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Preparation of δ-fluorinated homoallylic alcohol derivatives via regioselective hydride reduction of allylic alcohol derivatives

Yuko Nakamura[a], Midori Okada[a], Hiroaki Horikawa[a], Takeo Taguchi[b,*]

[a]*Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan*

[b]*School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

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Dedicated to Professor Lev M. Yagupolskii on the occasion of his 80th birthday.

Abstract

δ-Fluoro and δ,δ-difluorohomoallylic alcohol derivatives can be efficiently prepared by $LiAlH_4$ reduction of the δ,δ-difluoroallylic alcohols and the γ-chlorodifluoromethylallylic alcohols, respectively, through regioselective SN2′ reaction, in which the free hydroxyl group is essential for the reaction to proceed.

Keywords: Fluorohomoallyl alcohol; Difluorohomoallyl alcohol; Trimethylaluminum; Lithiumaluminum hydride

1. Introduction

It is well known that the introduction of fluorine atom into organic molecules brings about the strong modification of their chemical, physical and biological properties. Therefore, fluoro organic compounds attract considerable attention particularly in the field of medicinal chemistry and material science [1–5]. Fluorinated olefins are an important class of compounds as can be applied to enzyme inhibitors [6,7], bioisosteres of carboxamides [8,9] and building blocks [10,11], and development of new methods for the synthesis of fluoroolefins has been extensively investigated [12–14]. In this paper, we report the synthesis of δ-fluorohomoallylic alcohol derivatives **2** and δ,δ-difluorohomoallylic alcohol derivatives **5** or **8** by $LiAlH_4$ reduction of the difluoroallylic alcohols **1** and the chlorodifluoromethylenoates **3** or enones **7**, respectively, in which the free hydroxyl group to form an alkoxyaluminum intermediate is essential for the reaction to proceed.

2. Results and discussion

δ-Fluorohomoallylic alcohol derivative (e.g. **2a**∼**2c**) having another hydroxyl group at ε-position or an amino group at this position should be a useful synthetic intermediate for fluoroalkene depsipeptide or peptide isosteres [8,9], since fluoroolefin is recognized to be an ideal nonhydrolizable steric and electronic mimic for an amide bond [8,15]. For the synthesis of compound **2**, hydride reduction of δ,δ-difluoroallylic alcohols **1**[1] was conducted under a variety of reaction conditions. Results are summarized in Table 1. As shown in entries 2 and 3, with the ε-hydroxylated substrate ***E*-1a**, on using aluminum hydride reagent such as $LiAlH_4$ or DIBAL, SN2′ hydride reduction proceeded to give **2a** in moderate yield (47 and 42%, respectively) along with the formation of unidentified by-products. The stereoselectivity of the olefin part of **2a** was also moderate in *Z*-preferential manner, thus $Z/E = 2.0$ for $LiAlH_4$ and 3.5 for DIBAL, respectively. We found that the addition of trimethylaluminum (2.5 eq.) resulted in clean reaction to increase in the chemical yield (87%) and the *Z*-selectivity ($Z/E = 5.0$) as shown in entry 1. In comparison with the *E* isomer ***E*-1a**, reactivity of the corresponding *Z* isomer ***Z*-1a** was found to be lower resulting in a requirement of a long reaction time to consume the starting material and the *Z*-selectivity of the product **2a** was also lowered (entry 1 versus entry 4 and entry 2 versus entry 5, respectively). Similarly with the substrate ***E*-1b** (entry 6 versus entries 7, 8) and ***E*-1c** (entry 9 versus entry 10), the use of Me_3Al as an additive afforded better results with respect to the product yield and the *Z*-selectivity.

* Corresponding author. Tel.: +81-426-76-3257; fax: +81-426-76-3257.
E-mail address: taguchi@ps.toyaku.ac.jp (T. Taguchi).

[1] δ,δ-Difluoroallylic alcohol derivatives **1** were prepared by DIBAL reduction of the corresponding γ,γ-difluoroenoates, see ref. [9].

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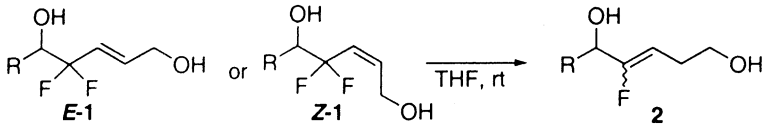
Table 1
Preparation of δ-fluorohomoallylic alcohol derivatives



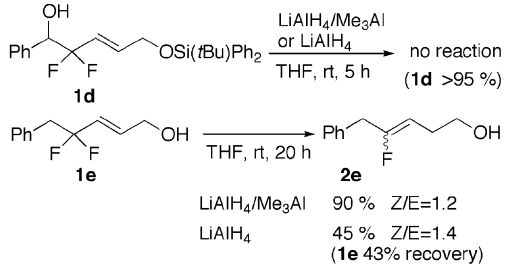
Entry	1	R	Reagent/additive	Time (h)	2	Yield (%)	*Z*/*E* ratio
1	***E*-1a**	Ph	$LiAlH_4/Me_3Al$	8	**2a**	87	5.0
2			$LiAlH_4$	5		47	2.0
3			DIBAL	2.5		42	3.5
4	***Z*-1a**	Ph	$LiAlH_4/Me_3Al$	22	**2a**	76	3.6
5			$LiAlH_4$	20		65	1.5
6	***E*-1b**	$PhCH_2CH_2$	$LiAlH_4/Me_3Al$	4	**2b**	90	4.4
7			$LiAlH_4$	6		71	2.0
8			DIBAL	6		46	3.3
9	***E*-1c**	$PhCH_2$	$LiAlH_4/Me_3Al$	5	**2c**	84	4.3
10			$LiAlH_4$	6		77	2.2
11	***Z*-1c**	$PhCH_2$	$LiAlH_4/Me_3Al$	23	**2c**	89	2.1
12			$LiAlH_4$	23		79	1.1

Moreover, a similar effect of the olefin geometry of the starting substrate on the reactivity and the *Z*-selectivity of the product was also observed as can be seen in the reaction of ***E*-1c** and ***Z*-1c** (entries 9, 10 versus entries 11, 12).

To see the effect of free hydroxyl groups in the substrate **1a** on the reactivity and stereoselectivity in the hydride reduction, we examined the reaction of the primary hydroxyl group protected substrate **1d** and the ε-hydroxyl group deleted substrate **1e** (Scheme 1). Selective silylation of the primary hydroxyl group of the diol **1a** with *tert*-butyldiphenylsilyl chloride (1.2 eq.) and imidazole in DMF gave **1d**. Under the similar reaction conditions employed for **1a** ($LiAlH_4/Me_3Al$ or $LiAlH_4$ alone in THF, rt, 5 h) no reaction occurred and most of the starting material **1d** was recovered. Thus, the free allylic alcohol moiety is likely to be essential for the reaction to proceed. This was further supported by the following results. With the allylic alcohol lacking ε-hydroxyl group **1e**, both $LiAlH_4/Me_3Al$ and $LiAlH_4$ provided the SN2′ hydride reduction product **2e** in 90 and 45% yield, respectively (Scheme 1). In the $LiAlH_4$ reduction of **1e**, reaction proceeded more slowly than that in the presence of Me_3Al and an appreciable amount of **1e** (43%) was recovered. In both cases reaction proceeded almost non-stereoselectively ($Z/E = 1.2 \sim 1.4$), while *Z*/*E* ratio in the reaction of **1a** was up to 5:1 (Table 1, entry 1).

From these results and on the basis of the relatively strong fluorine–aluminum coordination [9,16–18], we assume that (1) the formation of an alkoxyaluminum form **A** or **B** by the reaction of the aluminum hydride reagent with the primary hydroxyl group is the first step, then the hydride transfer efficiently occurs intramolecularly to give the δ-fluorohomoallyl alcohol derivatives **2a**∼**2c** or **2e**, since no reaction occurred with the *O*-silyl-protected substrate **1d**. (2) The role of Me_3Al as an additive to increase in chemical yield possibly caused by the coordination of a fluorine atom to aluminum to facilitate the substitution reaction. Furthermore, (3) in the case of ε-hydroxylated substrate **1a**∼**1c**, the formation of the five membered complex form **A**, in which *trans* stereochemistry of the substituent R and allylic alcohol part should be predominant due to the steric reason, would not only facilitate the reaction rate but also enhance the *Z*-selectivity of the product (see Fig. 1).

Next, we examined the hydride reduction of β-chlorodifluoromethyl or β-trifluoromethylenoates **3** to obtain δ,δ-difluorohomoallylic alcohol derivatives **5**. As shown in Table 2, with the chlorodifluoromethyl derivative **3a**, **3b**,



Scheme 1. Effect of the hydroxyl group.

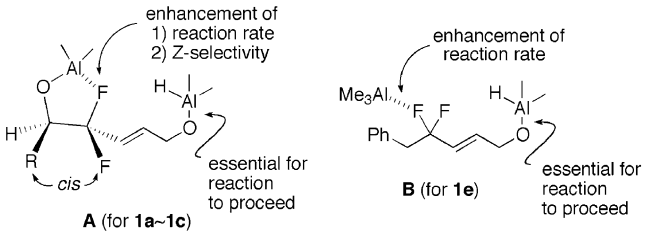
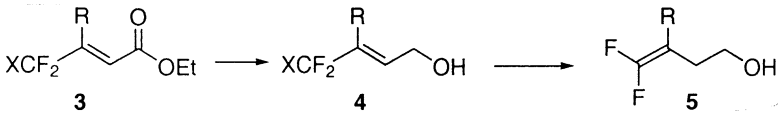
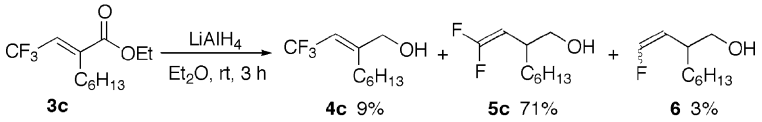


Fig. 1. Schematic roles of the hydroxyl groups on the reactivity and selectivity.

Table 2
Hydride reduction of enoates **3**



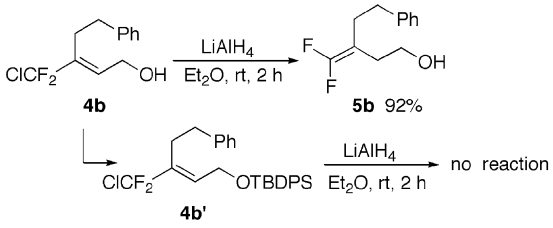
Entry	3	R	X	Reagent	Solvent	Temperature	Time (h)	4	Yield (%)	5	Yield (%)
1	**3a**	Ph	Cl	DIBAL	Et_2O	rt	1	**4a**	100	**5a**	–
2				DIBAL	THF	60 °C	1.5		–		100
3				$LiAlH_4$	Et_2O	rt	20		–		73
4	**3a′**	Ph	F	$LiAlH_4$	THF	rt	20		–		68
5	**3b**	$PhCH_2CH_2$	Cl	DIBAL	Et_2O	−78 °C	0.5	**4b**	96	**5b**	–
6				$LiAlH_4$	Et_2O	rt	1.5		–		87



Scheme 2.

while DIBAL reduction at low temperature is suitable to reduce the ester group to the alcohol form **4a**, **4b** in excellent yield (entries 1, 5), $LiAlH_4$ reduction at room temperature provided the difluorohomoallyl alcohol derivative **5a**, **5b** in good yield (entries 3 and 6). Trifluoromethyl derivative **3a′** and **3c** were also used in $LiAlH_4$ reduction leading to δ,δ-difluorohomoallylic alcohol derivative **5a** (68%, entry 4) and **5c** (71%, Scheme 2), respectively. In the case of **3c**, further reduction of the difluoride **5c** to monofluorinated product **6** competitively proceeded [19] (Scheme 2).

As in the cases of hydride reduction of δ,δ-difluoroallyl alcohol **1** mentioned earlier, the free hydroxyl group for the formation of an alkoxyaluminum intermediate similar to **B** should be essential for the reaction to proceed, since the hydroxyl-protected substrate **4b′** did not react with $LiAlH_4$ at all, while the allyl alcohol **4b** gave the difluorohomoallyl alcohol **5b** in a high yield (92%) under the similar reaction conditions (Scheme 3).

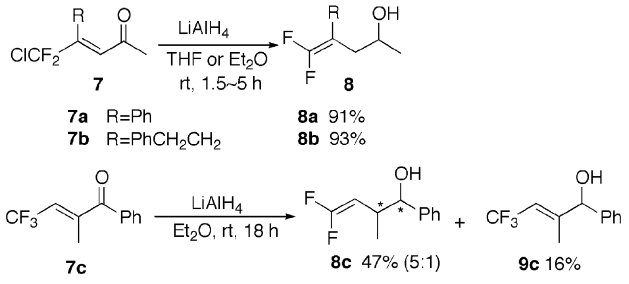


Scheme 3.

Examples of hydride reduction of β-chlorodifuoromethylenone **7a**, **7b** or β-trifluoromethylenone **7c** are shown in Scheme 4. $LiAlH_4$ reduction of these substrates provided terminally difluorinated secondary homoallylic alcohol derivatives **8a**∼**8c** in good yields. It should be noted that a moderate diastereoselectivity was observed in the reaction of α-substituted substrate **7c** to give a mixture of diastereomers **8c** in a ratio of 5:1.

Similar reductive elimination of a fluoride in the hydride reduction of β,β-bis(trifluoromethyl)acrylate or enones were reported, in which strong electron-withdrawing nature of geminal trifluoromethyl groups makes the double bond very electrophilic [20,21].

In conclusion, δ-fluoro- and δ,δ-difluorohomoallylic alcohol derivatives can be efficiently prepared by $LiAlH_4$ reduction of δ,δ-difluoroallylic alcohols and the γ-chlorodifluoromethylallylic alcohols formed from the corresponding enoates or enones, respectively, in which the free hydroxyl group to form the alkoxyaluminum intermediate is essential for the reaction to proceed.



Scheme 4. Hydride reduction of enones **7**.

3. Experimental details

General: ^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H-NMR,

and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer, and chemical shifts were reported in parts per million (ppm) using benzotrifluoride as a standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV detector.

3.1. Preparation of (E)-4,4-difluoro-5-substituted-2-pentene-1,5-diol *E*-1

Under an argon atmosphere, a mixture of ethyl (*E*)-4,4-difluoro-5-hydroxy-5-substituted-2-pentenoate [9] (5 mmol) and DIBAL (1 M hexane solution, 15 mmol) in THF was stirred at room temperature for 3 h. The reaction mixture was quenched by the addition of 5% HCl and extracted with Et_2O. The organic extract was dried over $MgSO_4$, then concentrated under vacuum. The residue was purified by silica gel column chromatography to give ***E*-1**.

(E)-4,4-Difluoro-5-phenyl-2-pentene-1,5-diol (***E*-1a**): 98% yield. Colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ; 2.66 (1H, brs), 3.62 (1H, brs), 4.10 (2H, brs), 4.84 (1H, t, $J = 9.6$ Hz), 5.73–5.85 (1H, m), 6.07–6.17 (1H, m), 7.26–7.43 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 61.6, 75.8 (t, $J = 30.5$ Hz), 119.7 (t, $J = 244.3$ Hz), 121.5 (t, $J = 25.4$ Hz), 127.7, 128.2, 128.7, 136.2 (d, $J = 2.7$ Hz), 136.6 (t, $J = 8.2$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −41.61 (1F, d, $J = 247$ Hz), −45.09 (1F, dt, $J = 247$, 11 Hz). IR (neat): 3622, 3150–3600, 2902, 1683 cm^{-1}. MS (EI) *m/z*; 196 (M^+–H_2O), 177, 107. HRMS. Calcd. for $C_{11}H_{10}OF_2$ (M^+–H_2O): 196.0700. Found: 196.0712.

(E)-4,4-Difluoro-7-phenyl-2-heptene-1,5-diol (***E*-1b**): 91% yield. Colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ; 1.70–1.84 (1H, m), 1.90–2.04 (1H, m), 2.60–2.74 (1H, m), 2.84–2.96 (1H, m), 3.45 (1H, s), 3.69 (1H, s), 3.74 (1H, m), 4.20 (2H, s), 5.80–5.96 (1H, m), 6.18–6.30 (1H, m), 7.21–7.32 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 31.5, 61.5, 72.7 (t, $J = 30.2$ Hz), 120.5 (t, $J = 243.3$ Hz), 121.6 (t, $J = 25.6$ Hz), 126.0, 128.4, 136.1 (t, $J = 8.4$ Hz), 141.1. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −42.42 (1F, d, $J = 248$ Hz), −47.98 (1F, d, $J = 248$ Hz). IR ($CHCl_3$): 3622, 2932, 2866, 1683 cm^{-1}. MS (EI) *m/z*; 242 (M^+), 224 (M^+–H_2O), 206, 117. HRMS. Calcd. for $C_{13}H_{16}O_2F_2$ (M^+): 242.1118. Found: 242.1104.

(E)-4,4-Difluoro-6-phenyl-2-hexene-1,5-diol (***E*-1c**): 97% yield. Colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ; 2.58 (1H, brs), 2.69 (1H, dd, $J = 14.2$, 10.4 Hz), 2.90 (1H, d, $J = 8.0$ Hz), 3.03 (1H, dd, $J = 14.2$, 2.4 Hz), 3.98 (1H, m), 4.23 (1H, s), 5.92–5.96 (1H, m), 6.29–6.34 (1H, m), 7.24–7.36 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 36.4, 61.7, 74.6 (t, $J = 30.3$ Hz), 120.2 (t, $J = 243.5$ Hz), 121.6 (t, $J = 25.4$ Hz), 126.7, 128.5, 129.4, 136.3 (t, $J = 8.4$ Hz), 137.3. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −42.38 (1F, d, $J = 249$ Hz), −48.46 (1F, dt, $J = 249$, 12 Hz). IR ($CHCl_3$): 3620, 3460, 2924, 1732, 1682 cm^{-1}. MS (EI) *m/z*; 228 (M^+), 210 (M^+–H_2O), 190, 121. HRMS. Calcd. for $C_{12}H_{14}O_2F_2$ (M^+): 228.0962. Found: 228.0954.

3.2. Typical procedure for hydride reduction of *1* in the presence of Me_3Al

A mixture of ***E*-1a** (180 mg, 0.85 mmol), $LiAlH_4$ (129 mg, 3.4 mmol) and trimethylaluminum (1 M hexane solution, 1.7 ml, 1.7 mmol) in THF (6 ml) was stirred at room temperature for 8 h. After the reaction mixture was quenched by the addition of 5% HCl followed by the extractive workup (AcOEt), the residue was purified by silica gel column chromatography (hexane: AcOEt = 2:3) to give an unseparable *Z*, *E* mixture ($Z/E = 5$) of **2a** (145 mg, 87%).

(E)- and (Z)-2-Fluoro-1-phenyl-2-pentene-1,5-diol (**2a**): colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ; 2.25–2.36 (2H, m), 3.05 (1H, brs), 3.58 (2H, t, $J = 6.2$ Hz), 4.18 (0.83H, brs), 4.45 (0.17H, brs), 4.95 (0.83H, dt, $J = 36.9$, 7.6 Hz), 5.15 (0.83H, d, $J = 13.1$ Hz), 5.20 (0.17H, ddd, $J = 21.1$, 8.9, 8.0 Hz), 5.53 (0.17H, d, $J = 24.7$ Hz), 7.25–7.48 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 26.8 (d, $J = 3.4$ Hz), 61.5, 72.5 (d, $J = 31.8$ Hz), 103.7 (d, $J = 13.2$ Hz), 126.6, 128.1, 128.4, 139.4, 161.6 (d, $J = 258.5$ Hz) for (*Z*)-**2a**; δ; 27.8 (d, $J = 8.3$ Hz), 61.2, 68.6 (d, $J = 28.8$ Hz), 105.1 (d, $J = 21.2$ Hz), 126.2, 127.9, 128.1, 139.2, 160.1 (d, $J = 250.7$ Hz) for (*E*)-**2a**. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.09 (0.17F, dd, $J = 24$, 21 Hz), −57.72 (0.83F, dd, $J = 37$, 13 Hz). IR (neat): 3000–3700, 3031, 2954, 2884, 1705 cm^{-1}.

(E)- and (Z)-4-Fluoro-7-phenyl-3-heptene-1,5-diol (**2b**): (*E*)-**2b**: colorless crystals; mp 38–39 °C. ^1H-NMR (400 MHz, $CDCl_3$) δ; 2.02–2.12 (2H, m), 2.21–2.27 (2H, m), 2.74 (2H, t, $J = 7.9$ Hz), 3.57–3.61 (1H, m), 3.70–3.73 (1H, m), 4.46 (1H, dt, $J = 26.0$, 7.1 Hz), 5.21 (1H, dt, $J = 21.3$, 8.7 Hz), 7.22–7.35 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 27.8 (d, $J = 8.8$ Hz), 31.6, 34.3, 61.2 (d, $J = 2.2$ Hz), 65.9 (d, $J = 28.7$ Hz), 105.0 (d, $J = 21.5$ Hz), 125.9, 128.4, 141.3, 161.2 (d, $J = 254.8$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −57.52 (1F, dd, $J = 26$, 21 Hz). IR ($CHCl_3$): 3622, 3436, 2962, 2884, 1698 cm^{-1}. MS (EI) *m/z*; 224 (M^+), 206 (M^+–H_2O), 188, 105. HRMS. Calcd. for $C_{13}H_{17}O_2F$ (M^+): 224.1213. Found: 224.1227. (*Z*)-**2b**: colorless oil. ^1H-NMR (400 MHz, $CDCl_3$) δ; 1.98–2.06 (2H, m), 2.33–2.43 (2H, m), 2.71–2.82 (2H, m), 3.64–3.71 (2H, m), 4.12 (1H, dt, $J = 16.5$, 6.7 Hz), 4.91 (1H, dt, $J = 37.5$, 7.5 Hz), 7.22–7.35 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 26.8 (d, $J = 3.8$ Hz), 31.5, 35.1, 61.6, 69.8 (d, $J = 30.2$ Hz), 103.0 (d, $J = 13.5$ Hz), 125.9, 128.4, 128.4, 141.4, 161.1 (d, $J = 259.0$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −61.06 (1F, dd, $J = 38$, 17 Hz). IR ($CHCl_3$): 3620, 3416, 3024, 3004, 2960, 2884, 1710 cm^{-1}. MS (EI) *m/z*; 225 ($M^+ + 1$), 224 (M^+), 206 (M^+–H_2O), 188. HRMS. Calcd. for $C_{13}H_{17}O_2F$ (M^+): 224.1213. Found: 224.1215.

(E)- and (Z)-4-Fluoro-6-phenyl-3-hexene-1,5-diol (**2c**): a *Z*/*E* mixture ($Z/E = 2$). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.85–1.95 (0.27H, m), 1.99–2.11 (0.27H, m), 2.18–2.37 (1.46H, m), 2.85–3.05 (2H, m), 3.27–3.35 (0.27H, m), 3.35–3.44 (0.27H, m), 3.53 (1.46H, ddd, $J = 23.2$, 10.8, 6.4 Hz), 4.27 (0.73H, dt, $J = 16.2$, 6.9 Hz), 4.61 (0.27H, dt, $J = 26.1$, 7.3 Hz), 4.76 (0.73H, dt, $J = 37.6$, 7.6 Hz), 5.07 (0.27H, ddd, $J = 21.4$, 9.2, 7.5 Hz), 7.21–7.32 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 26.6 (d, $J = 8.6$ Hz), 27.6 (d, $J = 8.6$ Hz), 39.4, 40.1, 60.9, 61.3, 67.8 (d, $J = 28.1$ Hz), 71.7 (d, $J = 30.3$ Hz), 103.3 (d, $J = 13.0$ Hz), 105.2 (d, $J = 21.2$ Hz), 126.4, 128.2, 129.3, 137.1, 137.2, 159.7 (d, $J = 253.5$ Hz), 160.1 (d, $J = 258.7$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −58.15 (0.27F, ddd, $J = 26$, 21, 10 Hz), −61.05 (0.73F, dd, $J = 37$, 16 Hz). IR ($CHCl_3$): 3616, 3412, 3036, 2932, 2884, 1708 cm^{-1}. MS (EI) *m/z*; 210 (M^+), 193, 190, 173. HRMS. Calcd. for $C_{12}H_{15}O_2F$ (M^+): 210.1056. Found: 210.1045.

(E)- and (Z)-4-Fluoro-5-phenyl-3-penten-1-ol (**2e**): (*E*)-**2e**: colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.48 (1H, brd), 2.30–2.37 (2H, m), 3.60 (2H, d, $J = 23.5$ Hz), 3.67 (2H, t, $J = 6.4$ Hz), 5.17 (1H, dt, $J = 20.9$, 8.1 Hz), 7.22–7.28 (3H, m), 7.28–7.34 (2H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 29.3 (d, $J = 8.7$ Hz), 34.4 (d, $J = 28.8$ Hz), 62.3, 102.9 (d, $J = 22.7$ Hz), 126.8, 128.4, 128.6, 136.5, 160.1 (d, $J = 249.6$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −36.10 (1F, td, $J = 23$, 22 Hz). IR (neat): 3125–3686, 3030, 2952, 1707 cm^{-1}. (*Z*)-**2e**: colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.48 (1H, brd), 2.30–2.39 (2H, m), 3.49 (2H, d, $J = 16.8$ Hz), 3.64 (2H, t, $J = 6.5$ Hz), 4.63 (1H, dt, $J = 37.0$, 7.5 Hz), 7.23–7.28 (3H, m), 7.29–7.35 (2H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 27.4 (d, $J = 3.9$ Hz), 38.6 (d, $J = 28.9$ Hz), 62.1, 102.7 (d, $J = 15.0$ Hz), 126.8, 128.5, 128.8, 136.4, 160.1 (d, $J = 256.0$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −43.60 (1F, dt, $J = 37$, 17 Hz). IR (neat): 3136–3662, 3030, 2949, 1701 cm^{-1}.

*3.3. Physical data of enoates **3**, enones **7** and their reduction products **4**, **5**, **8**, **9***

Ethyl 4-chloro-4,4-difluoro-3-phenyl-2-butenoate (**3a**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.05 (3H, t, $J = 7.1$ Hz), 4.03 (2H, q, $J = 7.1$ Hz), 6.58 (1H, t, $J = 1.1$ Hz), 7.28–7.47 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 13.6, 61.0, 122.7 (t, $J = 6.6$ Hz), 125.2 (t, $J = 292.2$ Hz), 128.0, 129.1, 131.5, 147.2 (t, $J = 24.5$ Hz), 164.2. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; +7.71 (2F, s). IR (neat): 3024, 2990, 1726 cm^{-1}. MS (EI) *m/z*; 260 ($M^+ + 1$), 215, 159. HRMS. Calcd. for $C_{12}H_{11}O_2F_2Cl$ (M^+): 260.0416. Found: 260.0420.

Ethyl 3-chlorodifluoromethyl-5-phenyl-2-pentenoate (**3b**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.30 (3H, t, $J = 7.1$ Hz), 2.86–2.92 (2H, m), 4.23 (2H, q, $J = 7.1$ Hz), 6.32 (1H, s), 7.17–7.21 (1H, m), 7.26–7.29 (4H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.1, 29.8, 35.4, 60.9, 120.7 (t, $J = 7.5$ Hz), 126.3, 126.5 (t, $J = 292.5$ Hz), 128.3, 128.5, 141.0, 150.2 (t, $J = 22.7$ Hz), 164.6. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 7.01 (2F, s). IR ($CHCl_3$): 2992, 2876, 1726, 1660 cm^{-1}. MS (EI) *m/z*; 289 ($M^+ + 1$), 243, 179, 159. Anal. Calcd. for $C_{14}H_{15}O_2ClF_2$: C, 58.24; H, 5.24. Found: C, 57.95; H, 5.16.

4-Chloro-4,4-difluoro-3-phenyl-2-buten-1-ol (**4a**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.56 (1H, brs), 4.08 (2H, brs), 6.51 (1H, tt, $J = 6.3$, 1.3 Hz), 7.25–7.29 (2H, m), 7.39–7.43 (3H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 59.5, 125.8 (t, $J = 291$ Hz), 128.5, 129.0, 129.8, 131.9, 132.8 (t, $J = 6.4$ Hz), 137.4 (t, $J = 23.8$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; +10.25 (2F, s). IR (neat): 3632, 2940, 1674 cm^{-1}. MS (EI) *m*/z; 220 (M^+(^{37}Cl)), 218 (M^+(^{35}Cl)), 182. Anal. Calcd. for $C_{10}H_9OClF_2$: C, 54.93; H, 4.15. Found: C, 55.33; H, 4.47.

3-Chlorodifluoromethyl-5-phenyl-2-penten-1-ol (**4b**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.31 (1H, s), 2.63 (2H, t, $J = 7.6$ Hz), 2.87 (2H, t, $J = 7.6$ Hz), 3.94 (2H, dt, $J = 6.5$, 1.9 Hz), 6.25 (1H, tt, $J = 6.5$, 1.3 Hz), 7.23–7.38 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 28.7, 35.0, 58.4, 126.4, 127.2 (t, $J = 291.4$ Hz), 128.5, 128.8, 132.2 (t, $J = 7.3$ Hz), 134.4 (t, $J = 22.1$ Hz), 140.6. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; +10.38 (2F, s). IR ($CHCl_3$): 3632, 3032, 2956, 2876, 1606 cm^{-1}. MS (EI) *m/z*; 192 (M^+–F, Cl), 174, 161, 91. Anal. Calcd. for $C_{12}H_{13}OClF_2$: C, 58.43; H, 5.31. Found: C, 58.45; H, 5.46.

4,4-Difluoro-3-phenyl-3-buten-1-ol (**5a**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.88 (1H, brs), 2.63 (2H, tt, $J = 6.8$, 2.3 Hz), 3.61 (2H, t, $J = 6.8$ Hz), 7.20–7.39 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 31.2, 60.3, 89.3 (dd, $J = 21.6$, 14.5 Hz), 127.4, 128.2 (t, $J = 2.8$ Hz), 128.5, 133.2 (t, $J = 3.6$ Hz), 154.3 (dd, $J = 290.0$, 287.7 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −27.05 (1F, d, $J = 41$ Hz), −27.92 (1F, d, $J = 41$ Hz). IR (neat): 3632, 2960, 2875, 1734 cm^{-1}. MS (EI) m/z; 184 (M^+), 166. Anal. Calcd. for $C_{10}H_{10}OF_2$: C, 65.21; H, 5.47. Found: C, 65.23; H, 5.51.

4,4-Difluoro-3-phenethyl-3-buten-1-ol (**5b**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.63 (1H, s), 2.26 (2H, tt, $J = 6.7$, 2.1 Hz), 2.34 (2H, tt, $J = 7.9$, 2.1 Hz), 2.75 (2H, t, $J = 7.9$ Hz), 3.69 (2H, t, $J = 6.7$ Hz), 7.19–7.23 (3H, m), 7.26–7.32 (2H,m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 28.5 (d, $J = 1.7$ Hz), 30.0, 34.0, 60.5, 86.7 (t, $J = 17.5$ Hz), 126.2, 128.3, 128.4, 141.1, 154.4 (t, $J = 285.2$ Hz), ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −31.49 (1F, d, $J = 53$ Hz), −30.23 (1F, d, $J = 53$ Hz). IR ($CHCl_3$): 3635, 3045, 2975, 2950, 1750 cm^{-1}. MS (EI) *m/z*; 194 (M^+–H_2O), 174, 91. Anal. Calcd. for $C_{12}H_{14}OF_2$: C, 67.91; H, 6.65. Found: C, 67.68; H, 6.87.

5-Chloro-5,5-difluoro-4-phenyl-3-penten-2-one (**7a**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.86 (3H, s), 6.67 (1H, s), 7.29–7.36 (2H, m), 7.38–7.49 (3H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 30.5, 125.4 (t, $J = 292.3$ Hz), 128.6, 129.6, 129.8, 130.5 (t, $J = 5.8$ Hz), 131.3, 144.0 (t, $J = 24.7$ Hz), 199.1. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −8.06 (2F, s). IR (neat): 3300–3400, 3010, 1710,

1683 cm^{-1}. MS (EI) *m/z*; 229 (M^+), 159, 155. Calcd. for $C_{11}H_9OF_2Cl$: C, 57.28; H, 3.93. Found: C, 57.40; H, 3.94.

4-Chlorodifluoromethyl-6-phenyl-3-hexen-2-one (**7b**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.33 (3H, s), 2.79–2.92 (4H, m), 6.58 (1H, s), 7.15–7.24 (1H, m), 7.25–7.32 (4H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 29.9, 32.1, 35.2, 125.3 (t, $J = 6.6$ Hz), 126.2, 126.4 (t, $J = 292.6$ Hz), 128.5, 128.6, 140.9, 147.7 (t, $J = 22.6$ Hz), 197.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; +6.44 (2F, s). IR ($CHCl_3$): 3024, 2956, 2872, 1702, 1634 cm^{-1}. MS (EI) *m/z*; 259 ($M^+ + 1$), 241, 222, 202, 91. Anal. Calcd. for $C_{13}H_{15}OClF_2$: C, 60.36; H, 5.07. Found: C, 60.08; H, 5.09.

5,5-Difluoro-4-phenyl-4-penten-2-ol (**8a**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.17 (3H, d, $J = 6.2$ Hz), 1.71 (1H, brs), 2.48 (1H, ddt, $J = 14.3$, 5.6, 2.8 Hz), 2.58 (1H, ddt, $J = 14.3$, 7.5, 2.1 Hz), 3.77 (1H, m), 7.23–7.36 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 22.9, 37.4, 66.1, 89.8 (dd, $J = 20.6$, 15.4 Hz), 127.4, 128.3 (t, $J = 2.7$ Hz), 128.5, 133.4 (m), 154.4 (dd, $J = 290.3$, 288.4 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −30.61 (1F, d, 45 Hz), −30.79 (1F, d, $J = 45$ Hz). IR (neat): 3696, 3624, 2980, 1734 cm^{-1}. MS (EI) *m/z*; 178 (M^+). Anal. Calcd. for $C_{11}H_{12}OF_2$: C, 66.66; H, 6.10. Found: C, 66.65; H, 6.03.

5,5-Difluoro-4-phenethyl-4-penten-2-ol (**8b**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.22 (3H, d, $J = 6$, 2 Hz), 1.68 (1H, s), 2.03–2.12 (1H, m), 2.13–2.22 (1H, m), 2.27–2.41 (2H, m), 2.74 (2H, t, $J = 8.0$ Hz), 3.92 (1H, dq, $J = 19.2$, 6.1 Hz), 7.19–7.32 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 23.1, 28.6 (d, $J = 1.6$ Hz), 33.9, 36.0 (d, $J = 2.0$ Hz), 66.1, 86.0 (t, $J = 17.2$ Hz), 126.1, 128.3, 128.4, 141.0, 154.5 (t, $J = 285.2$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −33.68 (1F, d, $J = 57.4$ Hz), −34.55 (1F, d, $J = 57.4$ Hz). IR ($CHCl_3$): 3693, 3628, 2936, 2868, 1750 cm^{-1}. MS (EI) *m/z*; 226 (M^+), 209, 182. HRMS. Calcd. for $C_{13}H_{14}F_2$ (M^+–H_2O): 208.1064. Found: 208.1040.

4,4-Difluoro-2-methyl-1-phenyl-3-buten-1-ol (**8c**): a mixture of diastereomers (ratio, 5:1). Colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.96 (2.49H, d, $J = 6.9$ Hz), 1.27 (0.51H, d, $J = 6.8$ Hz), 2.04 (1H, brs), 2.65–2.80 (1H, m), 4.06 (0.17H, ddd, $J = 25.5$, 10.0, 2.8 Hz), 4.18 (0.83H, ddd, $J = 25.5$, 10.0, 2.8 Hz), 4.40 (0.83H, d, $J = 6.7$ Hz), 4.55 (0.17H, d, $J = 6.0$ Hz), 7.25–7.38 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 17.5, 36.4 (d, $J = 4.0$ Hz), 78.1, 80.1 (t, $J = 20.5$ Hz), 126.5, 127.8, 128.3, 142.3, 156.6 (t, $J = 287$ Hz) **for major isomer**; 16.1, 35.7 (d, $J = 4.1$ Hz), 77.8, 80.4 (t, $J = 20.4$ Hz), 126.4, 127.7, 128.2, 142.2, 156.0 (t, $J = 287$ Hz) for **minor isomer**. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −24.52 (0.83F, d, $J = 45$ Hz), −25.48 (0.17F, d, $J = 45$ Hz), −26.77 (1F, dd, $J = 25.5$, 45 Hz). IR (neat): 3622, 2980, 2938, 2878, 1749 cm^{-1}. MS (EI) *m/z*; 183 (M^+–Me), 166. Calcd. for $C_{11}H_{12}OF_2$: C, 66.66; H, 6.10. Found: C, 66.52; H, 6.19.

4,4,4-Trifluoro-2-methyl-1-phenyl-2-buten-1-ol (**9c**): colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.73 (3H, m). 2.21 (1H, brd, $J = 3.0$ Hz), 5.05 (1H, s). 6.10 (1H, qm, $J = 8.5$ Hz), 7.26–7.45 (5H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.51, 77.52, 114.17 (q, $J = 33.8$ Hz), 124.01 (q, $J = 270.9$ Hz), 126.95, 128.62, 128.88, 140.25, 150.93 (q, $J = 5.3$ Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; +5.54 (3F, dm, $J = 8.5$ Hz). IR (neat): 3120–3680, 3033, 2875, 1683 cm^{-1}.

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