similarly, giving 2,2-difluoro-1-(2-methylphenyl)ethanol (**2c**) in 58% yield: ^{1}H NMR ($CDCl_3$) δ 2.35–2.40 (br, 1 H), 2.39 (s, 3 H), 5.05–5.10 (m, 1 H), 5.76 (ddd, 1 H, $J_{H,H}$ = 5.0, 55.3, 56.8 Hz), 7.20–7.50 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.31, 69.73 (dd, J = 23.7, 26.0 Hz), 116.28 (t, J = 245 Hz), 126.41, 126.60, 128.76, 130.67, 134.35 (dd, J = 2.0, 4.4 Hz), 136.39; ^{19}F NMR ($CDCl_3$) δ 34.08 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 284 Hz), 35.20 (ddd, 1 F, $J_{F,H}$ = 12.2, 56.5 Hz, $J_{F,F}$ = 284 Hz); IR (cm^{-1}) 3400 (OH). Anal. Calcd for $C_9H_{10}OF_2$: C, 62.79; H, 5.86. Found: C, 62.91; H, 5.74.

1,1-Difluoro-4-phenyl-2-butanol (2d). In the above reaction, 1 (0.25 g, 2.0 mmol) and (2-bromoethyl)benzene (0.60 mL, 4.4 mmol) were used, and the reaction was worked up similarly, giving 1,1-difluoro-4-phenyl-2-butanol (**2d**) in 60% yield: ^{1}H NMR ($CDCl_3$) δ 1.80–1.90 (m, 1 H), 1.90–2.00 (m, 1 H), 1.90–2.10 (br, 1 H), 2.72 (ddd, 1 H, $J_{H,H}$ = 7.6, 9.0, 13.9 Hz), 2.88 (ddd, 1 H, $J_{H,H}$ = 4.9, 9.3, 13.9 Hz), 3.80–3.90 (m, 1 H), 5.61 (dt, 1 H, $J_{H,H}$ = 4.1 Hz, $J_{H,F}$ = 56.1 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 30.89, 31.45 (t, J = 3.2 Hz), 70.15 (t, J = 23.3 Hz), 116.32 (t, J = 244 Hz), 126.11, 128.41, 128.48, 140.92; ^{19}F NMR ($CDCl_3$) δ 32.16 (dd, 2 F, $J_{F,H}$ = 10.7, 56.5 Hz); IR (cm^{-1}) 3368 (OH); high-resolution mass calcd for $C_{10}H_{12}OF_2$ (MH)$^+$ 187.0935, found 187.0951. Anal. Calcd for $C_{10}H_{12}OF_2$: C, 64.51; H, 6.50. Found: C, 64.86; H, 6.37.

1,1-Difluoro-2-decanol 2e. Compound 1 (0.25 g, 2.0 mmol) and 1-bromooctane (0.76 mL, 4.4 mmol) were used in the above reaction, and the reaction was worked up similarly, giving 1,1-difluoro-4-phenyl-2-butanol (**2e**) in 39% yield: ^{1}H NMR ($CDCl_3$) δ 0.88–1.65 (m, 17 H), 1.90 (br, 1 H), 3.70–3.75 (m, 1 H), 5.61 (dt, 1 H, $J_{H,H}$ = 4.1 Hz, $J_{H,F}$ = 56.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.21, 22.70, 24.90, 29.26, 29.46 (2 C), 30.05 (t, J = 3.2 Hz), 31.89, 71.20 (t, J = 23.0 Hz), 116.43 (t, J = 243 Hz); ^{19}F NMR ($CDCl_3$) δ 31.60 (ddd, 1 F, $J_{F,H}$ = 11.4, 56.5, $J_{F,F}$ = 286 Hz), 32.38 (ddd, 1 F, $J_{F,H}$ = 10.3, 56.5 Hz, $J_{F,F}$ = 286 Hz); IR (cm^{-1}) 3400 (OH); high-resolution mass calcd for $C_{10}H_{20}OF_2$ (M$^+$ + 1) 195.1482, found 195.1475. Anal. Calcd for $C_{10}H_{20}OF_2$: C, 61.83; H, 10.38. Found: C, 62.17; H, 10.61.

1,1-Difluoro-4-phenyl-3-butyn-2-ol (2f). To a solution of phenylacetylene (0.72 mL, 6.6 mmol) in dry THF (10 mL) was added a solution of *n*-butyllithium in hexane (2.5 M, 2.64 mL, 6.6 mmol) at −78 °C. After 30 min of stirring at the same temperature, 1 (0.38 g, 3.0 mmol) was added to the solution. The whole solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature. After 1 h of stirring, the mixture was quenched with 1 N HCl (20 mL) and then extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$ and the solvent removed. Flash chromatography (silica gel, 5:1 hexane–EtOAc) afforded 1,1-difluoro-4-phenyl-3-butyn-2-ol (**2f**) in 70% yield: ^{1}H NMR ($CDCl_3$) δ 2.50–2.60 (br, 1 H), 4.70–4.80 (m, 1 H), 5.77 (dt, 1 H, $J_{H,H}$ = 3.7 Hz, $J_{H,F}$ = 55.5 Hz), 7.30–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 62.43 (t, J = 27.4 Hz), 82.14 (t, J = 5.2 Hz), 87.93, 113.48 (t, J = 247.0 Hz), 121.34, 128.40, 129.24, 131.98; ^{19}F NMR ($CDCl_3$) δ 33.25 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7 Hz, $J_{F,F}$ = 282 Hz), 33.92 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7, $J_{F,F}$ = 282 Hz); IR (cm^{-1}) 3400 (OH); high-resolution mass calcd for $C_{10}H_8OF_2$ 182.0543, found 182.0548. Anal. Calcd for $C_{10}H_8OF_2$: C, 65.93; H, 4.43. Found: C, 66.31; H, 4.79.

1,1-Difluoro-3-decyn-2-ol (2g). To a solution of 1-octyne (0.65 mL, 4.4 mmol) in dry THF (10 mL) was added a solution of *n*-butyllithium in hexane (2.5 M, 1.76 mL, 4.4 mmol) at −78 °C. After 30 min of stirring at the same temperature, 1 (0.25 g, 2.0 mmol) was added to the solution and the reaction was worked up similarly, giving 1,1-difluoro-3-decyn-2-ol (**2g**) in 55% yield: ^{1}H NMR ($CDCl_3$) δ 0.80–2.30 (m, 13 H), 2.15–2.25 (br, 1 H), 4.45–4.55 (m, 1 H), 5.64 (dt, 1 H, $J_{H,H}$ = 3.8 Hz, $J_{H,F}$ = 55.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.04, 18.66, 28.23, 28.49, 31.03, 63.05 (t, J = 27.3 Hz), 73.69 (t, J = 5.3 Hz), 89.40, 113.99 (t, J = 246.5 Hz); ^{19}F NMR ($CDCl_3$) δ 32.93 (ddd, 1 F, $J_{F,H}$ = 9.9, 56.1 Hz, $J_{F,F}$ = 282 Hz), 33.61 (ddd, 1 F, $J_{F,H}$ = 9.5, 56.1 Hz, $J_{F,F}$ = 282 Hz); IR (cm^{-1}) 3306 (OH); high-resolution mass calcd for $C_{10}H_{16}OF_2$ (MH)$^+$ 191.1248, found 191.1237. Anal. Calcd for $C_{10}H_{16}OF_2$: C, 63.14; H, 8.48. Found: C, 62.81; H, 8.75.

1,1-Difluoro-3-dodecyn-2-ol (2h). In the above reaction, 1 (0.38 g, 3.0 mmol) and decyne (6.6 mmol) were used, and the reaction was worked up similarly, giving 1,1-difluoro-3-dodecyn-2-ol (**2h**) in 67% yield: ^{1}H NMR ($CDCl_3$) δ 0.80–2.30 (m, 17 H), 2.15–2.25 (br, 1 H), 4.45–4.55 (m, 1 H), 5.64 (dt, 1 H, $J_{H,H}$ = 3.7 Hz, $J_{H,F}$ = 55.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.12, 18.67, 22.69, 28.23, 28.83, 29.08, 29.19, 31.86, 63.07 (t, J = 27.3 Hz), 73.72 (t, J = 5.3 Hz), 89.40, 114.00 (t, J = 246.5 Hz); ^{19}F NMR ($CDCl_3$) δ 32.94 (ddd, 1 F, $J_{F,H}$ = 9.9, 56.1 Hz, $J_{F,F}$ = 281.5 Hz), 33.58 (ddd, 1 F, $J_{F,H}$ = 9.5, 56.1 Hz, $J_{F,F}$ = 281.5 Hz); IR (cm^{-1}) 3306 (OH); high-resolution mass calcd for $C_{12}H_{20}OF_2$, 218.1482, found 218.1471. Anal. Calcd for $C_{12}H_{20}OF_2$: C, 66.03; H, 9.24. Found: C, 67.84; H, 9.53.

1,1-Difluoro-2-hydroxy-6-methylheptan-4-one (3a). To a suspension of zinc chloride powder (90%, 0.91 g, 6.0 mmol) and 1 (0.25 g, 2.0 mmol) in dry THF (10 mL) was added the enol silyl ether of methyl isobutyl ketone (1.0 g, 6 mmol) at 0 °C. After 1 h of refluxing, the mixture was quenched with water (10 mL) and extracted with diethyl ether. The extract was dried over anhydrous $MgSO_4$, and the solvent was removed. Flash chromatography (silica gel, 5:1 hexane–EtOAc) gave 1,1-difluoro-2-hydroxy-6-methylheptan-4-one (**3a**) in 63% yield: ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 6 H, $J_{H,H}$ = 6.5 Hz), 2.10–2.20 (m, 1 H), 2.35 (d, 2 H, $J_{H,H}$ = 6.8 Hz), 2.73 (d, 2 H, $J_{H,H}$ = 5.6 Hz), 3.45 (br, 1 H), 4.20–4.30 (m, 1 H), 5.78 (dt, 1 H, $J_{H,H}$ = 3.5 Hz, $J_{H,F}$ = 56.3 Hz); ^{13}C NMR ($CDCl_3$) δ 22.54 (2 C), 24.63, 42.14 (t, J = 2.9 Hz), 52.75, 67.62 (t, J = 25.0 Hz), 118.82 (t, J = 244 Hz), 210.65, ^{19}F NMR ($CDCl_3$) δ 30.21 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 288 Hz), 33.29 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7 Hz, $J_{F,F}$ = 288 Hz); IR (cm^{-1}) 3408 (OH), 1702 (C═O); high-resolution mass calcd for $C_8H_{14}O_2F_2$ 180.0962, found 180.0974. Anal. Calcd for $C_8H_{14}O_2F_2$: C, 53.32; H, 7.83. Found: C, 52.94; H, 7.59.

6,6-Difluoro-5-hydroxy-2,2-dimethylhexan-3-one (3b). In the above reaction, 1 (0.25 g, 2.0 mmol) and the enol silyl ether of methyl *tert*-butyl ketone (1.0 g, 6.0 mmol) were combined, and the reaction was worked up similarly, giving 6,6-difluoro-5-hydroxy-2,2-dimethylhexan-3-one (**3b**) in 58% yield: ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9 H), 2.81 (dd, 1 H, $J_{H,H}$ = 4.2 Hz, $J_{H,F}$ = 17 Hz), 2.83 (dd, 1 H, $J_{H,H}$ = 7.5 Hz, $J_{H,F}$ = 17 Hz), 3.45–3.60 (br, 1 H), 4.15–4.35 (m, 1 H), 5.79 (1 H, ddd, $J_{H,H}$ = 3.5 Hz, $J_{H,F}$ = 56.3, 55.6 Hz); ^{13}C NMR ($CDCl_3$) δ 26.22, 36.16 (t, J = 2.9 Hz), 44.70, 67.88 (t, J = 24.8 Hz), 115.97 (t, J = 244 Hz), 216.21; ^{19}F NMR ($CDCl_3$) δ 30.30 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 288 Hz), 33.32 (ddd, 1 F, $J_{F,H}$ = 9.8, 55.7 Hz, $J_{F,F}$ = 288 Hz); IR (cm^{-1}) 3800 (OH), 1702 (C═O); high-resolution mass calcd for $C_8H_{14}O_2F_2$ (MH)$^+$ 181.1040, found 181.1057. Anal. Calcd for $C_8H_{14}O_2F_2$: C, 53.32; H, 7.83. Found: C, 53.10; H, 7.95.

4,4-Difluoro-3-hydroxy-1-phenylbutan-1-one (3c). In the above reaction, 1 (0.25 g, 2.0 mmol) and the enol silyl ether of methyl phenyl ketone (1.15 g, 6.0 mmol) were used, and the reaction was worked up similarly, giving 4,4-difluoro-3-hydroxy-1-phenylbutan-1-one (**3c**) in 75% yield: ^{1}H NMR ($CDCl_3$) δ 3.30 (dd, 2 H, $J_{H,H}$ = 6.1, 0.5 Hz), 3.20–3.40 (br, 1 H), 4.35 (dddt, 1 H, $J_{H,H}$ = 3.5, 6.1, 9.7 Hz, $J_{H,F}$ = 13.6 Hz), 5.83 (ddd, 1 H, $J_{H,H}$ = 3.5 Hz, $J_{H,F}$ = 55.4, 56.3 Hz), 7.20–8.00 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 37.83 (t, J = 3.0 Hz), 67.69 (t, J = 23.6 Hz), 115.56 (t, J = 243 Hz), 128.19, 128.80, 133.95, 136.21, 198.79; ^{19}F NMR ($CDCl_3$): δ 30.27 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.1 Hz, $J_{F,F}$ = 288 Hz), 33.17 (ddd, 1 F, $J_{F,H}$ = 9.2, 55.3 Hz, $J_{F,F}$ = 288 Hz); IR (cm^{-1}) 3440 (OH), 1680 (C═O); high-resolution mass calcd for $C_{10}H_{10}O_2F_2$ 200.0649, found 200.0639. Anal. Calcd for $C_{10}H_{10}O_2F_2$: C, 60.00; H, 5.04. Found: C, 60.34; H, 4.81.

4,4-Difluoro-3-hydroxy-2-methyl-1-phenylbutan-1-one (3d). In the above reaction, 1 (0.25 g, 2.0 mmol) and the enol silyl ether of ethyl phenyl ketone (1.24 g, 6.0 mmol) were used, and the reaction was worked up similarly, giving 4,4-difluoro-3-hydroxy-2-methyl-1-phenylbutan-1-one (**3d**) in 74% yield (diastereomeric ratio = 2.5:1). Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.17 (dd, 3 H, $J_{H,H}$ = 0.7, 7.2 Hz), 3.20–3.30 (br, 1 H), 3.77 (ddq, 1 H, $J_{H,H}$ = 0.8, 4.4, 7.2 Hz), 4.62 (dddd, 1 H, $J_{H,H}$ = 4.4, 4.4, 8.9 Hz, $J_{H,F}$ = 17.8 Hz), 5.76 (dt, 1 H, $J_{H,H}$ = 4.4 Hz, $J_{H,F}$ = 55.8 Hz), 7.40–8.00

(m, 5 H); ^{13}C NMR (CDCl$_3$) δ 12.55, 40.58 (t, J = 3.5 Hz), 71.44 (t, J = 23.6 Hz), 115.61 (t, J = 244 Hz), 128.96, 129.32, 134.25, 135.54, 203.96; ^{19}F NMR (CDCl$_3$) δ 31.25 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 290 Hz), 32.62 (ddd, 1 F, $J_{F,H}$ = 9.1, 54.9 Hz, $J_{F,F}$ = 290 Hz); IR (cm^{-1}) 3450 (OH), 1690 (C=O). Minor isomer: ^{1}H NMR (CDCl$_3$) δ 1.41 (dd, 3 H, $J_{H,H}$ = 0.6, 7.3, Hz), 3.83 (ddq, 1 H, $J_{H,H}$ = 1.0, 4.3, 7.3 Hz), 3.90–4.10 (m, 1 H), 4.15–4.25 (br, 1 H), 5.85 (dt, 1 H, $J_{H,H}$ = 3.5 Hz, $J_{H,F}$ = 55.7 Hz); ^{13}C NMR (CDCl$_3$) δ 15.50, 38.66 (t, J = 3.0 Hz), 74.46 (t, J = 23.8 Hz), 116.33 (t, J = 246 Hz), 128.96, 129.32, 139.43, 136.02, 205.81; ^{19}F NMR (CDCl$_3$) δ 33.13 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 289 Hz), 34.95 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 289 Hz); IR (cm^{-1}) 3450 (OH), 1650 (C=O); high-resolution mass calcd for $C_{11}H_{12}O_2F_2$ (M$^+$ + 1) 215.0806, found 215.0814. Anal. Calcd for $C_{11}H_{12}O_2F_2$: C, 61.68; H, 5.65. Found: C, 61.54; H, 5.94.

2-Chloro-4,4-difluoro-3-hydroxy-1-phenylbutan-1-one (3e). In the above reaction, 1 (0.25 g, 2.0 mmol) and the enol silyl ether of chloromethyl phenyl ketone (6.0 mmol) were used, and the reaction was worked up similarly, giving 2-chloro-4,4-difluoro-3-hydroxy-1-phenylbutan-1-one (**4e**) in 68% yield (diastereomeric ratio = 1:1): ^{1}H NMR (CDCl$_3$) δ 2.20–2.80 (br, 2 H), 4.40–4.60 (m, 2 H), 5.17 (d, 1 H, $J_{H,H}$ = 7.7 Hz), 5.32 (d, 1 H, $J_{H,H}$ = 3.2 Hz), 5.89 (ddd, 1 H, $J_{H,H}$ = 5.6 Hz, $J_{H,F}$ = 55.2 Hz), 6.12 (dt, 1 H, $J_{H,H}$ = 1.8 Hz, $J_{H,F}$ = 54.7 Hz), 7.20–8.0 (m, 10 H); ^{13}C NMR (CDCl$_3$) δ 50.98 (dd, J = 1.9, 4.6 Hz), 55.19 (dd, J = 2.8, 5.9 Hz), 70.38 (dd, J = 24.9, 26.8 Hz), 70.79 (dd, J = 21.2, 22.7 Hz), 111.7 (dd, J = 243, 245 Hz), 112.1 (dd, J = 242, 245 Hz), 128.7 (2 C), 128.95, 129.2 (2 C), 133.3, 133.9, 192.6, 193.2; ^{19}F NMR (CDCl$_3$) δ 28.54 (ddd, 1 F, $J_{F,H}$ 18.3, 54.9 Hz, $J_{F,F}$ = 295 Hz); 30.54 (ddd, 1 F, $J_{F,H}$ = 10.7, 56.5 Hz, $J_{F,F}$ = 295 Hz), 31.28 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 288 Hz), 32.27 (ddd, 1 F, $J_{F,H}$ = 6.1, 54.9 Hz, $J_{F,F}$ = 295 Hz); IR (cm^{-1}) 3450 (OH), 1650 (C=O); high-resolution mass calcd for $C_{10}H_9O_2F_2Cl$ 234.0259, found 234.0247. Anal. Calcd for $C_{10}H_9O_2F_2Cl$: C, 51.19; H, 3.87. Found: C, 50.82; H, 4.01.

Ethyl 4,4-Difluoro-3-hydroxybutanoate (3f). (a) In the above reaction, 1 (0.25 g, 2.0 mmol) and the silyl ketene acetal of ethyl acetate (0.96 g, 6.0 mmol) were used, and the reaction was worked up similarly, affording ethyl 4,4-difluoro-3-hydroxybutanoate (**3f**) in 25% yield: ^{1}H NMR (CDCl$_3$) δ 1.29 (3 H, t, $J_{H,H}$ = 7.1 Hz), 2.58 (1 H, dd, $J_{H,F}$ = 16.9 Hz, $J_{H,H}$ = 7.6 Hz), 2.69 (1 H, dd, $J_{H,F}$ = 16.9 Hz, $J_{H,H}$ = 4.6 Hz), 3.20–3.30 (1 H, br), 4.10–4.30 (1 H, m), 4.21 (2 H, q, $J_{H,H}$ = 7.1 Hz), 5.80 (1 H, dt, $J_{H,H}$ = 3.7 Hz, $J_{H,F}$ = 55.7 Hz); ^{13}C NMR (CDCl$_3$) δ 14.08, 34.56 (t, J = 3.7 Hz), 61.36, 67.87 (t, J = 25.0 Hz), 115.36 (t, J = 245 Hz), 171.58; ^{19}F NMR (CDCl$_3$) δ 29.97 (ddd, 1 F, $J_{F,H}$ = 12.2, 56.5 Hz, $J_{F,F}$ = 288 Hz), 33.00 (ddd, 1 F, $J_{F,H}$ = 9.1, 54.9 Hz, $J_{F,F}$ = 288 Hz); IR (cm^{-1}) 3450 (OH), 1730 (C=O); high-resolution mass calcd for $C_6H_{10}O_3F_2$ (MH)$^+$ 169.0676, found 169.0694. Anal. Calcd for $C_6H_{10}O_3F_2$: C, 42.86; H, 6.00. Found: C, 43.19; H, 6.41.

(b) To a suspension of zinc powder (85%, 0.60 g, 8.0 mmol) in dry THF (10 mL) were added 1 (0.25 g, 2.0 mmol) and ethyl bromoacetate (0.55 mL, 5.0 mmol) at 0 °C. After being refluxed for 3 h, the mixture was quenched with 1 N HCl (20 mL), and the oily materials were extracted with diethyl ether. The extracts were dried over anhydrous $MgSO_4$ and the solvent was removed. Flash chromatography on silica gel (5:1 hexane–EtOAc) afforded **3f** in 70% yield.

2-(Difluoromethyl)-2,3,5,6-tetrahydropyrone (4a). To a suspension of $ZnCl_2$ (0.91 g, 6.0 mmol) in THF (10 mL) was added **1** (0.25 g, 2.0 mmol) at room temperature. After 5 min, 2-[(trimethylsilyl)oxy]-1,3-butadiene (0.74 mL, 4.2 mmol) was added at the same temperature. After 1 h of stirring, the reaction mixture was quenched with water (15 mL) and extracted with Et_2O (10 mL × 3). The extracts were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography gave **4a** (0.23 g, 1.5 mmol, 75.0%): ^{1}H NMR (CDCl$_3$) δ 2.40 (dddd, 1 H, $J_{H,H}$ = 1.7, 1.7, 2.9, 15.1 Hz), 2.51 (ddd, 1 H, $J_{H,H}$ = 1.6, 3.5, 14.8 Hz), 2.55 (ddd, 1 H, $J_{H,H}$ = 0.9, 10.4, 14.8 Hz), 2.65 (dddd, 1 H, $J_{H,H}$ = 0.9, 7.3, 12.2, 15.1 Hz), 3.74 (dddd, 1 H, $J_{H,H}$ = 0.5, 2.9, 11.6, 12.2 Hz), 3.87 (ddddd, 1 H, $J_{H,H}$ = 3.3, 3.5, 8.0, 10.4, 13.0 Hz), 4.38 (ddd, 1 H, $J_{H,H}$ = 1.7, 7.3, 11.6 Hz), 5.78 (ddd, 1 H, $J_{H,H}$ = 3.3, $J_{H,F}$ = 54.6, 56.0 Hz); ^{13}C NMR (CDCl$_3$) δ 40.15 (dd, J = 2.3, 3.7 Hz), 41.89, 75.73 (dd, J = 25.2, 27.1 Hz), 111.7 (dd, J = 243, 244 Hz), 204.2; ^{19}F NMR (CDCl$_3$) δ 28.58 (ddd, 1 F, $J_{F,H}$ = 13.0, 55.7 Hz, $J_{F,F}$ = 293 Hz), 33.51 (ddd, 1 F, $J_{F,H}$ = 8.0, 54.5 Hz, $J_{F,F}$ = 293 Hz); IR (neat) 1730 (cm^{-1}); high-resolution mass calcd for $C_6H_8O_2F_2$ (MH)$^+$ 151.0492, found 151.0484. Anal. Calcd for $C_6H_8O_2F_2$: C, 48.00; H, 5.37. Found: C, 47.65; H, 5.67.

2-(Difluoromethyl)-2,3-dihydropyrone (4b). To a suspension of $ZnCl_2$ (0.91 g, 6.0 mmol) in dry THF (10 mL) was added hemiacetal 1 (0.25 g, 2.0 mmol) at room temperature. After 5 min of stirring, 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (0.82 mL, 4.2 mmol) was added at the same temperature. After 20 min of stirring, the reaction mixture was quenched with water (15 mL) and extracted with Et_2O (10 mL × 3). The extracts were dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography gave **4b** (0.17 g, 1.2 mmol, 59.0%): ^{1}H NMR (CDCl$_3$) δ 2.60 (ddd, 1 H, J = 0.9, 4.1, 16.8 Hz), 2.75 (dd, 1 H, J = 13.8, 16.8 Hz), 4.60 (dddddd, 1 H, J = 0.6, 3.4, 4.1, 8.4, 12.2, 13.8 Hz), 5.50 (dd, 1 H, J = 1.1, 6.1 Hz), 5.92 (ddd, 1 H, J = 3.4, 54.8, 55.3 Hz), 7.35 (dd, 1 H, J = 0.6, 6.1 Hz); ^{13}C NMR (CDCl$_3$) δ 34.40 (t, J = 2.8 Hz), 76.35 (dd, J = 26.6, 28.2 Hz), 108.0, 110.5 (dd, J = 243, 245 Hz), 161.5, 189.5; ^{19}F NMR (CDCl$_3$) δ 29.96 (ddd, 1 F, J = 12.2, 54.9, 296 Hz), 32.71 (ddd, 1 F, J = 8.4, 54.2, 296 Hz); IR (neat) 1690, 1600 (cm^{-1}); high-resolution mass calcd for $C_6H_6O_2F_2$ 148.0336, found 148.0324. Anal. Calcd for $C_6H_6O_2F_2$: C, 48.66; H, 4.08. Found: C, 48.47; H, 4.36.

Ethyl 4,4-Difluoro-3-hydroxybutanoate (5a) (= 3f). To a suspension of zinc powder (0.60 g) in dry THF (10 mL) were added 1 (0.25 g, 2.0 mmol) and ethyl bromoacetate (0.55 mL, 5.0 mmol) at 0 °C. After 3 h of stirring at room temperature, the mixture was quenched with 1 N HCl (20 mL), and the oily materials were then extracted with diethyl ether. The extracts were dried over magnesium sulfate. On removal of the solvent, flash chromatography gave **5a** in 70% yield.

Ethyl 4,4-Difluoro-3-hydroxy-2-methylbutanoate (5b). In the above Reformatsky-type reaction, 1 (0.25 g, 2.0 mmol) and ethyl 2-bromopropanoate (0.65 mL, 5.0 mmol) were used, and the reaction was worked up similarly, giving ethyl 4,4-difluoro-3-hydroxy-2-methylbutanoate (**5b**) in 70% yield (diastereomeric ratio = 53:47): ^{1}H NMR (CDCl$_3$) δ 1.27 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.28 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.29 (dt, 3 H, $J_{H,H}$ = 7.3, 0.6 Hz), 1.35 (d, 3 H, $J_{H,H}$ = 7.3 Hz), 2.76 (ddq, 1 H, $J_{H,H}$ = 0.9, 4.6, 7.3 Hz), 2.83 (ddq, 1 H, $J_{H,H}$ = 0.9, 4.3, 7.3 Hz), 2.70–2.80 (br, 1 H), 3.50–3.60 (br, 1 H), 3.75–3.85 (m, 1 H), 4.10–4.20 (m, 1 H), 4.18 (q, 2 H, $J_{H,H}$ = 7.1 Hz), 4.19 (dq, 2 H, $J_{H,H}$ = 2.6, 7.1 Hz), 5.70 (ddd, 1 H, $J_{H,H}$ = 4.8 Hz, $J_{H,F}$ = 55.3, 56.1 Hz), 5.83 (dt, 1 H, $J_{H,H}$ = 3.8 Hz, $J_{H,F}$ = 55.7 Hz); ^{13}C NMR (CDCl$_3$) δ 11.33 (2 C), 14.04, 14.07, 40.17 (dd, 2 C, J = 2.7, 4.2 Hz), 61.31, 61.34, 71.17 (t, J = 23.9 Hz), 73.00 (t, J = 23.9 Hz), 115.59 (t, J = 243 Hz), 115.77 (t, J = 244 Hz), 174.51, 174.99; ^{19}F NMR (CDCl$_3$) δ 31.58 (ddd, 1 F, $J_{F,H}$ = 13.0, 55.7 Hz, $J_{F,F}$ = 289 Hz), 31.86 (ddd, 1 F, $J_{F,H}$ = 13.0, 56.1 Hz, $J_{F,F}$ = 291 Hz), 32.98 (ddd, 1 F, $J_{F,H}$ = 8.4, 55.3 Hz, $J_{F,F}$ = 291 Hz), 34.21 (ddd, 1 F, $J_{F,H}$ = 11.4, 55.7 Hz, $J_{F,F}$ = 289 Hz); IR (cm^{-1}) 3475 (OH), 1720 (C=O); high-resolution mass calcd for $C_7H_{12}O_3F_2$ (MH)$^+$ 183.0833, found 183.0845. Anal. Calcd for $C_7H_{12}O_3F_2$: C, 46.15; H, 6.64. Found: C, 46.50; H, 6.51.

Ethyl 4,4-Difluoro-2-ethyl-3-hydroxybutanoate (5c). In the above reaction, 1 (0.38 g, 3.0 mmol) and ethyl 2-bromobutanoate (1.10 mL, 7.5 mmol) were used, and the reaction was worked up similarly, affording ethyl 4,4-difluoro-2-ethyl-3-hydroxybutanoate (**5c**) in 73% yield (diastereomeric ratio = 58: 42): ^{1}H NMR (CDCl$_3$) δ 0.97 (t, 3 H, $J_{H,H}$ = 7.5 Hz), 1.00 (t, 3 H, $J_{H,H}$ = 7.5 Hz), 1.29 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.30 (d, 3 H, $J_{H,H}$ = 7.1 Hz), 1.70–1.80 (m, 2 H), 1.82–1.92 (m, 2 H), 2.50–2.60 (m, 2 H), 2.60–2.70 (br, 2 H), 3.80–3.90 (m, 1 H), 4.02 (dddd, 1 H, $J_{H,H}$ = 4.1, 6.6, 7.6 Hz, $J_{H,F}$ = 14.1 Hz), 4.20–4.30 (m, 4 H), 5.73 (ddd, 2 H, $J_{H,H}$ = 4.1 Hz, $J_{H,F}$ = 55.1, 56.1 Hz); ^{13}C NMR (CDCl$_3$) δ 11.42, 11.58, 14.01, 14.08, 44.87 (t, J = 2.7 Hz), 47.30 (dd, J = 2.6, 3.7 Hz), 60.94, 61.11, 70.91 (dd, J = 22.5, 24.0 Hz), 71.62 (t, J = 24.0 Hz), 115.22 (t, J = 243 Hz), 115.63 (t, J = 245 Hz), 174.97, 175.53; ^{19}F NMR (CDCl$_3$) δ 31.35 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 290 Hz), 31.46 (ddd, 1 F, $J_{F,H}$ = 15.3, 56.4 Hz, $J_{F,F}$ = 288 Hz), 34.14 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7 Hz, $J_{F,F}$ = 288 Hz) 34.44 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 290 Hz); IR (cm^{-1}) 3475 (OH), 1720 (C=O); high-resolution mass calcd for $C_8H_{14}O_3F_2$ 196.0911, found 196.0927. Anal. Calcd for $C_8H_{14}O_3F_2$: C, 48.98; H, 7.19. Found: C, 49.24; H, 6.84.

Ethyl 4,4-Difluoro-2,2-dimethyl-3-hydroxybutanoate (5d). In the above reaction, 1 (0.25 g, 2.0 mmol) and ethyl 2-bromoisobutanoate (0.73 mL, 5.0 mmol) were used, and the reaction was worked up similarly, giving ethyl 4,4-difluoro-2,2-dimethyl-

3-hydroxybutanoate (**5d**) in 74% yield: ^{1}H NMR (CDCl$_3$) δ 1.27 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.28 (s, 3 H), 1.31 (s, 3 H), 3.30–3.40 (br, 1 H), 3.60–3.80 (m, 1 H), 4.18 (dq, 2 H, $J_{H,H}$ = 1.0, 7.1 Hz), 5.78 (ddd, 1 H, $J_{H,H}$ = 3.9 Hz, $J_{H,F}$ = 54.9, 55.7 Hz); ^{13}C NMR (CDCl$_3$) δ 14.01, 21.27, 22.07, 44.23 (t, J = 2.5 Hz), 61.26, 75.54 (dd, J = 21.4, 23.3 Hz), 115.22 (t, J = 244 Hz), 176.22; ^{19}F NMR (CDCl$_3$) δ 34.95 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.5 Hz, $J_{F,F}$ = 241 Hz), 36.45 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.9 Hz, $J_{F,F}$ = 241 Hz); IR (cm^{-1}) 3450 (OH), 1720 (C=O); high-resolution mass calcd for $C_8H_{14}O_3F_2$ (MH)$^+$ 197.0989, found 197.0971. Anal. Calcd for $C_8H_{14}O_3F_2$: C, 48.98; H, 7.19. Found: C, 48.76; H, 7.34.

2,2-Dimethyl-3-(difluoromethyl)oxetan-2-one (6a). A mixture of ethyl 4,4-difluoro-2,2-dimethyl-3-hydroxybutanoate (**5c**) (0.35 g, 1.8 mmol) and 1 N KOH (3 mL) in THF (3 mL) was stirred at room temperature overnight, and the solvent was then removed under dynamic vacuum. The crude acid obtained in pyridine (1 mL) was cooled to 0–5 °C, and benzenesulfonyl chloride (3.6 mmol) was added. The mixture was well shaken, sealed, and placed in the refrigerator overnight. The workup consisted of pouring the reaction mixture onto four volumes of crushed ice and extraction with ether (10 mL × 4). The combined ethereal layers were washed with saturated sodium bicarbonate and water and dried over anhydrous magnesium sulfate. Removal of the solvent and flash chromatography gave **6a** in 10% yield: ^{1}H NMR (CDCl$_3$) δ 1.41 (dd, 3 H, $J_{H,H}$ = 0.6, 1.4 Hz), 1.53 (d, 3 H), 4.25 (ddd, 1 H, $J_{H,H}$ = 5.9, 6.8, 10.3 Hz), 5.92 (ddd, 1 H, $J_{H,H}$ = 5.9 Hz, $J_{H,F}$ = 54.9, 53.5 Hz); ^{13}C NMR (CDCl$_3$) δ 11.39, 22.63, 55.19 (dd, J = 1.3, 4.4 Hz), 76.84 (dd, J = 25.5, 31.3 Hz), 111.07 (dd, J = 241.4, 224.1 Hz), 172.85; ^{19}F NMR (CDCl$_3$) δ 33.95 (ddd, 1 F, $J_{F,H}$ = 6.1, 53.4 Hz, $J_{F,F}$ = 311 Hz), 36.16 (ddd, 1 F, $J_{F,H}$ = 9.2, 54.9 Hz, $J_{F,F}$ = 311 Hz); IR (cm^{-1}) 1840 (C=O); high-resolution mass calcd for $C_6H_8O_2F_2$ (M + 1) 151.0492, found 151.0483. Anal. Calcd for $C_6H_8O_2F_2$: C, 48.00; H, 5.37. Found: C, 48.35; H, 5.71.

2-Phenyl-3-(difluoromethyl)oxetan-2-one (6b). A mixture of ethyl 4,4-difluoro-2,2-dimethyl-3-hydroxybutanoate, ethyl 4,4-difluoro-2-phenyl-3-hydroxybutanoate (0.20 g, 0.8 mmol), and 1 N KOH (3 mL) in THF (3 mL) was stirred at room temperature overnight and then worked up similarly. Flash chromatography gave **6b** in 43% yield: ^{1}H NMR (CDCl$_3$) δ 4.63 (dddd, 1 H, $J_{H,H}$ = 2.8, 4.3, 5.9, 14.0 Hz), 5.02 (d, 1 H, $J_{H,H}$ = 4.3 Hz), 6.13 (ddd, 1 H, $J_{H,H}$ = 2.8 Hz, $J_{H,F}$ = 55.6, 53.7 Hz); ^{13}C NMR (CDCl$_3$) δ 56.71 (dd, J = 2.3, 4.2 Hz), 73.66 (dd, J = 27.5, 31.7 Hz), 111.34 (dd, J = 242.6, 244.9 Hz), 127.14, 128.82, 129.43, 130.64, 166.42; ^{19}F NMR (CDCl$_3$) δ 28.86 (ddd, 1 F, $J_{F,H}$ = 13.7, 54.9 Hz, $J_{F,F}$ = 302 Hz), 33.42 (ddd, 1 F, $J_{F,H}$ = 5.3, 54.2 Hz, $J_{F,F}$ = 302 Hz); IR (cm^{-1}) 1850 (C=O); high-resolution mass calcd for $C_{10}H_8O_2F_2$ 198.0492, found 198.0481. Anal. Calcd for $C_{10}H_8O_2F_2$: C, 60.61; H, 4.07. Found: C, 60.43; H, 4.25.

1,1-Difluoro-3-nitro-2-propanol (7a). To a suspension of potassium carbonate (0.03 g, 0.2 mmol) in dry THF (10 mL) were added **1** (0.25 g, 2.0 mmol) and nitromethane (0.16 mL, 3.0 mmol) at 0 °C. After being stirred for 3 h at room temperature, the mixture was quenched with 1 N HCl (10 mL), and the oily materials were extracted with diethyl ether. The extracts were dried over anhydrous MgSO$_4$, and the solvent was removed. The residual oil was purified by distillation to give 1,1-difluoro-3-nitro-2-propanol (**7a**) in 65% yield: bp 75 °C (0.9 mmHg); ^{1}H NMR (CDCl$_3$) δ 2.95–3.10 (br, 1 H), 4.55–4.65 (m, 1 H), 4.60 (dd, 1 H, $J_{H,H}$ = 0.6, 12.6 Hz), 4.87 (dd, 1 H, $J_{H,H}$ = 2.44, 12.6 Hz), 6.00 (1 H, $J_{H,H}$ = 3.7 Hz, $J_{H,F}$ = 55.2 Hz); ^{13}C NMR (CDCl$_3$) δ 68.13 (dd, J = 24.4, 26.9 Hz), 74.58 (t, J = 3.9 Hz), 113.94 (dd, J = 245, 246 Hz); ^{19}F NMR (CDCl$_3$) δ 33.40 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.7 Hz, $J_{F,F}$ = 289 Hz), 34.90 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.7 Hz, $J_{F,F}$ = 289 Hz); IR (cm^{-1}) 3500 (OH), 1560, 1380 (NO$_2$); high-resolution mass calcd for $C_3H_5NO_3F_2$ (M$^+$ + 1) 142.0238, found 142.0244. Anal. Calcd for $C_3H_5NO_3F_2$: C, 25.54; H, 3.57; N, 9.93. Found: C, 25.86; H, 3.19; N, 9.77.

1,1-Difluoro-3-nitro-2-butanol (7b). In the above reaction, **1** (0.25 g, 2.0 mmol) and nitroethane (0.21 mL, 3.0 mmol) were used, and the reaction was worked up similarly, giving 1,1-difluoro-3-nitro-2-butanol (**7b**) in 68% yield (diastereomeric ratio = 52:48): bp 80 °C (0.9 mmHg); ^{1}H NMR (CDCl$_3$) δ 1.68 (t, 6 H, $J_{H,H}$ = 5.9 Hz), 1.80–2.60 (br, 1 H), 2.60–3.60 (br, 1 H), 4.52 (dddd, 1 H, $J_{H,H}$ = 1.0, 4.6, 9.3, 11.4 Hz), 4.10 (dddd, 1 H, $J_{H,H}$ = 3.9, 6.0, 10.2, 11.7 Hz), 4.72 (ddq, 1 H, $J_{H,H}$ = 1.0, 3.4, 6.8 Hz), 4.81 (dq, 1 H, $J_{H,H}$ = 6.8 Hz), 5.73 (dt, 1 H, $J_{H,H}$ = 4.9 Hz, $J_{H,F}$ = 55.2 Hz), 5.87 (dt, 1 H, $J_{H,H}$ = 3.9 Hz, $J_{H,F}$ = 54.9 Hz); ^{13}C NMR (CDCl$_3$) δ 12.76, 15.64 (t, J = 1.6 Hz), 71.09 (t, J = 25.1 Hz), 72.13 (t, J = 24.6 Hz), 81.53 (dd, J = 2.4, 4.1 Hz), 82.59 (t, J = 3.3 Hz), 114.31 (t, J = 245 Hz), 114.45 (t, J = 245 Hz); ^{19}F NMR (CDCl$_3$) δ 31.56 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 294 Hz), 32.45 (ddd, 1 F, $J_{F,H}$ = 9.5, 54.9 Hz, $J_{F,F}$ = 294 Hz), 33.58 (ddd, 1 F, $J_{F,H}$ = 11.4, 55.3 Hz, $J_{F,F}$ = 295 Hz), 34.51 (ddd, 1 F, $J_{F,H}$ = 11.8, 55.3 Hz, $J_{F,F}$ = 294 Hz); IR (cm^{-1}) 3450 (OH), 1560, 1365 (NO$_2$); high-resolution mass calcd for $C_4H_7NO_3F_2$ 155.0394, found 155.0387. Anal. Calcd for $C_4H_7NO_3F_2$: C, 30.98; H, 4.55; N, 9.03. Found: C, 31.31; H, 4.37; N, 8.79.

1,1-Difluoro-3-nitro-2-pentanol (7c). In the above reaction, **1** (0.25 g, 2.0 mmol) and nitropropane (0.27 mL, 3.0 mmol) were used, and the reaction was worked up similarly, giving 1,1-difluoro-3-nitro-2-pentanol **7c** in 68% yield; bp 80 °C (0.8 mmHg); ^{1}H NMR (CDCl$_3$) δ 1.02 (t, 3 H, $J_{H,H}$ = 7.4 Hz), 1.03 (t, 3 H, $J_{H,H}$ = 7.4 Hz), 1.85–2.30 (m, 4 H), 3.10–3.60 (br, 2 H), 4.10–4.40 (m, 2 H), 4.55–4.70 (m, 2 H), 5.69 (dt, 1 H, $J_{H,H}$ = 4.1, $J_{H,F}$ = 55 Hz), 5.73 (dt, 1 H, $J_{H,H}$ = 3.4, $J_{H,F}$ = 54.8 Hz); ^{13}C NMR (CDCl$_3$) s 10.0, 10.15, 22.27, 23.35, 71.01 (t, J = 25.6 Hz), 71.17 (t, J = 24.5 Hz), 86.40 (t, J = 3.1 Hz), 88.61 (t, J = 3.1 Hz), 114.09 (t, J = 245 Hz), 114.32 (t, J = 245 Hz); ^{19}F NMR (CDCl$_3$) δ 31.52 (ddd, 1 F, $J_{F,H}$ = 11.1, 54.5 Hz, $J_{F,F}$ = 294 Hz), 32.83 (ddd, 2 F, $J_{F,H}$ = 2.3, 54.9 Hz), 34.00 (ddd, 1 F, $J_{F,H}$ = 11.4, 54.9 Hz, $J_{F,F}$ = 294 Hz); IR (cm^{-1}) 3500 (OH), 1560 (NO$_2$); high-resolution mass calcd for $C_5H_9NO_3F_2$ 169.0550, found 169.0564. Anal. Calcd for $C_5H_9NO_3F_2$: C, 35.51; H, 5.36; N, 8.28. Found: C, 35.27; H, 5.49; N, 8.53.

1,1-Difluoro-3-methyl-3-nitro-2-butanol (7d). In the above reaction, **1** (0.25 g, 2.0 mmol) and 2-nitropropane (0.25 mL, 3.0 mmol) were used and the reaction was worked up similarly, giving 1,1-difluoro-3-methyl-3-nitro-2-butanol (**7d**) in 82% yield: bp 80 °C (0.8 mmHg); ^{1}H NMR (CDCl$_3$) δ 1.67 (s, 3 H), 1.68 (s, 3 H), 2.95–3.05 (br, 1 H), 4.34 (ddd, 1 H, $J_{H,H}$ = 4.7, 8.4, 13.1 Hz), 5.77 (ddd, 1 H, $J_{H,H}$ = 4.7 Hz, $J_{H,F}$ = 54.6, 55.2 Hz); ^{13}C NMR (CDCl$_3$) s 20.98, 23.37 (dd, J = 3.0, 1.5 Hz), 73.89 (dd, J = 24.7, 23.2 Hz), 89.10 (dd, J = 3.5, 1.5 Hz), 114.50 (t, J = 244 Hz); ^{19}F NMR (CDCl$_3$) δ, 35.29 (ddd, 1 F, $J_{F,H}$ = 13.0, 55.3 Hz, $J_{F,F}$ = 297 Hz), 37.02 (ddd, 1 F, $J_{F,H}$ = 8.0, 54.5 Hz, $J_{F,F}$ = 297 Hz); IR (cm^{-1}) 3500 (OH), 1550, 1360 (NO$_2$); high-resolution mass calcd for $C_5H_9NO_3F_2$ (M$^+$ + 1) 170.0550, found 170.0535. Anal. Calcd for $C_5H_9NO_3F_2$: C, 35.51; H, 5.36; N, 8.28. Found: C, 35.84; H, 5.69; N, 8.47.

Ethyl 4,4-Difluoro-3-hydroxy-2-nitrobutanoate (7e). In the above reaction, **1** (1.90 g, 15.0 mmol) and ethyl nitroacetate (1.66 mL, 15.0 mmol) were used, and the reaction was worked up similarly, affording ethyl 4,4-difluoro-3-hydroxy-2-nitrobutanoate (**7e**) in 92% yield: bp 140 °C (0.8 mmHg); ^{1}H NMR (CDCl$_3$) δ 1.34 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.35 (3 H, $J_{H,H}$ = 7.1 Hz), 3.50–3.60 (br, 1 H), 3.70–3.80 (br, 1 H), 4.36 (dq, 2 H, $J_{H,H}$ = 2.7, 7.1 Hz), 4.37 (q, 2 H, $J_{H,H}$ = 7.1 Hz), 4.59 (dddd, 1 H, $J_{H,H}$ = 4.0, 5.2, 9.6, 11.5 Hz), 4.68 (dddd, 1 H, $J_{H,H}$ = 3.3, 4.8, 9.3, 10.6 Hz), 5.38 (1 H, $J_{H,H}$ = 3.3 Hz), 5.38 (d, 1 H, $J_{H,H}$ = 5.3 Hz), 5.95 (ddd, 1 H, $J_{H,H}$ = 4.8 Hz, $J_{H,F}$ = 54.9, 55.7 Hz), 5.96 (dt, 1 H, $J_{H,H}$ = 4.0 Hz, $J_{H,F}$ = 54.9 Hz); ^{13}C NMR (CDCl$_3$) δ 13.75, 13.79 (t, J = 1.6 Hz), 64.18, 64.24, 70.05 (t, J = 25.4 Hz), 70.52 (t, J = 26.8 Hz), 85.68 (dd, J = 2.3, 4.9 Hz), 86.33 (t, J = 3.3 Hz), 111.28 (t, J = 246 Hz), 113.61 (t, J = 245 Hz), 162.06, 162.46; ^{19}F NMR (CDCl$_3$) δ 32.29 (ddd, 1 F, $J_{F,H}$ = 9.5, 54.9 Hz, $J_{F,F}$ = 294 Hz), 32.50 (ddd, 1 F, $J_{F,H}$ = 9.2, 54.9 Hz, $J_{F,F}$ = 295 Hz), 33.15 (ddd, 1 F, $J_{F,H}$ = 11.4, 54.9 Hz, $J_{F,F}$ = 294 Hz), 35.00 (ddd, 1 F, $J_{F,H}$ = 10.7, 55.7 Hz, $J_{F,F}$ = 295 Hz); IR (cm^{-1}) 3450 (OH), 1560, 1365 (NO$_2$); high-resolution mass calcd for $C_6H_9NO_5F_2$ (MH)$^+$ 214.0527, found 214.0543. Anal. Calcd for $C_6H_9NO_5F_2$: C, 33.81; H, 4.26; N, 6.57. Found: C, 34.04; H, 4.62; N, 6.19.

Ethyl 5,5-Difluoro-4-hydroxy-3-nitropentanoate (7f). In the above reaction, **1** (0.25 g, 2.0 mmol) and ethyl nitropropanoate (0.29 g, 2.0 mmol) were used and the reaction was worked up similarly, affording ethyl 5,5-difluoro-4-hydroxy-3-nitropentanoate (**7f**) in 82% yield: bp 220 °C (0.8 mmHg); ^{1}H NMR (CDCl$_3$) δ 1.29 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 1.30 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 2.93 (dd, 1 H, $J_{H,H}$ = 3.7, 17.5 Hz), 2.96 (dd, 1 H, $J_{H,H}$ = 5.0, 17.5 Hz), 3.28 (dd, 1 H, $J_{H,H}$ = 4.8, 17.7 Hz), 3.30 (3 H, dd, $J_{H,H}$ = 5.2, 17.5 Hz), 3.25–3.35 (br, 2 H), 4.15–4.20 (m, 1 H), 4.21 (q, 2 H, $J_{H,H}$ = 7.1 Hz), 4.22 (q, 2 H, $J_{H,H}$ = 7.1 Hz), 4.60–4.70 (m, 1 H), 5.10 (dt, 1 H, $J_{H,H}$ = 3.7, 8.8 Hz), 5.14 (dt, 1 H, $J_{H,H}$ = 4.3, 8.5 Hz), 5.85 (dt, 1 H, $J_{H,H}$ = 4.0 Hz, $J_{H,F}$ = 54.9 Hz), 5.94 (ddd, 1 H, $J_{H,H}$ = 5.2 Hz, $J_{H,F}$ = 54.6, 56.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.96, 32.08 (t, J = 1.6 Hz), 34.18, 61.93, 70.89 (t, J = 24.9 Hz), 71.01 (t, J = 26.6 Hz), 81.50 (dd, J = 2.4, 5.1 Hz), 81.98 (t, J = 2.9 Hz), 114.33 (dd, J = 244, 245 Hz), 169.47, 170.03; ^{19}F NMR ($CDCl_3$) δ 32.29 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 295 Hz), 34.42 (ddd, 1 F, $J_{F,H}$ = 11.1, 56.5 Hz, $J_{F,F}$ = 295 Hz); IR (cm^{-1}) 3500 (OH), 1730 (C=O), 1570 (NO_2); high-resolution mass calcd for $C_7H_{11}NO_5F_2$ 227.0605, found 227.0617. Anal. Calcd for $C_7H_{11}NO_5F_2$: C, 37.01; H, 4.88; N, 6.17. Found: C, 36.87; H, 4.64; N, 5.96.

Methyl 6,6-Difluoro-5-hydroxy-4-nitrohexanoate (7g). In the above reaction, 1 (0.25 g, 2.0 mmol) and ethyl 4-nitrobutanoate (0.29 g, 2.0 mmol) were used, and the reaction was worked up similarly, affording ethyl 6,6-difluoro-5-hydroxy-4-nitrohexanoate (**7g**) in 90% yield by chromatography: ^{1}H NMR ($CDCl_3$) δ 2.20–2.60 (m, 8 H), 3.10–3.40 (br, 2 H), 3.72 (s, 6 H), 4.00–4.20 (m, 1 H), 4.30–4.50 (m, 1 H), 4.70–4.90 (m, 2 H), 5.86 (dt, 1 H, $J_{H,H}$ = 4.2 Hz, $J_{H,F}$ = 55.3 Hz), 5.91 (dt, 1 H, $J_{H,H}$ = 4.0 Hz, $J_{H,F}$ = 55.0 Hz); ^{13}C NMR ($CDCl_3$) δ 23.51, 24.75 (t, J = 1.5 Hz), 29.72, 29.79, 52.23, 52.26, 71.14 (t, J = 24.9 Hz), 71.35 (t, J = 25.0 Hz), 85.56 (t, J = 3.2 Hz), 86.06 (t, J = 3.3 Hz), 114.17 (t, J = 245 Hz), 114.34 (t, J = 245 Hz), 172.76, 173.17; ^{19}F NMR ($CDCl_3$) δ 32.00 (ddd, 1 F, $J_{F,H}$ = 10.3, 54.5 Hz, $J_{F,F}$ = 294 Hz), 32.49 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.9 Hz, $J_{F,F}$ = 295 Hz), 33.33 (ddd, 1 F, $J_{F,H}$ = 11.1, 54.9 Hz, $J_{F,F}$ = 295 Hz), 34.30 (ddd, 1 F, $J_{F,H}$ = 11.1, 55.3 Hz, $J_{F,F}$ = 294 Hz); IR (cm^{-1}) 3500 (OH), 1730 (C=O), 1560 (NO_2); high-resolution mass calcd for $C_8H_{13}NO_5F_2$ (MH)$^+$ 242.0840, found 242.0827. Anal. Calcd for $C_8H_{13}NO_5F_2$: C, 39.84; H, 5.43; N, 5.81. Found: C, 39.51; H, 5.61; N, 5.57.

Ethyl 4,4-Difluorothreonate (8) (Threo).[6] To a suspension of 10% Pd–C (0.25 g) as a catalyst in dry AcOH (7.0 mL) was added **7f** (0.43 g, 2.0 mmol). The reaction mixture was stirred under hydrogen. After 24 h of stirring at room temperature, the catalyst was removed by filtration, and then the filtrate was washed with saturated aqueous $NaHCO_3$. Removal of the solvent and flash chromatography (silica gel, 1:1 hexane–EtOAc) gave 8 (threo) (0.06 g, 0.53 mmol, 16.3%) and *allo*-8 (erythro) (0.27 g, 1.47 mmol, 73.7%): ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 2.20–2.60 (br, 3 H), 3.80 (d, 1 H, $J_{H,H}$ = 2.3 Hz), 4.08 (dddd, 1 H, $J_{H,H}$ = 2.3, 4.4, 9.5, 12.5 Hz), 4.25 (q, 2 H, $J_{H,H}$ = 7.1 Hz), 5.85 (dt, 1 H, $J_{H,H}$ = 4.4 Hz, $J_{H,F}$ = 55.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.27, 54.24 (dd, J = 2.2, 5.6 Hz), 62.01, 71.12 (dd, J = 24.4, 26.6 Hz), 116.22 (t, J = 244 Hz), 173.67; ^{19}F NMR ($CDCl_3$) δ 31.02 (ddd, 1 F, $J_{F,H}$ = 12.2, 56.1 Hz, $J_{F,F}$ = 290 Hz), 31.98 (ddd, 1 F, $J_{H,H}$ = 9.5, 56.1 Hz, $J_{F,F}$ = 290 Hz); IR (neat) 3100, 2900, 1730 (cm^{-1}).

***allo*-Ethyl 4,4-difluoroallothreonate 8 (erythro):**[6] ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 2.20–2.50 (br, 3 H), 3.71 (d, 1 H, $J_{H,H}$ = 4.7 Hz), 4.02 (dddd, 1 H, $J_{H,H}$ = 4.3, 4.7, 10.7, 11.4 Hz), 4.27 (dq, 2 H, $J_{H,H}$ = 0.96, 7.1 Hz), 5.85 (dt, 1 H, $J_{H,H}$ = 4.3 Hz, $J_{H,F}$ = 55.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.08, 54.74 (t, J = 3.7 Hz), 61.79, 71.86 (t, J = 24.1 Hz), 115.35 (t, J = 244 Hz), 172.25; ^{19}F NMR ($CDCl_3$) δ 32.23 (ddd, 1 F, $J_{H,H}$ = 11.4, 55.7 Hz, $J_{F,F}$ = 292 Hz), 33.03 (ddd, 1 F, $J_{H,H}$ = 10.7, 55.7 Hz, $J_{F,F}$ = 292 Hz); IR (neat) 3150, 2900, 1720 (cm^{-1}).

Synthesis of Methyl 3-Acetamido-5,5-difluoro-2,3,5-trideoxypentafuranoside (10). 5,5-Difluoro-3-nitro-2,3,5-trideoxypentafuranose 7f–1. To a solution of **7f** (6.40 g, 28.2 mmol) in freshly dried Et_2O (30.0 mL) was added dropwise a hexane solution of diisobutylaluminum hydride (DIBAL-H, 1M, 62.0 mL, 62.0 mmol) at −78 °C. After 0.5 h of stirring, 3 N HCl was added and then the whole solution was allowed to warm to room temperature. Oily materials were extracted with Et_2O (20 mL × 2), and then the extracts were dried over anhydrous $MgSO_4$. Removal of the solvent and flash chromatography gave **7f-1** (3.3 g, 18.0 mmol, 63.8%, diastereoselectivity = 35:30:22:13): ^{1}H NMR ($CDCl_3$) δ 2.60–3.00 (m, 8 H), 3.20–3.40 (br, 4 H), 4.80–4.95 (m, 4 H), 5.00–5.40 (m, 4 H), 5.60–5.80 (m, 2 H), 5.68 (ddd, 1 H, $J_{H,H}$ = 4.45 Hz, $J_{H,F}$ = 55.5, 55.9 Hz), 5.79 (ddd, 1 H, $J_{H,H}$ = 5.5 Hz, $J_{H,F}$ = 55.5, 55.7 Hz), 5.88 (ddd, 1 H, $J_{H,H}$ = 1.9 Hz, $J_{H,F}$ = 53.3, 56.1 Hz), 5.88 (ddd, 1 H, $J_{H,H}$ = 4.7 Hz, $J_{H,F}$ = 55.0, 55.7 Hz), 6.50–6.60 (m, 1 H), 6.80–6.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 38.32, 38.77, 39.00, 70.64 (t, J = 25.1 Hz), 77.30 (dd, J = 25.9, 29.2 Hz), 79.58 (dd, J = 22.2, 28.6 Hz), 81.0 (t, J = 27.0 Hz), 82.74 (dd, J = 1.5, 4.0 Hz), 83.76 (dd, J = 2.3, 4.4 Hz), 84.83 (dd, J = 2.1, 4.3 Hz), 98.84, 99.24, 99.76, 110.69 (dd, J = 244, 246 Hz), 110.88 (dd, J = 242, 244 Hz), 113.94 (t, J = 246 Hz), 114.71 (t, J = 246 Hz); ^{19}F NMR ($CDCl_3$) δ 27.46 (ddd, 1 F, $J_{F,H}$ = 20.6, 56.5 Hz, $J_{F,F}$ = 291 Hz), 32.49 (ddd, 1 F, $J_{F,H}$ = 10.7, 55.7 Hz, $J_{F,F}$ = 290 Hz), 33.29 (dddd, 1 F, $J_{F,H}$ = 2.3, 11.8, 55.7 Hz, $J_{F,F}$ = 295 Hz), 33.63 (ddd, 1 F, $J_{F,H}$ = 5.3, 53.4 Hz, $J_{F,F}$ = 291 Hz), 35.16 (dddd, 1 F, $J_{F,H}$ = 1.5, 4.6, 53.8 Hz, $J_{F,F}$ = 308 Hz), 35.20 (ddd, 1 F, $J_{F,H}$ = 9.9, 56.1 Hz, $J_{F,F}$ = 290 Hz), 35.51 (ddd, 1 F, $J_{F,H}$ = 9.2, 54.9 Hz, $J_{F,F}$ = 295 Hz), 36.91 (ddd, 1 F, J = 12.6, 55.7, 308 Hz), IR (neat) 3450, 1560 (cm^{-1}).

Methyl 5,5-Difluoro-3-nitro-2,3,5-trideoxypentafuranoside (9). To a solution of *p*-toluenesulfonic acid (catalytic amount) in methanol (30 mL) was added **7f–1** (3.3 g, 18.0 mmol) at room temperature. After 12 h of stirring, methanol was removed under reduced pressure. Flash chromatography gave **9** (2.9 g, 14.7 mmol, 81.7%, diastereoselectivity = 37.0:36.8:18.5:7.7): ^{1}H NMR ($CDCl_3$) δ 2.40–2.48 (m, 2 H), 2.49 (dddd, 1 H, $J_{H,H}$ = 0.37, 4.6, 8.6, 14.9 Hz), 2.55–2.60 (m, 1 H), 2.80 (dddd, 1 H, $J_{H,H}$ = 0.49, 5.2, 6.9, 14.0 Hz), 2.86 (dddd, 1 H, $J_{H,H}$ = 0.99, 3.9, 5.4, 14.8 Hz), 2.94 (dt, 1 H, $J_{H,H}$ = 14.8, 0.73 Hz), 3.06 (dd, 1 H, $J_{H,H}$ = 0.49, 7.7 Hz), 3.34 (s, 3 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.42 (s, 3 H), 4.09–4.14 (m, 1 H), 4.41–4.49 (m, 1 H), 4.70–4.76 (m, 1 H), 4.85–4.90 (m, 1 H), 4.93 (ddd, 1 H, $J_{H,H}$ = 1.5, 2.9, 9.0 Hz), 5.11 (dddd, 1 H, $J_{H,H}$ = 2.1, 2.9, 6.3, 20.3 Hz), 5.19 (dd, 1 H, $J_{H,H}$ = 1.5, 4.7 Hz), 5.20–5.25 (m, 1 H), 5.27–5.32 (m, 3 H), 5.40 (ddd, 1 H, $J_{H,H}$ = 1.8, 2.3, 5.5 Hz), 5.80 (ddd, 1 H, $J_{H,H}$ = 5.6, 53.6 Hz, $J_{H,F}$ = 55.8 Hz), 5.81 (dt, 1 H, $J_{H,H}$ = 5.2 Hz, $J_{H,F}$ = 55.5 Hz), 5.84 (ddd, 1 H, $J_{H,H}$ = 4.3 Hz, $J_{H,F}$ = 54.6, 55.6 Hz), 5.91 (ddd, 1 H, $J_{H,H}$ = 2.1 Hz, $J_{H,F}$ = 53.3, 56.1 Hz); ^{13}C NMR ($CDCl_3$) δ 30.09, 37.70, 38.37, 38.61, 55.00, 55.07, 55.50, 55.93, 71.46 (t, J = 25.3 Hz), 77.31 (dd, J = 25.7, 30.2 Hz), 78.53 (dd, J = 22.0, 28.6 Hz), 81.24 (t, J = 27.4 Hz), 82.06 (dd, J = 1.3, 4.2 Hz), 83.69 (dd, J = 2.0, 4.7 Hz), 84.61 (dd, J = 1.6, 4.7 Hz), 108.78, 104.87, 105.10, 105.99, 110.93 (dd, J = 239, 247 Hz), 113.31 (t, J = 245 Hz), 113.86 (t, J = 246 Hz); ^{19}F NMR ($CDCl_3$) δ 28.00 (ddd, 1 F, $J_{F,H}$ = 20.2, 56.1, $J_{F,F}$ = 291 Hz), 32.36 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.9 Hz, $J_{F,F}$ = 294 Hz), 33.57 (ddd, 1 F, $J_{F,H}$ = 6.5, 53.4 Hz, $J_{F,F}$ = 291 Hz), 33.85 (dddd, 1 F, $J_{F,H}$ = 2.3, 10.7, 55.7 Hz, $J_{F,F}$ = 295 Hz), 33.90 (ddd, 1 F, $J_{F,H}$ = 11.4, 54.9 Hz, $J_{F,F}$ = 294 Hz), 35.16 (ddd, 1 F, $J_{F,H}$ = 5.3, 53.4 Hz, $J_{F,F}$ = 308 Hz), 36.01 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7 Hz, $J_{F,F}$ = 295 Hz), 37.30 (ddd, 1 F, $J_{F,H}$ = 12.6, 55.7 Hz, $J_{F,F}$ = 308 Hz); IR (neat) 1560 (cm^{-1}). Anal. Calcd for $C_6H_9NO_4F_2$: C, 36.56; H, 4.60; N, 7.11. Found: C, 36.38; H, 4.71; N, 7.09.

Methyl 3-Amino-5,5-difluoro-2,3,5-trideoxypentafuranoside (9′). To a suspension of 10% Pd–C (0.90 g) in Et_2O was added **9** (2.90 g, 14.7 mmol). The mixture was stirred under 1 atm of hydrogen. After 12 h of stirring, the catalyst was removed by filtration and then the filtrate was concentrated. Flash chromatography gave **9′** (1.84 g, 11.0 mmol, 75%, diastereoselectivity = 1:1): ^{1}H NMR ($CDCl_3$) δ 1.95–2.20 (m, 6 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.78 (ddd, 1 H, $J_{H,H}$ = 1.1, 2.4, 8.2 Hz), 3.85–3.94 (m, 1 H), 4.02–4.08 (m, 1 H), 4.15–4.27 (m, 1 H), 4.36 (ddt, 1 H, $J_{H,H}$ = 2.4, 10.7, 16.6 Hz), 4.58–4.60 (m, 1 H), 5.09–5.10 (m, 1 H), 5.12 (d, 1 H, $J_{H,H}$ = 5.2 Hz), 5.26–5.27 (m, 1 H), 4.0–5.0 (br, 6 H), 5.72 (ddd, 1 H, $J_{H,H}$ = 5.9 Hz, $J_{H,F}$ = 55.8, 56.6 Hz), 5.75 (ddd, 1 H, $J_{H,H}$ = 2.4 Hz, $J_{H,F}$ = 54.4, 55.9 Hz), 6.12 (dt, 1 H, $J_{H,H}$ = 4.6 Hz, $J_{H,F}$ = 54.8 Hz); ^{13}C NMR ($CDCl_3$) δ 35.87, 36.18, 36.56, 55.00, 55.15, 55.32, 61.16 (dd, J = 2.0, 3.5 Hz), 61.36 (dd, J = 1.6, 4.9 Hz), 79.71 (dd, J = 23.1, 27.3 Hz), 80.03 (dd, J = 22.7, 23.4 Hz), 104.61, 105.75, 105.95, 113.12 (dd, J = 243, 244 Hz), 114.42 (t, J = 244 Hz); ^{19}F NMR ($CDCl_3$) δ 30.05 (ddd, 1 F, $J_{F,H}$ = 16.8, 55.7 Hz, $J_{F,F}$ = 288 Hz), 32.13 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.2 Hz, $J_{F,F}$ = 288 Hz), 34.45 (ddd, 1 F, $J_{F,H}$ = 8.4, 55.7 Hz, $J_{F,F}$ = 292 Hz), 35.73 (dd, 2 F, $J_{F,H}$ = 11.1, 55.3 Hz), 37.39 (ddd, 1 F, $J_{F,H}$ = 11.4, 54.5 Hz, $J_{F,F}$ = 292 Hz); IR (neat) 3300, 2900 (cm^{-1}).

Methyl 3-Acetamido-5,5-difluoro-2,3,5-trideoxypentafuranoside (10). To a solution of **9′** (0.50 g, 3.0 mmol) in CH_2Cl_2 (5.0 mL) were added acetic acid anhydride (0.34 mL, 3.6 mmol) and pyridine (0.32 mL, 4.0 mol) at 0 °C. After 2 h of stirring at room temperature, the mixture was quenched with 1 N HCl (5.0 mL) and then extracted with CH_2Cl_2 (4.0 mL × 2). The extracts were dried over anhydrous $MgSO_4$, and the solvent was removed. Flash chromatography gave **10** (0.62 g, 3.0 mmol, >98%): ^{1}H NMR ($CDCl_3$) δ 2.00–2.10 (m, 4 H), 2.11 (s, 3 H), 3.35 (s, 3 H), 3.39 (s, 3 H), 3.94 (ddd, 1 H, $J_{H,H}$ = 1.2, 2.6, 8.4 Hz), 4.15–4.20 (m, 1 H), 4.21 (dddd, 1 H, $J_{H,H}$ = 2.6, 2.6, 8.3, 18.0 Hz), 4.30–4.40

(m, 1 H), 5.13 (dd, 2 H, $J_{H,H}$ = 1.2, 4.7 Hz), 5.65 (ddd, 1 H, $J_{H,H}$ = 6.0 Hz, $J_{H,F}$ = 55.9, 56.5 Hz), 5.73 (ddd, 1 H, $J_{H,H}$ = 2.6 Hz, $J_{H,F}$ = 54.3, 56.2 Hz); ^{13}C NMR ($CDCl_3$) δ 19.05, 20.39, 36.25, 36.80, 54.99, 55.14, 59.43 (dd, J = 2.0, 3.9 Hz), 60.27 (dd, J = 1.5, 5.4 Hz), 80.07–81.10 (m, 2 C), 105.51, 105.76, 111.68 (dd, J = 243, 245 Hz), 112.75 (dd, J = 243, 246 Hz); ^{19}F NMR ($CDCl_3$) δ 28.99 (ddd, 1 F, $J_{F,H}$ = 17.9, 56.1, $J_{F,F}$ = 290 Hz), 32.24 (ddd, 1 F, $J_{F,H}$ = 8.4, 54.2, $J_{F,F}$ = 290 Hz), 34.23 (dddd, 1 F, $J_{F,H}$ = 2.3, 8.7, 56.2, $J_{F,F}$ = 293 Hz), 36.92 (ddd, 1 F, $J_{F,H}$ = 11.1, 56.4, $J_{F,F}$ = 293 Hz); IR (neat) 1780 (cm^{-1}); high-resolution mass calcd for $C_8H_{13}NO_3F_2$ $(MH)^+$ 210.0942, found 210.0959. Anal. Calcd for $C_8H_{13}NO_3F_2$: C, 45.93; H, 6.26; N, 6.70. Found: C, 45.76; H, 6.51; N, 6.37.

Methyl 4-Acetamido-6,6-difluoro-2,3,4,6-tetradeoxyhexapyranoside (12). 6,6-Difluoro-4-nitro-2,3,4,6-tetradeoxyhexapyranose (7g-1). In a manner similar to the synthesis of **10**, the reaction was performed with **7g** (3.90 g, 17.2 mmol) and DIBAL-H (34.4 mL, 34.4 mmol) to give **7g-1** (2.50 g, 12.7 mmol, 73.8%, diastereoselectivity = 35:35:15:15): ^{1}H NMR ($CDCl_3$) δ 1.70–2.80 (m, 16 H), 2.97–3.00 (br, 1 H), 3.00–3.20 (br, 1 H), 3.35–3.45 (br, 2 H), 3.92 (ddt, 1 H, $J_{H,H}$ = 6.2, 14.2, 2.3 Hz), 4.39 (ddt, 1 H, $J_{H,H}$ = 3.8, 7.9, 9.8 Hz), 4.40–4.50 (m, 1 H), 4.60–4.80 (m, 5 H), 4.95–5.00 (m, 1 H), 5.05–5.10 (m, 1 H), 5.40–5.47 (br, 2 H), 5.79 (ddd, 1 H, $J_{H,H}$ = 2.5 Hz, $J_{H,F}$ = 54.0, 54.6 Hz), 5.90 (ddd, 1 H, $J_{H,H}$ = 3.9 Hz, $J_{H,F}$ = 54.2, 55.3 Hz), 6.08 (ddd, 1 H, $J_{H,H}$ = 6.3 Hz, $J_{H,F}$ = 53.5, 58.7 Hz), 6.16 (ddd, 1 H, $J_{H,H}$ = 6.2 Hz, $J_{H,F}$ = 53.2, 58.3 Hz); ^{13}C NMR ($CDCl_3$) δ 21.33, 23.22, 24.58, 25.46, 25.84, 27.38, 27.84, 29.91, 67.50 (dd, J = 23.2, 25.2 Hz), 67.85 (dd, J = 27.0, 32.0 Hz), 73.96 (t, J = 25.4 Hz), 77.56 (dd, J = 1.8, 7.2 Hz), 77.60–78.00 (m, 2 C), 78.31 (t, J = 2.90 Hz), 79.14 (dd, J = 2.2, 3.8 Hz), 90.53, 91.44, 94.96, 96.78, 113.3 (t, J = 245 Hz), 113.4 (dd, J = 240, 245 Hz), 113.8 (t, J = 245 Hz), 114.1 (dd, J = 240, 244 Hz); ^{19}F NMR ($CDCl_3$) δ 29.94 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 294 Hz), 31.62 (dd, 1 F, $J_{F,H}$ = 53.4, $J_{F,F}$ = 299 Hz), 32.14 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.3 Hz, $J_{F,F}$ = 296 Hz), 32.45 (dd, 1 F, $J_{F,H}$ = 51.9 Hz, $J_{F,F}$ = 299 Hz), 32.58 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.2 Hz, $J_{F,F}$ = 294 Hz), 33.82 (ddd, 1 F, $J_{F,H}$ = 9.5, 54.2 Hz, $J_{F,F}$ = 296 Hz), 37.60 (ddd, 1 F, $J_{F,H}$ = 15.3, 58.7 Hz, $J_{F,F}$ = 299 Hz), 37.92 (ddd, 1 F, $J_{F,H}$ = 11.5, 58.9, $J_{F,F}$ = 299 Hz); IR (neat) 3450, 2950, 1550 (cm^{-1}).

Methyl 6,6-Difluoro-4-nitro-2,3,4,6-tetradeoxyhexapyranoside (11). The reaction was performed with **7g-1** (2.57 g, 12.7 mmol) to give **11** (1.96 g, 9.3 mmol, 73.1%, diastereoselectivity = 46.8:40.9:8.9:3.4): ^{1}H NMR ($CDCl_3$) δ 1.70–2.55 (m, 16 H), 3.40 (s, 3 H), 3.44 (s, 3 H), 3.50 (s, 3 H), 3.51 (s, 3 H), 3.92 (ddt, 1 H, $J_{H,H}$ = 6.2, 14.2, 2.3 Hz), 4.39 (ddt, 1 H, $J_{H,H}$ = 3.8, 7.9, 9.8), 4.15–4.25 (m, 1 H), 4.40–4.50 (m, 3 H), 4.60–4.70 (m, 6 H), 4.80–4.85 (m, 2 H), 5.82 (ddd, 1 H, $J_{H,H}$ = 3.9 Hz, $J_{H,F}$ = 54.7, 55.2 Hz), 5.85 (dt, 1 H, $J_{H,H}$ = 2.7 Hz, $J_{H,F}$ = 54.3 Hz), 5.90 (ddd, 1 H, $J_{H,H}$ = 4.4 Hz, $J_{H,F}$ = 54.6, 55.5 Hz), 6.10 (ddd, 1 H, $J_{H,H}$ = 6.5 Hz, $J_{H,F}$ = 53.5, 58.8 Hz); ^{13}C NMR ($CDCl_3$) δ 21.98, 23.93, 24.38, 24.66, 24.70, 27.40, 27.70, 28.54, 53.28, 55.09, 55.28, 56.61, 67.45 (dd, J = 23.4, 25.3 Hz), 67.87 (dd, J = 27.5, 32.2 Hz), 71.25 (t, J = 24.7 Hz), 73.73 (t, J = 26.0 Hz), 77.54 (dd, J = 1.6, 7.5 Hz), 78.38 (t, J = 3.3 Hz), 78.38 (dd, J = 2.2, 3.7 Hz), 86.69 (t, J = 3.1 Hz), 97.17, 98.07, 101.23, 103.65, 118.8 (dd, J = 239, 244 Hz), 113.6 (t, J = 245 Hz), 113.8 (t, J = 245 Hz), 114.3 (t, J = 245 Hz); ^{19}F NMR ($CDCl_3$) δ 29.82 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.9 Hz, $J_{F,F}$ = 294 Hz), 31.60 (dd, 1 F, $J_{F,H}$ = 53.4 Hz, $J_{F,F}$ = 298 Hz), 32.56 (dddd, 1 F, $J_{F,H}$ = 3.8, 11.2, 53.9 Hz, $J_{F,F}$ = 294 Hz), 32.83 (dd, 1 F, $J_{F,H}$ = 53.0, $J_{F,F}$ = 298 Hz), 33.38 (ddd, 1 F, $J_{F,H}$ = 9.1, 54.8 Hz, $J_{F,F}$ = 297 Hz), 34.73 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.7 Hz, $J_{F,F}$ = 297 Hz), 37.87 (ddd, 1 F, $J_{F,H}$ = 14.5, 58.0 Hz, $J_{F,F}$ = 298 Hz), 38.12 (ddd, 1 F, $J_{F,H}$ = 16.0, 58.7 Hz, $J_{F,F}$ = 298 Hz); IR (neat) 2950, 1550 (cm^{-1}). Anal. Calcd for $C_7H_{11}NO_4F_2$: C, 39.82; H, 5.25; N, 6.63. Found: C, 39.71; H, 5.54; N, 6.90.

Methyl 4-Amino-6,6-difluoro-2,3,4,6-tetradeoxyhexapyranoside (11′). The reaction was performed with **11** (1.05 g, 5.0 mmol) to give **11′** (0.44 g, 2.45 mmol, 49.0%, diastereoselectivity = 1:1): ^{1}H NMR ($CDCl_3$) δ 1.60–2.10 (m, 8 H), 3.10 (ddd, 1 H, J = 4.6, 9.9, 10.6 Hz), 3.28–3.30 (m, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.87–3.95 (m, 1 H), 4.00–4.10 (m, 1 H), 4.40–4.50 (m, 3 H), 4.78–4.80 (br, 2 H), 5.00–5.90 (br, 4 H), 5.95 (ddd, 1 H, $J_{H,H}$ = 6.5 Hz, $J_{H,F}$ = 53.5, 58.3 Hz), 6.05 (dt, 1 H, $J_{H,H}$ = 6.5 Hz, $J_{H,F}$ = 54.1 Hz); ^{13}C NMR ($CDCl_3$) δ 19.94, 21.54, 23.94, 28.45, 54.29 (d, J = 6.05 Hz), 54.82 (2 C), 56.03 (t, J = 2.8 Hz), 69.10 (dd, J = 22.5, 31.1 Hz), 69.19 (t, J = 21.3 Hz), 97.50, 98.25, 112.0 (dd, J = 239, 243 Hz), 115.4 (t, J = 243 Hz); ^{19}F NMR ($CDCl_3$) δ 30.62 (ddd, 1 F, $J_{F,H}$ = 11.4, 54.9 Hz, $J_{F,F}$ = 286 Hz), 31.74 (ddd, 1 F, $J_{F,H}$ = 14.5, 54.2 Hz, $J_{F,F}$ = 286 Hz), 32.05 (ddd, 1 F, $J_{F,H}$ = 4.6, 53.4 Hz, $J_{F,F}$ = 293 Hz), 35.50–36.27 (br, 1 F); IR (neat) 3275, 2950 (cm^{-1}).

Methyl 4-Acetamido-6,6-difluoro-2,3,4,6-tetradeoxyhexapyranoside (12). The reaction was performed with **11′** (0.36 g, 2.0 mmol) to give **12** (0.36 g, 1.61 mmol, 80.6%): ^{1}H NMR ($CDCl_3$) δ 1.80–2.00 (m, 8 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 3.05–3.10 (m, 1 H), 3.37–3.40 (m, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 3.85–3.95 (m, 1 H), 4.03 (dddd, 1 H, $J_{H,H}$ = 2.2, 4.4, 6.7, 13.4 Hz), 4.80–4.82 (m, 2 H), 5.89 (ddd, 1 H, $J_{H,H}$ = 6.7 Hz, $J_{H,F}$ = 53.6, 58.2 Hz), 6.13 (dt, 1 H, $J_{H,H}$ = 1.4 Hz, $J_{H,F}$ = 53.9 Hz), 7.45–7.55 (br, 1 H), 7.82–7.90 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.02 (2 C), 19.96, 21.25, 23.88, 28.40, 52.98 (d, J = 6.40 Hz), 54.81 (2 C), 55.96 (dd, J = 1.8, 5.0 Hz), 68.84 (dd, J = 23.2, 31.4 Hz), 69.54 (t, J = 19.8 Hz), 97.37, 98.12, 112.0 (dd, J = 239, 244 Hz), 114.5 (t, J = 243 Hz), 170.85 (2 C); ^{19}F NMR ($CDCl_3$) δ 26.30–27.30 (br, 1 F), 29.48 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.2, $J_{F,F}$ = 283 Hz), 31.05 (dd, 1 F, $J_{F,H}$ = 53.8, $J_{F,F}$ = 294 Hz); 34.66 (ddd, 1 F, $J_{F,H}$ = 13.3, 58.4, $J_{F,F}$ = 294 Hz); IR (neat) 3275, 2950, 1780 (cm^{-1}); high-resolution mass calcd for $C_9H_{15}NO_3F_2$ $(MH)^+$ 224.1098, found 224.1079. Anal. Calcd for $C_9H_{15}NO_3F_2$: C, 48.43; H, 6.77; N, 6.28. Found: C, 48.67; H, 6.59; N, 6.19.

***N*-(2,2-Difluoroethylidene)benzylamine (13a).** To a solution of benzylamine (3.21 g, 30 mmol) in toluene was added **1** (3.78 g, 30.0 mmol) at 0 °C, and the mixture was stirred at 100 °C for 1 h. After water and ethanol were removed under reduced pressure, the residual oil was purified by distillation to afford *N*-(difluoroethylidene)bezylamine (**13a**) in 78% yield: ^{1}H NMR ($CDCl_3$) δ 4.72 (m, 2 H), 6.15 (dd, 1 H, $J_{H,H}$ = 5.3 Hz, $J_{H,F}$ = 54.9 Hz), 7.20–7.40 (m, 5 H), 7.70 (ddt, 1 H, $J_{H,H}$ = 1.8, 3.5, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 64.17, 112.96 (t, J = 238 Hz), 127.64, 128.19, 128.76, 136.89, 156.02 (t, J = 31.9 Hz); ^{19}F NMR ($CDCl_3$) δ 41.63 (ddd, 2 F, $J_{F,H}$ = 3.0, 5.3, 54.9 Hz); IR (cm^{-1}) 3000; high-resolution mass calcd for $C_9H_9NF_2$ $(MH)^+$ 170.0781, found 170.0794. Anal. Calcd for $C_9H_9NF_2$: C, 63.90; H, 5.36; N, 8.28. Found: C, 63.68; H, 5.69; N, 8.54.

***N*-(2,2-Difluoroethylidene)-4-methoxyaniline (13b).** To a solution of *p*-anisidine (3.69 g, 30.0 mmol) in toluene was added **1** (3.78 g, 30.0 mmol) at 0 °C, and then the mixture was stirred at 100 °C for 3 h. After water and ethanol were removed under reduced pressure, the residual oil was purified by distillation to afford *N*-(difluoroethylidene)-4-methoxyaniline (**13b**) in 91% yield: ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 3 H), 6.10 (dt, 1 H, $J_{H,H}$ = 5.3 Hz, $J_{H,F}$ = 54.9 Hz), 6.90–7.30 (m, 5 H), 7.84 (dt, 1 H, $J_{H,H}$ = 2.6, 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 55.47, 111.79 (t, J = 237 Hz), 114.49, 122.78, 141.25, 150.88 (t, J = 31.9 Hz), 159.87; ^{19}F NMR ($CDCl_3$) δ 42.73 (ddd, 2 F, $J_{F,H}$ = 3.0, 54.9 Hz); IR (cm^{-1}) 3050; high-resolution mass calcd for $C_{10}H_{11}NOF_2$ $(MH)^+$ 200.0887, found 200.0895. Anal. Calcd for $C_{10}H_{11}NOF_2$: C, 60.30; H, 5.57; N, 7.03. Found: C, 60.68; H, 5.41; N, 7.41.

2-(*N*-Benzylamino)-3,3-difluoropropyl Phenyl Ketone (14a). To a solution of **13a** (0.34 g, 2 mmol) and the enol silyl ether of methyl phenyl ketone (0.46 g, 2.4 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}Et_2O$ (0.3 mL, 2.4 mmol) at 0 °C. After 1 h of stirring, the reaction mixture was quenched with water (10 mL), and oily materials were extracted with CH_2Cl_2 (10 mL × 3). The extracts were dried over anhydrous $MgSO_4$. Removal of the solvent and flash chromatography on silica gel using a mixture of hexane–EtOAc (5:1) as an eluent afforded in **14a** 62% yield: ^{1}H NMR ($CDCl_3$) δ 1.70–1.80 (bs, 1 H), 3.17 (ddd, 1 H, $J_{H,H}$ = 1.0, 7.6, 17.3 Hz), 3.30 (dd, 1 H, $J_{H,H}$ = 4.6, 17.3 Hz), 3.60 (m, 1 H), 3.89 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 3.93 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 5.95 (dt, 1 H, $J_{H,H}$ = 3.2 Hz, $J_{H,F}$ = 56.4 Hz), 7.20–8.00 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 37.48 (t, J = 3.6 Hz), 52.13, 55.51 (t, J = 21.7 Hz), 115.31 (t, J = 244 Hz), 127.2, 128.1, 128.4, 128.7, 133.4, 136.6, 139.8, 197.7; ^{19}F NMR ($CDCl_3$) δ 34.99 (ddd, 1 F, $J_{F,H}$ = 15.3, 56.5 Hz, $J_{F,F}$ = 289 Hz), 36.97 (ddd, 1 F, $J_{F,H}$ = 10.7, 56.5 Hz, $J_{F,F}$ = 289 Hz); IR (cm^{-1}) 3348, 3300 (NH), 1756 (C=O); high-resolution mass calcd for $C_{17}H_{17}NOF_2$ 289.1278, found 289.1291. Anal. Calcd for $C_{17}H_{17}NOF_2$: C, 70.57; H, 5.92; N, 4.84. Found: C, 70.19, H, 6.24; N, 5.09.

5-(*N*-Benzylamino)-6,6-difluoro-2,2-dimethylhexan-3-one (14b). The reaction was performed with **13a** (0.34 g, 2.0

mmol) and the enol silyl ether of methyl *tert*-butyl ketone (0.42 g, 2.4 mmol) to give **14b** (0.28 g, 1.22 mmol, 61.0%): ^{1}H NMR (CDCl$_3$) δ 1.14 (9 H, s), 2.69 (ddd, 1 H, $J_{H,H}$ = 1.2, 7.3, 17.8 Hz), 2.81 (dd, 1 H, $J_{H,H}$ = 4.8, 17.8 Hz), 3.38–3.64 (m, 1 H), 3.84 (d, 1 H, $J_{H,H}$ = 12.9 Hz), 3.90 (d, 1 H, $J_{H,H}$ = 12.9 Hz), 5.55 (dt, 1 H, $J_{H,H}$ = 3.2 Hz, $J_{H,F}$ = 56.5 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 25.70, 36.08 (t, J = 3.5 Hz), 44.80, 52.66, 55.90 (t, J = 21.6 Hz), 117.40 (t, J = 245 Hz), 127.6, 128.6, 128.9, 140.4, 214.1; ^{19}F NMR (CDCl$_3$) δ 34.92 (ddd, 1 F, $J_{F,H}$ = 15.3, 56.5, $J_{F,F}$ = 282 Hz), 36.97 (ddd, 1 F, $J_{F,H}$ = 12.2, 56.5, $J_{F,F}$ = 282 Hz); IR (neat) 3400, 3000, 1709 (cm^{-1}); high-resolution mass calcd for $C_{15}H_{21}NOF_2$ (MH)$^+$ 270.1670, found 270.1657. Anal. Calcd for $C_{15}H_{21}NOF_2$: C, 66.89; H, 7.86; N, 5.20. Found: C, 67.18; H, 7.51; N, 5.41.

5-(*N*-Benzylamino)-6,6-difluoro-2-methylheptan-4-one (14c). The reaction was performed with **13a** (0.34 g, 2.0 mmol) and the enol silyl ether of methyl isobutyl ketone (0.42 g, 2.4 mmol) to give **14C** (0.30 g, 1.12 mmol, 55.8%): ^{1}H NMR (CDCl$_3$) δ 0.91 (d, 3 H, J = 2.0 Hz), 0.93 (d, 3 H, $J_{H,H}$ = 2.1 Hz), 2.10–2.18 (m, 1 H), 2.30 (d, 2 H, $J_{H,H}$ = 7.0 Hz), 2.58 (ddd, 1 H, $J_{H,H}$ = 0.8, 7.4, 17.2 Hz), 2.69 (dd, 1 H, $J_{H,H}$ = 4.7, 17.2 Hz), 3.36–3.44 (m, 1 H), 3.84 (d, 1 H, $J_{H,H}$ = 13.0 Hz), 3.90 (d, 1 H, $J_{H,H}$ = 13.0 Hz), 5.77 (dt, 1 H, $J_{H,H}$ = 3.3 Hz, $J_{H,F}$ = 56.4 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 22.49, 22.54, 24.47, 41.76 (t, J = 3.3 Hz), 52.02, 52.41, 55.31 (t, J = 21.7 Hz), 116.77 (t, J = 244 Hz), 127.2, 128.1, 128.5, 138.8, 208.4; ^{19}F NMR (CDCl$_3$) δ 34.88 (ddd, 1 F, $J_{F,H}$ = 15.3, 56.5 Hz, $J_{F,F}$ = 282 Hz), 36.97 (ddd, 1 F, $J_{F,H}$ = 10.7, 56.5 Hz, $J_{F,F}$ = 282 Hz); IR (neat) 3346, 3000, 1715 (cm^{-1}); high-resolution mass calcd for $C_{15}H_{21}NOF_2$ 269.1591, found 269.1578. Anal. Calcd for $C_{15}H_{21}NOF_2$: C, 66.89; H, 7.86; N, 5.20. Found: C, 66.56, H, 7.67; N, 5.01.

Ethyl 3-(*N*-Benzylamino)-4,4-difluorobutanoate (14d). The reaction was performed with **13a** (0.51 g, 3.0 mmol) and the enol silyl ether of ethyl acetate (0.51 g, 3.2 mmol) to give **14d** (0.38 g, 1.47 mmol, 49.0%): ^{1}H NMR (CDCl$_3$) δ 1.26 (dd, J = 6.9, 7.0 Hz), 2.49 (ddd, 1 H, $J_{H,H}$ = 0.8, 7.8, 15.9 Hz), 2.64 (dd, 1 H, $J_{H,H}$ = 4.8, 15.9 Hz), 3.31–3.39 (m, 1 H), 3.89 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 3.92 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 4.18 (dq, 1 H, $J_{H,H}$ = 14.0, 7.0 Hz), 4.19 (1 H, dq, $J_{H,H}$ = 14.0, 6.9 Hz), 5.78 (1 H, dt, $J_{H,H}$ = 3.4 Hz, $J_{H,F}$ = 56.3 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR (CDCl$_3$) δ 14.14, 33.77 (t, J = 4.0 Hz), 51.77, 56.04 (t, J = 22.0 Hz), 60.88, 116.6 (t, J = 245 Hz), 127.2, 128.1, 128.5, 139.7, 171.1; ^{19}F NMR (CDCl$_3$) δ 34.92 (ddd, 1 F, $J_{F,H}$ = 15.3, 56.5 Hz, $J_{F,F}$ = 282 Hz), 36.97 (ddd, 1 F, $J_{F,H}$ = 12.2, 56.5 Hz, $J_{F,F}$ = 282 Hz); IR (neat) 3000, 1680 (cm^{-1}); high-resolution mass calcd for $C_{13}H_{17}NO_2F_2$ (MH)$^+$ 258.1306, found 258.1324. Anal. Calcd for $C_{13}H_{17}NO_2F_2$: C, 60.69; H, 6.66; N, 5.44. Found: C, 60.35, H, 6.76; N, 5.73.

Ethyl 3-(*N*-Benzylamino)-4,4-difluoro-2-methylbutanoate (14e). The reaction was performed with **13a** (0.51 g, 3.0 mmol) and the enol silyl ether of ethyl propanoate (0.58 g, 3.3 mmol) to give **14e** (0.53 g, 1.95 mmol, 65.0%, diastereoselectivity = 68:32). Major isomer: ^{1}H NMR (CDCl$_3$) δ 1.22 (d, 3 H, $J_{H,H}$ = 7.1 Hz), 1.25 (t, 3 H, $J_{H,H}$ = 7.1 Hz), 2.75 (ddq, 1 H, $J_{H,H}$ = 0.6, 5.7, 7.1 Hz), 3.01 (dddd, 1 H, $J_{H,H}$ = 4.0, 5.9, 8.9, 14.8 Hz), 3.89 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 4.01 (d, 1 H, $J_{H,H}$ = 13.1 Hz), 4.05–4.20 (m, 2 H), 5.84 (ddd, 1 H, $J_{H,H}$ = 3.9 Hz, $J_{H,F}$ = 55.7, 56.6 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 11.97, 14.14, 40.12 (t, J = 4.1 Hz), 52.63, 60.74, 61.00 (t, J = 22.0 Hz), 117.3 (t, J = 245 Hz), 127.1, 128.3, 128.4, 140.0, 174.1; ^{19}F NMR (CDCl$_3$) δ 36.05 (ddd, 1 F, $J_{F,H}$ = 14.9, 56.8 Hz, $J_{F,F}$ = 285 Hz), 36.97 (ddd, 1 F, $J_{F,H}$ = 10.3, 55.3 Hz, $J_{F,F}$ = 285 Hz); IR (neat) 3400, 3000, 1720 (cm^{-1}). Minor: ^{1}H NMR (CDCl$_3$) δ 1.22 (t, 3 H, J = 7.1 Hz), 1.23 (d, 3 H, J = 7.1 Hz), 2.75 (ddq, 1 H, J = 0.6, 5.7, 7.1 Hz), 3.25–3.35 (m, 1 H), 3.84 (d, 1 H, J = 13.1 Hz), 3.95 (d, 1 H, J = 13.1 Hz), 4.05–4.20 (m, 2 H), 5.76 (ddd, 1 H, $J_{H,H}$ = 3.8 Hz, $J_{H,F}$ = 55.8, 56.3 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 11.94, 14.10, 32.30 (t, J = 4.1 Hz), 52.46, 59.73 (t, J = 22.0 Hz), 60.74, 117.3 (dd, J = 245, 246 Hz), 127.2, 128.3, 128.4, 140.0, 174.3; ^{19}F NMR (CDCl$_3$) δ 35.28 (ddd, 1 F, $J_{F,H}$ = 13.7, 56.4 Hz, $J_{F,F}$ = 284 Hz), 39.31 (ddd, 1 F, $J_{F,H}$ = 11.7, 55.7 Hz, $J_{F,F}$ = 284 Hz); IR (neat) 3400, 3000, 1720 (cm^{-1}). Anal. Calcd for $C_{14}H_{19}NO_2F_2$: C, 61.98; H, 7.06; N, 5.16. Found: C, 61.73; H, 7.38; N, 4.97.

***N*-Benzyl-4-(difluoromethyl)-2-azetidinone (15a).** (a) To a suspension of zinc powder (0.23 g, 3.0 mmol) in dry THF (5 mL) were added *N*-(difluoroethylidene)benzylamine (**13a**) (0.34 g, 2.0 mmol) and ethyl bromoacetate (0.24 mL, 2.2 mmol) at 0 °C. After 3 h of refluxing, the mixture was quenched with 1 N HCl (10 mL), the oily materials were extracted with diethyl ether and the extracts were dried over anhydrous MgSO$_4$. Removal of the solvent and flash chromatography on silica gel using a mixture of hexane–EtOAc (5:1) as an eluent afforded *N*-benzyl-4-(difluoromethyl)-2-azetidinone (**15a**) in 45% yield: ^{1}H NMR (CDCl$_3$) δ 2.90 (ddd, 1 H, $J_{H,H}$ = 0.8, 2.4, 14.9 Hz), 3.05 (ddd, 1 H, $J_{H,H}$ = 0.8, 5.4, 14.9 Hz), 3.67 (ddddd, 1 H, $J_{H,H}$ = 2.4, 4.3, 5.4, 7.8, 10.5 Hz), 4.14 (d, 1 H, $J_{H,F}$ = 14.5 Hz), 4.71 (1 H, $J_{H,F}$ = 14.5 Hz), 5.73 (dt, 1 H, $J_{H,H}$ = 4.3, $J_{H,F}$ = 54.6 Hz), 7.28–7.36 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 37.93 (t, J = 3.6 Hz), 45.95, 50.51 (t, J = 26.2 Hz), 115.31 (t, J = 242.3 Hz), 128.04, 128.51, 128.94, 135.21, 165.75; ^{19}F NMR (CDCl$_3$) δ 37.08 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9, $J_{F,F}$ = 294 Hz), 38.14 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 294 Hz); IR (cm^{-1}) 3000, 1756 (C=O); high-resolution mass calcd for $C_{11}H_{11}NOF_2$ 211.0809, found 211.0824. Anal. Calcd for $C_{11}H_{11}NOF_2$: C, 62.55; H, 5.25; N, 6.63. Found: C, 62.84; H, 5.54; N, 6.92.

(B) To a solution of diisopropylamine (0.15 mL, 1.1 mmol) in THF (3 mL) was added a hexane solution of *n*-BuLi (2.5 M, 0.44 mL, 1.1 mmol) at −78 °C. After the solution was stirred for 30 min at this temperature, ethyl acetate (0.10 mL, 1.0 mmol) was added to the mixture. After the mixture was stirred for 30 min at −78 °C, a solution of *N*-(difluoroethylidene)benzylamine **7** (0.17 g, 1.0 mmol) in THF (1 mL) was added slowly. The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. After being stirred for 1 h at room temperature, the mixture was quenched with 1 N HCl (5 mL) and extracted with diethyl ether. The extracts were dried over anhydrous MgSO$_4$, and the solvent was removed. Flash chromatography on silica gel using a solution of hexane–EtOAc (5:1) as an eluent afforded *N*-benzyl-4-(difluoromethyl)-2-azetidinone (**15a**) in 71%.

***N*-Benzyl-4-(difluoromethyl)-3-methyl-2-azetidinone (15b).** In the above reaction, *N*-(difluoroethylidene)benzylamine **7** (0.34 g, 2.0 mmol) and ethyl 2-bromopropanoate (0.29 mL, 2.2 mmol) were used, and the reaction was worked up similarly, affording *trans*- and *cis*-**15b** in 78% yield (diastereomeric ratio = 1:1). Anal. Calcd for $C_{12}H_{13}NOF_2$: C, 63.99; H, 5.82; N, 6.22. Found: C, 64.33; H, 6.04; N, 6.54. ***trans*-15b**: ^{1}H NMR (CDCl$_3$) δ 1.30 (t, 3 H, $J_{H,H}$ = 7.4 Hz), 3.15 (dq, 1 H, $J_{H,H}$ = 2.1, 7.3 Hz), 3.26 (dddd, 1 H, $J_{H,H}$ = 2.1, 4.6, 7.6, 10.1 Hz), 4.05 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 4.73 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 5.73 (dt, 1 H, $J_{H,H}$ = 4.8 Hz, $J_{H,F}$ = 54.9 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 12.47, 45.58, 46.07 (t, J = 3.5 Hz), 58.14 (dd, J = 24.4, 26.9 Hz), 115.36 (t, J = 243 Hz), 127.98, 128.42, 128.85, 135.37, 169.57; ^{19}F NMR (CDCl$_3$) δ 34.98 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 296 Hz), 39.00 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 296 Hz); IR (cm^{-1}) 3000, 1763 (C=O); high-resolution mass calcd for $C_{12}H_{13}NOF_2$ 225.0965, found 225.0953.

***cis*-15b**: ^{1}H NMR (CDCl$_3$) δ 1.30 (dt, 3 H, $J_{H,H}$ = 1.0, 7.7 Hz), 3.15 (dq, 1 H, $J_{H,H}$ = 5.6, 7.7 Hz), 3.62 (dddd, 1 H, $J_{H,H}$ = 5.6, 5.9, 6.0, 11.6 Hz), 4.07 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 4.73 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 5.80 (1 H, ddd, $J_{H,H}$ = 5.9 Hz, $J_{H,F}$ = 54.2, 55.9 Hz), 7.30–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 9.16, 35.55, 46.30 (d, J = 6.1 Hz), 53.92 (dd, J = 21.6, 29.3 Hz), 115.63 (t, J = 243 Hz), 127.94, 128.52, 128.77, 135.36, 169.83; ^{19}F NMR (CDCl$_3$) δ 40.02 (ddd, 1 F, $J_{F,H}$ = 10.7, 56.5 Hz, $J_{F,F}$ = 303 Hz), 41.85 (ddd, 1 F, $J_{F,H}$ = 6.1, 53.4 Hz, $J_{F,F}$ = 303 Hz); IR (cm^{-1}) 2986, 1756 (C=O); high-resolution mass calcd for $C_{12}H_{13}NOF_2$ 225.0965, found 225.0950.

***trans*-*N*-Benzyl-4-(difluoromethyl)-3-ethyl-2-azetidinone (15c).** In the above reaction, *N*-(difluoroethylidene)benzylamine **7** (0.34 g, 2.0 mmol) and ethyl 2-bromobutanoate (0.32 mL, 2.2 mmol) were used, and the reaction was worked up similarly, giving *trans*- and *cis*-**15c** in 71% yield (diastereomeric ratio = 1:1). Anal. Calcd for $C_{13}H_{15}NOF_2$: C, 65.26; H, 6.32; N, 5.85. Found: C, 65.41; H, 6.70; N, 5.59. ***trans*-15c**: ^{1}H NMR (CDCl$_3$) δ 0.97 (t, 3 H, $J_{H,H}$ = 7.3 Hz), 1.59 (ddq, 1 H, $J_{H,H}$ = 7.3, 8.6, 14.2 Hz), 1.80 (ddq, 1 H, $J_{H,H}$ = 7.3, 6.2, 14.2 Hz), 3.07 (ddd, 1 H, $J_{H,H}$ = 2.4, 6.2, 8.6 Hz), 3.32 (dddd, 1 H, $J_{H,H}$ = 2.4, 4.9, 7.4, 10.0 Hz), 4.07 (1 H, $J_{H,H}$ = 0.7 Hz, $J_{H,F}$ = 14.9 Hz), 4.75 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 5.73 (dt, 1 H, $J_{H,H}$ = 4.9 Hz, $J_{H,F}$ = 54.9 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 11.16, 20.87, 45.54, 52.90 (t, J = 3.1 Hz), 56.25 (dd, J = 24.8, 26.9 Hz), 115.51 (t, J = 243 Hz), 127.98, 128.51, 128.90, 135.40, 169.99; ^{19}F NMR (CDCl$_3$) δ 38.61 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 297 Hz), 39.00 (ddd, 1 F, $J_{F,H}$ = 10.7, 54.9 Hz, $J_{F,F}$ = 297 Hz); IR (cm^{-1}) 2956, 1760 (C=O); high-resolution mass calcd for $C_{13}H_{15}NOF_2$ 239.1122, found 239.1109.

***cis*-15c**: ^{1}H NMR (CDCl$_3$) δ 1.10 (t, 3 H, $J_{H,H}$ = 7.4 Hz), 3.18 (dq, 1 H, $J_{H,H}$ = 5.9, 7.4 Hz), 3.19 (dddd, 1 H, $J_{H,H}$ = 5.9, 6.0, 6.2, 9.8 Hz), 3.65 (dq, 1 H, $J_{H,H}$ = 5.9, 11.7 Hz), 4.04 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 4.75 (d, 1 H, $J_{H,F}$ = 14.9 Hz), 5.80 (ddd, 1 H, $J_{H,H}$ = 6.0 Hz, $J_{H,F}$ = 54.3, 55.9 Hz), 7.20–7.40 (5 H, m); ^{13}C NMR (CDCl$_3$) δ 12.43 (d, J = 1.3 Hz), 18.51, 53.35 (dd, J = 1.6, 5.4 Hz), 53.95 (dd, J = 21.7, 29.1 Hz), 115.57 (t, J = 243 Hz), 127.90, 128.52, 128.85, 135.51, 169.03; ^{19}F NMR (CDCl$_3$) δ 40.60 (ddd, 1 F, $J_{F,H}$ = 11.4, 56.7 Hz, $J_{F,F}$ = 303 Hz), 39.00 (ddd, 1 F, $J_{F,H}$ = 6.1, 54.2 Hz, $J_{F,F}$ = 303 Hz); IR (cm^{-1}) 2986, 1756 (C=O); high-resolution mass calcd for $C_{13}H_{15}NOF_2$ 239.1122, found 239.1114.

***N*-Benzyl-4-(difluoromethyl)-3-methyl-2-azetidinone (15d) (=15b).** To a solution of diisopropylamine (0.30 mL, 2.2 mmol) in THF (6 mL) was added a solution of *n*-BuLi (2.5 M in hexane, 0.88 mL, 2.2 mmol) at −78 °C. After 30 min of stirring at this temperature, ethyl propionate (0.25 mL, 2.2 mmol) was added dropwise, and the whole was stirred at −78 °C for 30 min. To the above solution was added a solution of **13a** (0.34 g, 2.0 mmol) in THF (2 mL) dropwise. The mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature. After 1 h of stirring, the mixture was quenched with 1 N HCl (5 mL) and extracted with ether (10 mL × 3). The extracts were dried over anhydrous $MgSO_4$. On removal of the solvent, flash chromatography (silica gel, 5:1 hexane–EtOAc) gave **15d** (0.45 g, 77%).

***N*-Benzyl-4-(difluoromethyl)-3-ethyl-2-azetidinone (15e).** The reaction was performed with **13a** (0.34 g, 2.0 mmol) and ethyl butylate (0.32 mL, 2.2 mmol) to give **15e** (0.39 g, 82%).

***N*-Benzyl-4-(difluoromethyl)-3-propyl-2-azetidinone (15f).** The reaction was performed with **13a** (0.34 g, 2.0 mmol) and ethyl valerate (0.33 mL, 2.2 mmol) to give **15f** (0.38 g, 75%). Anal. Calcd for $C_{14}H_{17}NOF_2$: C, 66.39; H, 6.77; N, 5.53. Found: C, 66.70; H, 6.98; N, 5.36. ***trans*-15f**: ^{1}H NMR (CDCl$_3$) δ 0.91 (t, 2 H, $J_{H,H}$ = 7.3 Hz), 1.30–1.50 (m, 2 H), 1.50–1.80 (m, 2 H), 3.12 (ddd, 1 H, $J_{H,H}$ = 2.4, 5.8, 8.7 Hz), 3.29 (dddd, 1 H, $J_{H,H}$ = 2.4, 4.8, 7.6, 10.0 Hz), 4.07 (dd, 1 H, $J_{H,H}$ = 0.6, 14.9 Hz), 4.73 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 5.66 (ddd, 1 H, $J_{H,H}$ = 4.8 Hz, $J_{H,F}$ = 55.0, 55.5 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 13.72, 20.22, 29.83, 45.58, 51.38, (dd, J = 2.3, 3.8 Hz), 56.89 (dd, J = 24.2, 27.3 Hz), 115.50 (t, J = 244 Hz), 128.00, 128.54, 128.92, 135.42, 169.21; ^{19}F NMR (CDCl$_3$) δ 42.08 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 296 Hz), 42.86 (ddd, 1 F, $J_{F,H}$ = 9.9, 55.7 Hz, $J_{F,F}$ = 296 Hz); IR (neat) 1750 (cm^{-1}). ***cis*-15f**: ^{1}H NMR δ 0.95 (t, 2 H, $J_{H,H}$ = 7.2 Hz), 1.30–1.80 (m, 4 H), 3.27–3.30 (m, 1 H), 3.64 (dddd, 1 H, $J_{H,H}$ = 5.9, 5.9, 5.9, 11.7 Hz), 4.05 (dd, 1 H, $J_{H,H}$ = 14.9 Hz), 4.73 (d, 1 H, $J_{H,H}$ = 0.37, 14.9 Hz), 5.76 (ddd, 1 H, $J_{F,H}$ = 5.9 Hz, $J_{F,F}$ = 54.3, 55.8 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 13.92, 21.12, 27.10, 45.47, 51.53 (dd, J = 1.6, 5.4 Hz), 53.85 (dd, J = 21.7, 29.0 Hz), 115.62 (t, J = 243 Hz), 127.89, 128.49, 128.91, 135.46, 169.65; ^{19}F NMR (CDCl$_3$) δ 40.46 (ddd, 1 F, $J_{F,H}$ = 11.4, 55 Hz, $J_{F,F}$ = 303 Hz), 42.86 (ddd, 1 F, $J_{F,H}$ = 6.5, 54.5 Hz); IR (neat) 1750 (cm^{-1}).

***N*-Benzyl-4-(difluoromethyl)-3-heptyl-2-azetidinone (15g).** The reaction was performed with **13a** (0.34 g, 2.0 mmol) and ethyl nonanoate (0.43 mL, 2.2 mmol) to give **15g** (0.47 g, 76%). Anal. Calcd for $C_{19}H_{27}NOF_2$: C, 70.56; H, 8.42; N, 4.33. Found: C, 70.19; H, 8.80; N, 4.71. ***trans*-15g**: ^{1}H NMR (CDCl$_3$) δ 0.87 (t, 3 H, $J_{H,H}$ = 7.0 Hz), 1.20–1.80 (m, 12 H), 3.10 (ddd, 1 H, $J_{H,H}$ = 2.2, 6.3, 8.7 Hz), 3.20 (dddd, 1 H, $J_{H,H}$ = 2.2, 4.8, 7.6, 9.1 Hz), 4.06 (dd, 1 H, $J_{H,H}$ = 0.5, 14.9 Hz), 4.71 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 5.67 (dt, 1 H, $J_{H,H}$ = 4.8 Hz, $J_{H,F}$ = 55.3 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 14.07, 22.62, 26.87, 27.72, 29.00, 29.23, 31.68, 45.57, 51.58 (t, J = 3.1 Hz), 56.58 (dd, J = 25.0, 26.5 Hz), 115.5 (t, J = 244 Hz), 128.0, 128.5, 128.9, 135.4, 169.2; ^{19}F NMR (CDCl$_3$) δ 38.64 (ddd, 1 F, $J_{F,H}$ = 7.6, 54.9 Hz, $J_{F,F}$ = 296 Hz), 39.40 (ddd, 1 F, $J_{F,H}$ = 9.1, 54.9 Hz, $J_{F,F}$ = 296 Hz); IR (neat) 1760 (cm^{-1}). ***cis*-15g**: ^{1}H NMR (CDCl$_3$) δ 0.87 (t, 3 H, $J_{H,H}$ = 7.0 Hz), 1.20–1.80 (m, 12 H), 3.26 (ddd, 1 H, $J_{H,H}$ = 5.9, 6.0, 9.8 Hz), 3.62 (dddd, 1 H, $J_{H,H}$ = 5.8, 5.9, 6.0, 9.1 Hz), 4.04 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 4.75 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 5.67 (ddd, 1 H, $J_{H,H}$ = 6.0 Hz, $J_{H,F}$ = 4.3, 55.8 Hz), 7.20–7.40 (m, 5 H); ^{13}C NMR (CDCl$_3$) δ 14.08, 22.63, 25.07, 27.73, 27.85, 29.46, 31.77, 45.54, 51.80 (dd, J = 1.5, 5.3 Hz), 55.92 (dd, J = 21.0, 29 Hz), 115.6 (t, J = 243 Hz), 127.9, 128.0, 128.8, 135.5, 169.7; ^{19}F NMR (CDCl$_3$) δ 40.48 (ddd, 1 F, $J_{F,H}$ = 11.4, 55.7 Hz, $J_{F,F}$ = 303 Hz), 42.73 (ddd, 1 F, $J_{F,H}$ = 6.5, 54.2 Hz, $J_{F,F}$ = 303 Hz); IR (neat) 1760 (cm^{-1}).

***N*-Benzyl-4-(difluoromethyl)-3-phenyl-2-azetidinone (15h).** The reaction was performed with **13a** (0.34 g, 2.0 mmol) and ethyl phenylacetate (0.35 mL, 2.2 mmol) to give **15g** (0.42 g, 73%). Anal. Calcd for $C_{17}H_{15}NOF_2$: C, 71.07; H, 5.26; N, 4.88. Found: C, 71.34; H, 5.60; N, 5.01. ***trans*-15h**: ^{1}H NMR (CDCl$_3$) δ 3.66 (dddd, 1 H, $J_{H,H}$ = 2.6, 4.3, 9.0, 9.5 Hz), 4.19 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 4.32 (d, 1 H, $J_{H,H}$ = 2.6 Hz), 4.83 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 5.66 (dt, 1 H, $J_{H,H}$ = 4.3 Hz, $J_{H,F}$ = 55.0 Hz), 7.20–7.40 (m, 10 H); ^{13}C NMR (CDCl$_3$) δ 45.80, 55.53 (t, J = 3.5 Hz), 58.86 (t, J = 25.5 Hz), 114.98 (t, J = 244 Hz), 127.31, 127.94, 128.11, 128.53, 128.97, 133.38, 135.22, 166.94; ^{19}F NMR (CDCl$_3$) δ 37.64 (ddd, 1 F, $J_{F,H}$ = 9.9, 54.9 Hz, $J_{F,F}$ = 296 Hz), 38.29 (ddd, 1 F, $J_{F,H}$ = 8.8, 54.9 Hz, $J_{F,F}$ = 296 Hz); IR (neat) 1750 (cm^{-1}). ***cis*-15h**: ^{1}H NMR (CDCl$_3$) δ 3.83 (dddd, 1 H, $J_{H,H}$ = 6.1, 6.5, 6.9, 8.9 Hz), 4.11 (d, 1 H, $J_{H,H}$ = 14.9 Hz), 4.62 (d, 1 H, $J_{H,H}$ = 6.1 Hz), 4.90 (d, 1 H, $J_{H,H}$ = 4.9 Hz), 5.30 (dddd, 1 H, $J_{H,H}$ = 6.5 Hz, $J_{H,F}$ = 53.7, 56.1 Hz), 7.20–7.30 (m, 5 H); ^{19}F NMR (CDCl$_3$) δ 38.12 (ddd, 1 F, $J_{F,H}$ = 8.8, 56.5 Hz, $J_{F,F}$ = 304 Hz), 41.41 (ddd, 1 F, $J_{F,H}$ = 6.7, 53.4 Hz, $J_{F,F}$ = 304 Hz); IR (neat) 1750 (cm^{-1}).