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Synthesis of stereocontrolled α,α-difluoro-β-hydroxycarbonyl materials

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Abstract

Synthesis and synthetic utilities of stereocontrolled α,α-difluoro-β-hydroxy-γ,δ-unsaturated carbonyl compounds via enzymatic resolution with lipase PS (*Pseudomonas cepacia*, Amano Pharmaceutical Co. Ltd.) or lipase MY (*Candida rugosa*, Meito Sangyo Co. Ltd.) were described, and then the absolute configuration of obtained chiral materials was determined by the modified Mosher's method.

Keywords: Enzymatic resolution; Chiral fluorinated compounds

1. Introduction

The β-hydroxycarbonyl structure is frequently found in natural products, and this framework is widely used as a key intermediate in organic synthesis to afford highly functionalized compounds [1-4]. Substitution of the two geminal hydrogens attached to α-methylene group by fluorines would inhibit such reactions because of the difficulty to generate a fluorocation species, and would exert a pronounced influence on its chemical property with no significant effect on its geometry, which has possibility to show unexpected biological properties [2-7]. Furthermore, much attention has been paid to the β-hydroxycarbonyl materials possessing fluorine(s) at the α-position due to the remarkable ability of these materials to function as biologically active materials, or optical devices [8]. The synthesis of chiral difluorinated β-hydroxycarbonyl materials have been based on asymmetric synthesis by chemical processes and/or enzymatic resolution of racemates: (1) the asymmetric synthesis using chiral aminoalcohol ligands in Reformatsky-type reaction [9], (2) the asymmetric aldol reaction of allyl acetals catalyzed by a chiral Lewis acid [10], and a kinetic resolution by lipase OP [11]. However, those methods are not enough in a practical sense if considering a large scale handling and/or high optical purity.

In our continuous study of stereocontrolled fluorinated materials [12], we would like to describe a practical enzymatic method for α,α-difluoro-β-hydroxy-γ,δ-unsaturated carbonyl materials with high optical purity in a large scale handling. The absolute configuration of the obtained α,α-difluoro-β-hydroxy-γ,δ-unsaturated carbonyl materials was determined by the modified Mosher's method with NMR spectral data. Furthermore, synthesis of several types of stereocontrolled difluoromethylene compounds based on the transformation of chiral unsaturated materials, is described.

2. Results and discussion

2.1. Preparation of optically active α,α-difluoro-β-hydroxy derivatives

Based on the recent impressive progress made on chiral fluorinated materials, we designed α,α-difluoro-β-hydroxy-γ,δ-unsaturated amides as a chiral building block with high optical purity. For the purpose of the enzymatic resolution to search for a practical route to chiral α,α-difluoro-β-

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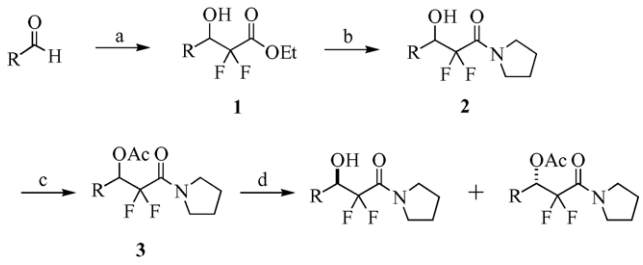


Scheme 1. [a]CF_2BrCO_2Et, Zn, THF, 0 °C [b]pyrrolidine, toluene, reflux [c]Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C [d]lipase PS (*P. cepacia*, Amano Pharmaceutical Co. Ltd.), phosphate, pH 7.4 buffer.

hydroxy-γ,δ-unsaturated amides prepared by synthetic strategies shown in Scheme 1, we have examined following methods; (1) the search of the carbon chain length to enhance the enantioselectivity of asymmetric hydrolysis by lipase, and (2) the modification of the structure α,α-difluoro-β-hydroxy-γ,δ-unsaturated amides for the enzymatic transformation.

The first synthetic strategy to obtain chiral α,α-difluoro-β-hydroxy-γ,δ-unsaturated amides is the enzymatic route based on the use of a wide range of lipases under the different reaction conditions: (a) enzymatic resolution in water, (b) organic medium, and (c) medium in phosphate pH 7.4 buffer. Since enzymatic resolution in water and/or organic media was insufficient for practical resolution with high optical purity, we examined various modification of the substrate structures to increase enantio-selectivity of enzymatic resolution in a buffer solution. The results shown in Table 1 support that products would be obtained with high enantioselectivity by controlling the extent of hydrolysis conversion.

The asymmetric hydrolysis of the ester *rac*-**3e** (R = *n*-C_5H_{11}) with lipase PS (*Pseudomonas cepacia,* Amano Pharmaceutical Co. Ltd.) produces the corresponding chiral carbinol **2e** (R = *n*-C_5H_{11}; 97% ee) at 47% conversion, while 49% conversion of *rac*-**3h** (R = (*E*)-$CH_3CH{=}CH_2$) afford 41 h in 95%ee. However, *rac*-**3d** (R = *i*-Bu), **3f** (R = Ph) and **3g** (R = CH_2Ph) was not hydrolysed under this reaction condition after 1 week. Lipase MY (*Candida rugosa*, Meito Sangyo Co. Ltd.) is a reasonable choice for these cases to obtain the chiral carbinols (**2d**, **2f** and **2g**) (Figs. 1–3).

The absolute configuration of the obtained chiral secondary alcohols was confirmed by the Mosher's method [13]. This methodology has been widely accepted for elucidating the absolute stereochemistries of various types of materials. The $\Delta\delta$ values ($\delta_S - \delta_R$) obtained for these complexes are summarized in Fig. 3. It is evident from Figs. 1 and 2 that protons with $\Delta\delta > 0$ are located on the right side of the MTPA plane, while those oriented on the left side of MTPA plane are $\Delta\delta < 0$. Also, $\Delta\delta$ values are almost proportional to the distance between the protons and the MTPA moiety.

These results suggest that the absolute configuration of all alkanols shown in Fig. 3 is the *R*-configuration from the model indicated by Fig. 2. Another trial to determine the absolute configuration was the conversion from the acetate of compound **2f** to (+)-2,2-difluoro-1-hydroxy-1-phenyl-heptan-3-one which was (*S*)-configuration in the literature [14].

Table 1
Asymmetric hydrolysis of compound **3** with lipase MY or PS

Entry	R	Compound no.	Time (h)	Lipase	Conversion[a] (%)	Compound **2** (% ee)[b]	*E* value	$[\alpha]_D$ (c, $CHCl_3$)
1	Me	**3a**	51	PS	53	96 (*R*)	>200	−29.3 (c, 1.3)
2	C_2H_5	**3b**	17	PS	48	75 (*R*)	14.3	−18.1 (c, 1.1)
3	*i*-Pr	**3c**	72	MY	47	12 (*R*)	1.4	
4			330	PS	31	76 (*R*)	10.2	−21.5 (c, 1.2)
5	*i*-Ba	**3d**	36	MY	41	89 (*R*)	31.7	+2.9 (c, 0.3)
6			>150	PS	No reaction	–	–	
7	*n*-C_5H_{11}	**3e**	47	PS	47	97 (*R*)	183	−12.6 (c, 1.4)
8	Ph	**3f**	120	MY	20	36 (*R*)	2.3	−17.2 (c, 0.3)
9			>150	PS	No reaction	–	–	
10	$PhCH_2$	**3g**	60	MY	42	>99 (*R*)	>200	+5.8 (*c*, 0.3)
11			>150	PS	No reaction	–	–	
12	(*E*)-$CH_3CH{=}CH$	**3h**	12	MY	49	85 (*R*)	29.2	−19.9 (*c*, 1.0)
13			41	PS	49	95 (*R*)	125	
14	(*Z*)-$CH_3CH{=}CH$	**3i**	24	MY	49	>99 (*R*)	>200	−65.3 (*c*, 1.1)
15	$CH{\equiv}C$	**3j**	0.25	MY	32	74 (*R*)	9.2	
16			18	PS	58	78 (*R*)	>20	+16.3 (c, 0.8)
17	$CH_3C{\equiv}C$	**3k**	12	MY	48	82 (*R*)	22.1	+20.1 (*c,* 0.7)
18	(*E*)-$CH_3CH{=}C(CH_3)$	**3l**	6	MY	38	91 (*R*)	30.5	+1.5 (c, 1.0)
19	(*E*)-*n*-$C_3H_7CH{=}CH$	**3m**	6	MY	38	89 (*R*)	30.5	
20			41	PS	49	*96* (*R*)	125	−21.1 (c, 1.5)
21	*n*-$C_3H_7CH{=}C(C_2H_5)$	**3n**	24	MY	36	89 (*R*)	34.1	−23.8 (*c*, 1.0)

[a] Determined by ^{19}F NMR 99.5/0.5, 1.0 ml).
[b] Determined by HPLC analysis (Daicel chiralpak OD-H, *n*-hexane/*i*-propanol.

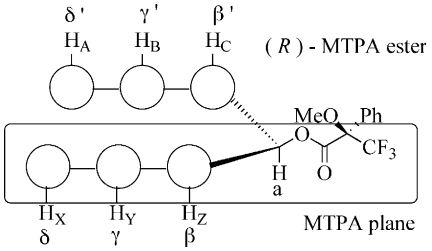


Fig. 1. MTPA plane of an MTPA ester is shown. $H_{A,B,C}$ and $H_{X,Y,Z}$ are on the left and right sides of the plane, respectively.

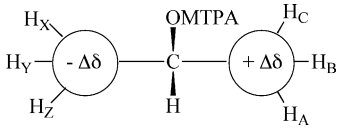
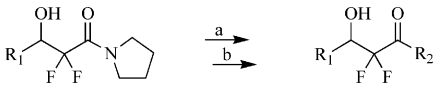


Fig. 2. Illustrations to determine the absolute configurations of secondary alcohols.

In the next step, we examined a large scale process for substrate **3e** (13.4 g). Treatment with lipase PS at room temperature gave the corresponding chiral alcohol **2e** in >97% ee and ester **3e** after 51% conversion with 92% recovered material balance as shown in Fig. 4.

Synthetic applications of chiral compounds **2**. The transformation of the chiral compound **2m** (96% ee) by ozonolysis and the followed Wittig reaction successfully proceeded to give the corresponding alkene. However, the optical purity of obtained alkene decreased to 54% ee. The transformations of chiral difluoromethylated materials to a various kinds of functionalized fluorinated compounds were carried out in the next step.

Table 2
Synthesis of chiral ketones



2 **4**

[a] RLi, THF, -78 °C [b] MeOH, -78 °C

Entry	R_1	R_2	Yield (%)[a]	o.p.(% ee)[b]	$[\alpha]_D$ (c, $CHCl_3$)
1	C_5H_n	*n*-Bu	74	83	+ 7.6 (c, 0.6)
2		Ph	84	91	−3.7 (c,0.7)
3	*E*-C_3H_7CH=CH	*n*-Bu	80	94	−14.6 (c, 0.5)
4		Ph	80	94	−16.9 (c, 0.7)

[a] Isolated yields.
[b] Determined by HPLC analysis (Daicel chiralcel OD).

As expected, the reaction of chiral amides **2** with a variety of lithium compounds at −78 °C gave the corresponding chiral ketones **4**. Every instance in Table 2 showed good to excellent chemical yields as well as very high optical purity as expected.

Optically active epoxides have had much attention during past few years [15–17]. However, the epoxidation in the field of fluorinated materials with a strongly electron-withdrawing group such as fluoromethyl groups is particularly troublesome as traditional methods commonly employ

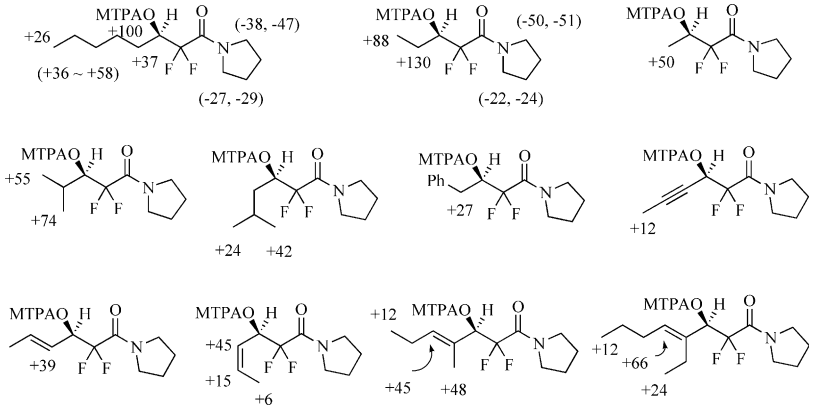


Fig. 3. $\Delta\delta$ ($\delta_S - \delta_R$) values obtained for the MTPA esters of alkanols. Δδ values are expressed in hertz (300 MHz).

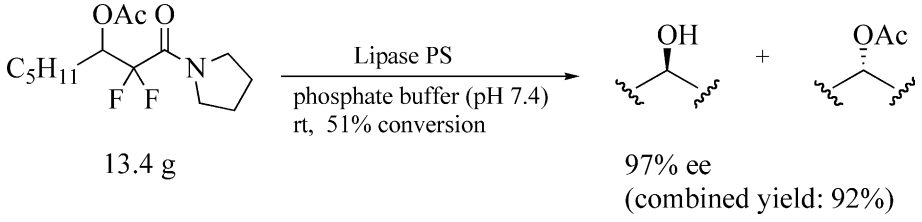
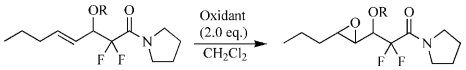


Fig. 4. Large scale asymmetric hydrolysis.

Table 3
Diasteeomeric epoxidation

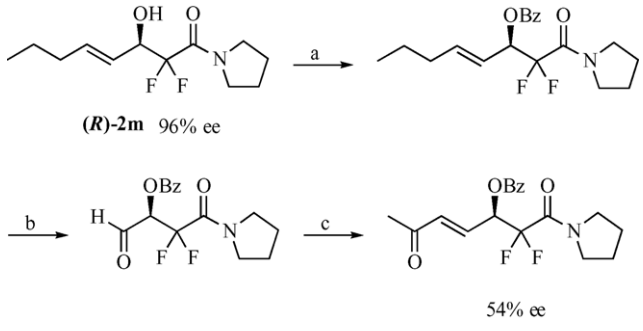


Entry	R	Oxidant	Temp (°C)	Yield (%)	*syn/anti*
1	H	mCPBA	rt	85	86/14
2	Ac		rt	No reaction	
3	TBS		rt	No reaction	
4	H	$Ti(OPr^6)_4$ (+)-DET/ TBHP	−20	No reaction	
5	H	$VO(acac)_2$/TBHP	0	Complex	
6	H	H_2O_2	0	Complex	

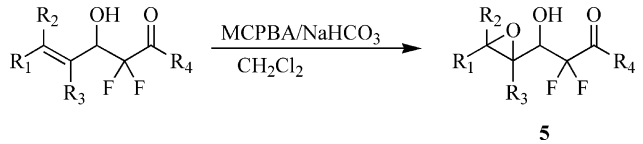
organic solvents and Lewis acid. Especially, the chiral epoxidations of fluorinated allylic alcohols does not proceed except the epoxidation with biocatalyst (*Nocardia corallina* B-276) [18] or Darzens reaction [19]. One of the reagents studied extensively to effect stereoselective epoxidations is MCPBA. Therefore, we examined the MCPBA epoxidation of chiral α, α-difluoro-β-hydroxy-γ,δ-unsaturated carbonyl compounds at different reaction temperatures. From the results shown in Table 3, we have found that the reaction temperature affect the diastereomeric ratios (Scheme 2).

Several epoxy alcohols with an amido group have been prepared high stereoselectively starting from allyl alcohols having a difluoromethylene group (Scheme 3). However, α,α-difluoro-β-hydroxyketones and/or esters were not obtained in high selectivity in the above epoxidation. In those materials, the transformation of the corresponding epoxyamide to epoxyketone is a reasonable way to obtain the chiral materials (Table 4).

In conclusion, we have shown that asymmetric hydrolysis of 2,2-difluoro-3-hydroxyamides is proved to be good



Scheme 2. [a]Bz_2O, pyr., DMAP/CH_2Cl_2, rt [b] (i) O_3/CH_2Cl_2, −78 °C (ii) Me_2S/CH_2Cl_2, −78 °C to rt [c]$Ph_3PCHC(O)CH_3$/THF, rt.



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Scheme 3.

Table 4
Diastereomeric ratios in the epoxidation

Entry	R_1	R_2	R_2	R_3	Time (h)	Temperature (°C)	Yield (%)	*syn/anti*[a]
1	Me	H	H	Pyrrolidyl	72	0	64	>99/<1
2	H	Me	H		72	0	67	94/6
3	re-Pr	H	H		15	rt	85	86/14
4	*n*-Pr	H	H		48	0	80	90/10
5	*n*-Pr	H	H		72	−10	80	>99/<1
6	n-Pr	H	Et		15	−10	76	75/25
7	Me	H	H	*n*-Bu	15	−10	85	64/36
8	Me	H	H	Ph	15	−10	82	61/39
9	Me	H	H	OEt	15	−10	79	69/31

[a] Determined by ^1H and ^{19}F NMR.

alternative reaction to obtain the chiral difluorinated materials in a large scale.

3. Experimental

3.1. General

All commercially available reagents were used without further purification. Chemical shifts of ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in ppm β downfield from the following internal standard (Me_4Si, δ 0.00) in $CDCl_3$. The ^{19}F (282 MHz) NMR spectra were recorded in ppm downfield from internal standard C_6F_6 in $CDCl_3$ using a VXR 300 instrument.

3.2. General procedure: α,α-difluoro-β-hydroxyethylester

A suspension of activated zinc powder (1.3 equiv.) in THF (0.5 mol/L) was cooled to 0 °C under an argon atmosphere and the mixture was treated with α-bromo-α, α-difluoroethylacetate (1.2 equiv.). The mixture was allowed to warm carefully to room temperature or a hot bath temperature to start a reaction. On a generation of heat, the mixture was cooled to 0 °C and then the whole was treated with an aldehyde (1.0 equiv.). After the whole was stirred for 2–3 h at room temperature, the mixture was quenched with 3N HCl and then the precipitates were removed by filtration. Oily materials were extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated under vacuum. Products were purified by column chromatography on silica gel using a mixture of hexane-ethyl acetate or a distillation.

3.3. General procedure: α,α-difluoro-β-hydroxypyrrolidium amide

A mixture solution of α,α-difluoro-β-hydroxyester (1 equiv.) and pyrrolidine (1.5 equiv.) in toluene was heated at 110 °C under a nitrogen atmosphere. After heating for 2–5 h, the mixture was quenched with aq. NH_4Cl solution at 0 °C, and then the precipitates were removed by filtration.

The solution was poured into 3N HCl, and then the organic materials were extracted with diethyl ether. On removal of the solvent, products were purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (10:1).

3.4. Asymmetric hydrolysis

(a) A mixture of *N*-(2,2-difluoro-3-acetoxyoctanoyl)pyrrolidine (1 g) and lipase PS (1 g, *P. cepacia*, Amano Pharmaceutical Co. Ltd.) in phosphate pH 7.4 buffer (10 ml) was stirred at room temperature. After the reaction, the whole was filtered over Celite pad in vacuo. The organic materials were extracted with diethyl ether, and then the extract was dried over $MgSO_4$. On removal of the solvent, the residues were purified by column chromatography on silica gel, eluting with a mixture of hexane-ethyl acetate, giving *N*-(2,2-difluoro-3-hydroxyoctanoyl)-pyrrolidine (**2a**) and *N*-(2,2-difluoro-3-acetoxyoctanoyl) pyrrolidine. Optical purity was determined by HPLC analysis (Daicel Chiralcel OD-H, *n*-hexane-*i*-propanol 99.5: 0.5; flow speed 1.0 ml/mim. t_R (major), 26.1 min; t_R (minor), 28.9 min.

(b) To a solution of substrate (1 mmol) in phosphate buffer (2 ml, pH 7.4), lipase MY (w/w = 1/2, *C. rugosa*, Meito Sangyo Co. Ltd.) was added at room temperature. After the reaction, the whole was filtered with Celite pad in vacuo. The solution was diluted with ethyl acetate and then the separated aqueous phase was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated. The conversion ratio of crude oil was determined by ^{19}F NMR analysis. The residual was subjected to column chromatography (hexane/ethyl acetate). Optical purity was determined by HPLC using a chiral column (DAICEL Chiralcel OD or Chiralpac AD).

3.5. N-(2,2-Difluoro-3-hydroxybutanoyl)pyrrolidine (**2a**)

^1H NMR ($CDCl_3$): δ 1.33 (3 H, d, J = 6.6 Hz), 1.85–2.03 (4 H, m), 2.18 (1 H, s), 3.54 (2 H, t, J = 7.1 Hz), 3.72-3.77 (2 H, m), 4.24–4.39 (1 H, m). ^{19}F NMR ($CDCl_3$): δ 37.4 (dd, J = 19.0, 289.5 Hz), 50.7 (d, J = 288.7 Hz). ^{13}C NMR ($CDCl_3$): δ 14.2 (dd, J = 2.3, 4.6 Hz), 23.1, 26.2, 46.4 (dd, J = 5.4, 7.2 Hz), 47.1, 67.4 (dd, J = 24.9, 29.2 Hz), 115.4 (dd, J = 256.2, 262.5 Hz), 162.1 (t, J = 29.2 Hz). IR (KBr): 3406, 1644 cm^{-1}. Anal. Calcd. for $C_8H_{13}F_2NO_2$: C, 49.74; H, 6.78; N, 7.25. Found: C, 49.64; H, 7.01; N, 7.19.

3.6. N-(2,2-Difluoro-3-hydroxypentanoyl)pyrrolidine (**2b**)

^1H NMR ($CDCl_3$): δ 1.08 (3 H, t, J = 7.4 Hz), 1.57–1.72 (2 H, m), 1.84–2.03 (4 H, m), 3.54 (2 H, t, J = 7.1 Hz), 3.62–3.64 (1 H, m), 3.74 (2 H, t, J = 6.6 Hz), 3.95–4.08 (1 H, m). ^{19}F NMR ($CDCl_3$): δ 39.6 (dd, J = 19.8, 288.7 Hz), 50.9 (dd, J = 2.6, 288.7 Hz). ^{13}C NMR ($CDCl_3$): δ 10.0, 21.5 (dd, J = 2.0, 3.7 Hz), 23.2, 26.3, 46.4 (dd, J=5.4, 7.4 Hz), 47.2, 72.8 (dd, J = 24.3, 28.1 Hz), 115.6 (dd, J = 256.5, 262.8 Hz), 162.3 (t, J = 29.5 Hz). IR (KBr): 3421, 1653, 1636 cm^{-1}. Anal. Calcd. for $C_9H_{15}F_2NO_2$: C, 52.17; H, 7.30; N, 6.76. Found: C, 52.42; H, 6.88; N, 6.72.

3.7. N-(2,2-Difluoro-3-hydroxy-4-methylpentanoyl)pyrrolidine (**2c**)

^1H NMR ($CDCl_3$): δ 1.04–1.08 (6 H, m), 1.83–2.03 (4 H, m), 2.08–2.15 (1 H, m), 3.53 (2 H, t, J = 7.1 Hz), 3.60 (1 H, d, J = 4.7 Hz), 3.74 (2 H, t, J = 6.6 Hz), 3.87–3.99 (1 H, ddd, J = 4.7, 9.1, 22.3 Hz). ^{19}F NMR ($CDCl_3$): δ 41.7 (dd, J = 22.4, 285.2 Hz), 54.0 (d, J = 285.2 Hz). ^{13}C NMR ($CDCl_3$). δ 17.4 (d, J = 2.6 Hz), 20.2, 23.1, 26.3, 27.9, 46.6 (dd, J = 4.9, 8.0 Hz), 47.3, 74.7 (dd, J = 22.9, 27.2 Hz), 116.7 (dd, J = 256.5, 264.5 Hz), 162.7 (t, J = 28.9 Hz). IR (KBr): 3405, 1643 cm^{-1}. Anal. Calcd. for $C_{10}H_{17}F_2NO_2$: C, 54.29; H, 7.74; N, 6.33. Found: C, 54.02; H, 7.62; N, 6.21.

3.8. N-(2,2-Difluoro-3-hydroxy-5-methylhexanoyll)pyrrolidine (**2d**)

^1H NMR ($CDCl_3$): δ 0.94 (3 H, d, J = 6.6 Hz), 0.99 (3 H, d, J = 6.6 Hz), 1.36–1.43 (1 H, m), 1.64 (1 H, s), 1.56–1.68 (1 H, m), 1.83–2.03 (5 H, m), 3.51–3.56 (2 H, m), 3.74 (2 H, t, J = 6.6 Hz), 4.12–4.26 (1 H, m). ^{19}F NMR ($CDCl_3$): δ 39.6 (dd, J = 19.8, 288.4 Hz), 50.9 (d, J = 288.4 Hz). ^{13}C NMR ($CDCl_3$): δ 21.323.3, 23.7, 24.1, 26.4, 46.5 (dd, J = 5.4, 7.2 Hz), 47.2, 69.8 (dd, J = 24.3, 28.1 Hz), 115.6 (dd, J = 256.8, 262.8 Hz), 162.5 (t, J = 29.5 Hz). IR (KBr): 3386, 1659 cm^{-1}. Anal. Calcd. for $C_{11}H_{19}F_2NO_2$: C, 57.81; H, 8.49; N, 5.62. Found: C, 58.22; H, 8.89; N, 5.41. HPLC analysis: t_R (major), 22.5 min; t_R (minor), 21.4 min (Chiralpac AD, *n*-hexane/*i*-propanol: 98/2, 1.0 ml/min).

3.9. N-(2,2-Difluoro-3-hydroxyoctanoyl)pyrrolidine (**2e**)

1H NMR ($CDCl_3$): δ 0.89–0.92 (3 H, m), 1.29–1.42 (6 H, m), 1.60–1.67 (2 H, m), 1.84–2.02 (4 H, m), 3.52–3.56 (2 H, m), 3.74 (2 H, t, J = 6.8 Hz), 4.05–4.13 (1 H, m). ^{19}F NMR ($CDCl_3$): δ 39.6(dd, J = 19.8, 289.2 Hz), 50.9 (d, J = 288.4 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7, 22.3, 22.9, 24.9, 26.1, 28.1, 31.4, 46.3 (dd, J = 5.2, 7.5 Hz), 47.0, 71.0 (dd, J = 24.3, 27.8 Hz), 115.6 (dd, J = 255.7, 262.0 Hz), 162.1 (t, J = 29.5 Hz). IR (KBr): 3412, 1636 cm^{-1}. Anal. Calcd. for $C_{12}H_{21}F_2NO_2$: C, 57.81; H, 8.49; N, 5.62. Found: C, 58.22; H, 8.89; N, 5.41. $[\alpha]_D$ −12.6 (*c* 1.4, $CHCl_3$): HPLC analysis: t_R (major), 26.1 min; t_R (minor), 28.9 min (Chiralcel OD-H, *n*-hexane/*i*-propanol 99.5/0.5, 1.0 ml).

3.10. N-(2,2-Difluoro-3-hydroxy-3-phenylpropanoyl)pyrrolidine (**2f**)

^{1}H NMR ($CDCl_3$): δ 1.81–1.92 (4 H, m), 3.52–3.61 (4 H, m), 4.35 (1 H, d, J = 3.9 Hz), 5.22–5.28 (1 H, m), 7.36–7.49 (Ar-H). ^{19}F NMR ($CDCl_3$): δ 41.4 (dd, J = 19.8, 285.3 Hz), 53.7 (d, J = 285.3 Hz). ^{13}C NMR ($CDCl_3$): δ 23.0, 26.2, 46.5 (dd, J = 5.2, 7.5 Hz), 47.3, 73.2 (dd, J = 23.5, 28.6 Hz), 114.8 (dd, J = 256.2, 264.0 Hz), 127.7, 127.8, 128.3, 134.8, 162.3 (t, J = 28.9 Hz). IR (KBr): 3406, 1774, 1648 cm^{-1}. HPLC analysis: t_R (major), 30.3 min; t_R (minor), 28.5 min (Chiralpac AD, *n*-hexane/*i*-propanol 98/2, 2.0 ml/min).

3.11. N-(2,2-Difluoro-3-hydroxy-4-phenylbutanoyl)pyrrolidine (**2g**)

^{1}H NMR ($CDCl_3$): δ 1.83–2.02 (4 H, m), 2.87 (1 H, dd, J = 9.9, 14.0 Hz), 3.05 (1 H, d, J = 14.3 Hz), 3.51 (2 H, t, J = 6.9 Hz), 3.62 (1 H, d, J = 3.0 Hz), 3.76 (2 H, t, J = 6.6 Hz), 4.33–4.43 (1 H, m), 7.21–7.35 (Ar–H). ^{19}F NMR ($CDCl_3$): δ 39.8 (dd, J = 19.0, 286.1 Hz), 51.3 (dd, J = 2.6, 287.8 Hz). ^{13}C NMR ($CDCl_3$): δ 23.1, 26.2, 34.9, 46.5 (dd, J = 4.9, 7.7 Hz), 47.2, 72.5 (dd, J = 23.8, 28.3 Hz), 115.5 (dd, J = 256.5, 263.7 Hz), 126.2, 128.0, 129.2, 137.5, 162.0 (t, J = 28.9 Hz). IR (KBr): 3418, 1648 cm^{-1}. Anal. Calcd. for $C_{14}H_{17}F_2NO_2$: C, 62.44; H, 6.36; N, 5.20. Found: C, 62.39; H, 6.24; N, 5.15. HPLC analysis: t_R (major), 23.0 min; t_R (minor), 20.2 min (Chiralpac AD, *n*-hexane/*i*-propanol: 98/2, 2.0 ml/min).

3.12. N-((E)-2,2-Difluoro-3-hydroxy-4-hexenoyl)pyrrolidine (**2h**)

^{1}H NMR ($CDCl_3$): δ 0.91 (3 H, t, J = 7.3 Hz), 1.40–1.48 (2 H, m), 1.85–1.91 (2 H, m), 1.95–2.01 (2 H, m), 2.05–2.11 (2 H, m), 3.54 (2 H, t, J = 7.1 Hz), 3.73 (2 H, t, J = 6.6 Hz), 4.56 (1 H, ddd, J = 6.1, 6.1, 17.1 Hz), 5.58 (1 H, dd, J = 7.1, 15.6 Hz), 5.60–5.89 (1 H, m). ^{19}F NMR ($CDCl_3$): δ42.6 (dd, J = 16.8, 285.3 Hz), 52.6 (d, J = 287.2 Hz). ^{13}C NMR ($CDCl_3$): δ 13.6, 21.9, 23.2, 26.3, 34.4, 46.5 (dd, J = 5.2, 7.2 Hz), 47.2, 72.9 (dd, J = 24.9, 28.6 Hz), 114.8 (dd, J = 256.5, 262.2 Hz), 122.9, 137.1, 162.2 (t, J = 30.0 Hz). IR (KBr): 3403, 1644 cm^{-1}. Anal. Calcd. for $C_{12}H_{19}F_2NO_2$: C, 58.29; H, 7.74; N, 5.66. Found: C, 58.19; H, 7.92; N, 5.52. HPLC analysis: t_R (major), 16.8 min; t_R (minor), 14.6 min (Chiralpac AD, *n*-hexane/*i*-propanol: 98/2, 2.0 ml/min).

3.13. N-((Z)-2,2-Difluoro-3-hydroxy-4-hexenoyl)pyrrolidine (**2i**)

^{1}H NMR ($CDCl_3$): δ 1.74 (3 H, dd, J = 1.92, 7.14 Hz), 1.83–2.03 (4 H, m), 3.54 (2 H, t, J = 6.87 Hz), 3.69 (1 H, d, J = 5.49 Hz), 3.73 (2 H, t, J = 6.73 Hz), 4.96 (1 H, dtdd, J = 1.10, 5.22, 8.79, 17.03 Hz), 5.56 (1 H, qdd, J = 1.92, 8.79, 10.99 Hz), 5.90 (1 H, dqd, J = 1.10, 7.14, 10.99 Hz). ^{13}C NMR($CDCl_3$): δ 13.74, 23.26, 26.35 (dd, J = 1.44, 2.00 Hz), 46.45 (dd, J = 5.30, 7.01 Hz), 47.22, 67.86 (dd, J = 25.05, 29.35 Hz), 115.23 (dd, J = 257.09, 262.24 Hz), 123.85 (dd, J = 1.87, 3.30 Hz), 131,61, 162.38 (t, J = 29.92 Hz). ^{19}F NMR ($CDCl_3$): δ 42.12 (dd, J = 17.03, 288.66 Hz), 52.43 (dd, J = 5.22, 288.66 Hz); Anal. Calcd. for $C_{10}H_{15}F_2NO_2$: C, 54.79; H, 6.90; N, 6.39. Found: C, 54.30; H, 7.25; N, 6.30. HPLC analysis: t_R (major), 36.6 min; t_R (minor), 34.6 min (Chiralpac AD, n-hexane/i-propanol 98/2, 1.0 ml/min).

3.14. N-(2,2-Difluoro-3-hydroxy-4-pentynoyl)pyrrolidine (**2j**)

^{1}H NMR ($CDCl_3$): δ 1.88–2.03 (4 H, m), 2.56 (1 H, d, J = 2.2 Hz), 3.54–3.59 (2 H, m), 3.74–3.78 (2 H, m), 4.86 (1 H, ddd, J = 2.2, 6.0, 12.1 Hz). ^{19}F NMR ($CDCl_3$): δ 46.8 (dd, J = 12.1, 286.9 Hz), 51.9 (dd, J = 6.6, 287.0 Hz). ^{13}C NMR ($CDCl_3$): δ 23.2, 26.3, 46.5 (dd, J = 4.6, 7.4 Hz), 47.3, 64.0 (dd, J = 27.5, 31.2 Hz), 75.3, 77.5 (dd, J = 2.0, 5.2 Hz), 113.3 (dd, J = 260.0, 265.1 Hz), 161.4 (t, J = 28.6 Hz). IR (KBr): 3300, 1649 cm^{-1}. Anal. Calcd. for $C_9H_{11}F_2NO_2$: C, 53.20; H, 5.46; N, 6.89. Found: C, 53.51; H, 5.09; N, 6.48.

3.15. N-(2,2-Difluoro-3-hydroxy-4-hexynoyl)pyrrolidine (**2k**)

^{1}H NMR ($CDCl_3$): δ 1.86–1,93 (2 H, m), 1.89 (3 H, d, J = 2.20 Hz), 1.95–2.04 (2 H, m), 3.52-3.59 (2 H, m), 3.72–3.80 (2 H, m), 3.91 (1 H, d, J = 7.32 Hz), 4.84 (1 H, qdd, J = 2.20, 5.98, 7.32, 13.30 Hz). ^{13}C NMR ($CDCl_3$): δ 3.81, 23.29, 26.36 (dd, J = 1.43, 2.29 Hz), 46.49 (dd, J = 4.87, 7.44 Hz), 47.30, 64.34 (dd, J = 27.19, 30.92 Hz), 72.87 (dd, J = 2.29, 4.87 Hz), 83.84, 113.40 (dd, J = 259.09, 264.53 Hz), 161.43 (t, J = 28.92 Hz). ^{19}F NMR ($CDCl_3$): δ 45.92 (dd, J = 13.30, 285.35 Hz), 52.12 (dd, J = 5.98, 285.35 Hz); Anal. Calcd. for $C_{10}H_{13}F_2NO_2$: C, 55.29; H, 6.03; N, 6.45. Found: C, 55.49; H, 5.68; N, 6.47. HPLC analysis: t_R (major), 22.6 min; t_R (minor), 32.0 min (Chiralpac AD, *n*-hexane/*i*-propanol: 98/2, 2.0 ml/min).

3.16. N-(2,2-Difluoro-3-hydroxy-4-methyl-4-heptenoyl)pyrrolidine (**2l**)

^{1}H NMR ($CDCl_3$): δ 1.00 (3 H, t, J = 7.45 Hz), 1.74 (3 H, s), 1.85–1.91 (2 H, m), 1.94–2.00 (2 H, m), 2.11 (2 H, dq, J = 7.33, 7.33 Hz), 3.54 (2 H, t, J = 7.04 Hz), 3.69–3.75 (2 H, m), 3.80 (1 H, dd, J = 0.67, 3.84 Hz), 4.56 (1 H, td, J = 3.72, 11.97 Hz), 5.59 (1 H, dqt, J = 1.22, 1.34, 7.20 Hz); ^{13}C NMR ($CDCl_3$): δ 12.66 (dd, J = 1.43, 3.15 Hz), 13.67, 20.98, 23.19, 26.36 (dd, J = 1.43, 2.29 Hz), 46.57 (dd, J = 5.16, 7.44 Hz), 47.34, 75.83 (dd, J = 22.62, 28.92 Hz), 115.51 (dd, J = 255.80, 264.39 Hz), 128.57, 133.76 (d, J = 0.57 Hz), 162.64 (dd, J = 29.20, 30.06 Hz). ^{19}F NMR ($CDCl_3$): δ 41.40 (dd, J = 11.75, 284.20 Hz), 53.86 (d,

J = 284.20 Hz); Anal. Calcd. for $C_{12}H_{19}F_2NO_2$: C, 58.29; H, 7.74; N, 5.66. Found: C, 57.82; H, 7.87; N, 5.53. HPLC analysis: t_R (major), 26.7 min; t_R (minor), 32.6 min (Chiralcel OD, *n*-hexane/*i*-propanol 99/1, 1.0 ml/min).

3.17. N-(2,2-Difluoro-3-hydroxy-4-octenoyl)pyrrolidine (**2m**)

^{1}H NMR ($CDCl_3$): δ 5.60–5.89 (1 H, m), 5.58 (1 H, dd, J = 7.1, 15.6 Hz), 4.56 (1 H, ddd, J = 6.1, 6.1, 17.1 Hz), 3.73 (2H, t, J = 6.6 Hz), 3.54 (2 H, t, J = 7.1 Hz), 2.11–2.05 (2 H, m), 2.01–1.95 (2 H, m), 1.91–1.85 (2 H, m), 1.48–1.40 (2 H, m), 0.91 (3 H, t, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 162.2 (t, J = 30.0 Hz), 137.1, 122.9, 114.8 (dd, J = 256.5, 262.2 Hz), 72.9 (dd, J = 24.9, 28.6 Hz), 47.2, 46.5 (dd, J = 5.2, 7.2 Hz), 34.4, 26.3, 23.2, 21.9, 13.6; ^{19}F NMR ($CDCl_3$): δ 52.6 (d, J = 287.2 Hz), 42.6 (dd, J = 16.8, 285.3 Hz); IR (neat): 1738, 1644 cm^{-1}; Anal. Calcd. for $C_{12}H_{19}F_2NO_2$: C, 58.29; H, 7.74; N, 5.66. Found: C, 58.19; H, 7.92; N, 5.52.

3.18. N-(2,2-Difluoro-3-hydroxy-4-ethyl-4-octenoyl)pyrrolidine (**2n**)

^{1}H NMR ($CDCl_3$): δ 0.92 (3 H, t, J = 7.41 Hz), 1.03 (3 H, t, J = 7.41 Hz), 1.42 (2 H, sex, J = 7.41 Hz), 1.82–2.02 (4 H, m), 2.10 (2 H, sex, J = 7.42 Hz), 2.27 (2 H, qd, J=7.42, 13.73 Hz), 3.57 (2 H, t, J=6.60 Hz), 3.68–3.75 (2 H, m), 4.62 (1 H, dd, J = 3.76, 21.57 Hz), 5.62 (1 H, t, J=7.28 Hz). ^{13}C NMR ($CDCl_3$): δ 13.89, 13.93 (d, J = 1.43 Hz), 21.45 (t, J = 1.72 Hz), 22.73, 23.28, 26.43 (dd, J = 1.72, 2.29 Hz), 29.64, 46.64 (dd, J = 5.15, 7.44 Hz), 47.39, 74.43 (dd, J = 22.62, 28.34 Hz), 115.32 (dd, J = 256.23, 264.53 Hz), 131.93, 135.06, 162.81 (t, J = 29.78 Hz). ^{19}F NMR ($CDCl_3$): δ 40.85 (dd, J = 15.51, 284.14 Hz), 54.16 (dd, J = 20.90, 284.14 Hz); Anal. Calcd. for $C_{14}H_{23}F_2NO_2$: C, 61.07; H, 8.42; N, 5.09. Found: C, 60.58; H, 8.16; N, 4.78. HPLC analysis: t_R (major), 20.0 min (95.4%); t_R (minor), 24.6 min (4.6%) (Chiralcel OD, *n*-hexane/*i*-propanol: 99/1, 1.0 ml/min).

3.19. (R)-(+)-6,6-Difluoro-7-hydroxydodecan-5-one (**4a**)

Into a mixture of (*R*)-(−)-*N*-(2,2-difluoro-3-hydroxyoctanoyl)pyrrolidine **2e** (1.26 g, 5 mmol) in THF (20 ml) under an atmosphere of nitrogen, butyl lithium (1 M in hexane, 2.0 equiv.) was added at −78 °C. After 10 min of stirring at that temperature, the mixture was quenched with methanol at −78 °C, and the solution was poured into 3N HCl and the organic materials were extracted with diethyl ether. On removal of the solvent, the residue was purified by column chromatography on silica gel, eluting with a mixture of hexane-ethyl acetate, giving (*R*)-(+)-6,6-difluoro-7-hydroxydodecan-5-one **4a** in 83% yield.

^{1}H NMR ($CDCl_3$): δ 0.90–0.95 (6 H, m), 1.32–1.68 (2 H, m), 2.19 (1 H, d, J = 6.6 Hz), 2.72 (2 H, t, J = 7.1 Hz), 3.97–4.07 (1 H, m). ^{19}F NMR ($CDCl_3$): δ 36.7 (dd, J = 16.4, 276.6 Hz), 47.5 (dd, J = 6.6, 276.6 Hz). ^{13}C NMR ($CDCl_3$): δ 13.7 (d, J = 8.9 Hz), 13.9 (d, J = 8.6 Hz), 22.0 (d, J = 4.3 Hz), 22.5, 24.5, 25.0, 28.9, 31.5, 37.5, 70.5–71.3 (m), 115.6 (t, J = 254.8 Hz), 202.9 (t, J = 30.3 Hz). IR (KBr): 3448, 1741 cm^{-1}. Anal. Calcd. for $C_{12}H_{22}F_2O_2$: C, 60.99; H, 9.38. Found: C, 60.64; H, 9.32. $[\alpha]_D$ +7.6 (*c* 0.6, $CHCl_3$), 83% ee. HPLC analysis (Daicel Chiralcel OD-H, *n*-hexane–*i*-propanol 99.5:0.5; flow speed 1.0 ml/mim. t_R (major), 15.4 min; t_R (minor), 16.7 min.

3.20. (R)-(−)-2,2-Difluoro-3-hydroxy-1-phenyloctan-1-one (**4b**)

^{1}H NMR ($CDCl_3$): δ 0.88–0.93 (3 H, m), 1.29–1.76 (8 H, m), 2.48 (1 H, d, J = 6.3 Hz), 4.17–4.31 (1 H, m), 8.10–8.13 (Ar-H). ^{19}F NMR ($CDCl_3$): δ 44.6 (dd, J = 17.2, 294.7 Hz), 53.9 (dd, J = 6.0, 294.7 Hz). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.5, 25.1, 28.2, 31.5, 71.6 (dd, J = 24.1, 27.2 Hz), 116.7 (dd, J = 256.5, 260.8 Hz), 128.5, 130.0 (t, J = 3.4 Hz), 132.2, 134.3, 190.5 (t, J = 29.5 Hz). IR (KBr): 3446, 1698 cm^{-1}. Anal. Calcd. for $C_{14}H_{18}F_2O_2$: C, 65.61; H, 7.08. Found: C, 65.41; H, 7.02. $[\alpha]_D$ –3.7 (*c* 0.7, $CHCl_3$), 91% ee. HPLC analysis (Daicel Chiralcel AD-H, *n*-hexane–*i*-propanol 98:2; flow speed 1.0 ml/min. t_R (major), 18.8 min; t_R (minor), 22.2 min.

3.21. (R)-(-)-(E)-6,6-Difluoro-7-hydroxy-8-dodecen-5-one (**4c**)

^{1}H NMR ($CDCl_3$): δ 0.91 (3 H, t, J = 7.4 Hz), 0.92 (3 H, t, J = 7.1 Hz), 1.28–1.49 (4 H, m), 1.54–1.65 (2 H, m), 2.08 (2 H, q, J = 6.9 Hz), 2.19 (1 H, J = 6.1 Hz), 2.70 (2 H, t, J = 7.1 Hz), 4.45–4.57 (1 H, m), 5.52 (1 H, dd, J = 7.1, 15.4 Hz), 5.90 (1 H, td, J = 6.1, 15.4 Hz). ^{19}F NMR ($CDCl_3$): δ 38.6 (dd, J = 14.7, 271.4 Hz), 47.3 (dd, J = 7.8, 270.6 Hz). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 21.9, 22.1, 24.5, 34.4, 37.7, 72.3 (dd, J = 24.9, 28.3 Hz), 114.9 (dd, J = 255.3, 259.4 Hz), 122.8 (dd, J = 2.3, 3.4 Hz), 138.1, 202.0 (dd, J = 27.8, 30.6 Hz). IR (KBr): 3454, 1740 cm^{-1}. Anal. Calcd. for $C_{12}H_{20}F_2O_2$: C, 61.52; H, 8.60. Found: C, 61.36; H, 8.68. [a]$_D$ –14.6 (*c* 0.5, $CHCl_3$), 94% ee. HPLC analysis (Daicel Chiralcel OD-H, *n*-hexane–*i*-propanol 99.5: 0.5; flow speed 1.0 ml/min. t_R (major), 20.8 min; t_R (minor), 22.4 min.

3.22. (R)-(−)-(E)-2,2-Difluoro-3-hydroxy-1-phenyl-4-octen-1-one (**4d**)

^{1}H NMR ($CDCl_3$): δ 0.90 (3 H, t, J = 7.4 Hz), 1.43 (2 H, dq, J = 7.4, 7.4 Hz), 2.09 (2 H, q, J = 6.9 Hz), 2.49 (1 H, d, J = 6.0 Hz), 4.66–4.78 (1 H, m), 5.62 (1 H, dd, J = 6.9, 15.1 Hz), 5.94 (1 H, td, J = 6.0, 15.4 Hz), 7.46–8.12 (Ar-H). ^{19}F NMR ($CDCl_3$): δ 46.4 (dd, J = 15.5, 290.4 Hz), 54.6 (dd, J = 7.6, 291.2 Hz). ^{13}C NMR ($CDCl_3$): δ 13.6, 21.9, 34.4, 72.7 (dd, J = 24.3, 27.8 Hz), 116.0 (dd, J = 256.8, 261.1 Hz), 122.8 (dd, J = 2.3, 3.4 Hz), 128.5, 130.0 (t,

J = 3.2 Hz), 132.3, 134.3, 137.9, 190.3 (dd, J = 28.9, 30.6 Hz). IR (KBr): 3454, 1698 cm^{-1}. Anal. Calcd. for $C_{14}H_{16}F_2O_2$: C, 66.13; H, 6.34. Found: C, 66.39; H, 6.71. $[a]_D$ -16.9 (c 0.7, $CHCl_3$), 94% ee. HPLC analysis (Daicel Chiralcel AD-H, *n*-hexane–*i*-propanol 98: 2; flow speed 1.0 ml/min. t_R (major), 22.8 min; t_R (minor), 30.8 min.

3.23. (E)-5,5-Difluoro-4-hydroxy-2-decen-6-one (**4e**)

^1H NMR ($CDCl_3$): δ 0.99 (3 H, t, J = 7.28 Hz), 1.34 (2 H, sex, J = 7.28 Hz), 1.56–1.65 (2 H, m), 1.77 (3 H, ddd, J = 0.82, 1.65, 6.59 Hz), 2.22 (1 H, br), 2.70 (2 H, tt, J = 0.82, 7.28 Hz), 4.43–4.55 (1 H, m), 5.55 (1 H, qdd, J = 1.65, 7.14, 15.38 Hz), 5.92 (1 H, dqd, J = 1.10, 6.59, 15.38 Hz). ^{13}C NMR($CDCl_3$): δ 13.54, 17.67, 21.87, 24.33, 37.64, 71.99 (dd, J = 25.10, 28.48 Hz), 115.06 (dd, J = 254.99, 259.24 Hz), 123.58 (dd, J = 2.00, 3.44 Hz), 132.61, 202.17 (dd, J = 27.49, 30.64 Hz). ^{19}F NMR ($CDCl_3$): δ 38.47 (dd, J = 15.51, 271.43 Hz), 47.52 (dd, J = 7.76, 271.4 Hz). Anal. Calcd. for $C_{10}H_{16}F_2O_2$: C, 58.24; H, 7.82. Found: C, 57.84; H, 8.27.

3.24. (E)-2,2-Difluoro-3-hydroxy-1-phenyl-4-hexen-1-one (**4f**)

Rf= (*n*-hexane:AcOEt=2:1). ^1H NMR ($CDCl_3$): δ 1.78 (3 H, dd, J = 1.92, 6.59 Hz), 2.55 (1 H, br), 4.64–4.76 (1 H, m), 5.65 (1 H, qdd, J = 1.65, 7.14, 15.38 Hz), 5.97 (1 H, dqd, J = 1.10, 6.59, 15.38 Hz), 7.48–7.54 (2 H, m), 7.62–7.68 (1 H, m), 8.08 (1 H, q, J = 1.10 Hz), 8.11 (1 H, q, J = 1.10 Hz). ^{13}C NMR($CDCl_3$): δ 17.89, 72.57 (dd, J = 24.48, 27.92 Hz), 116.13 (dd, J = 256.51, 260.81 Hz), 124.04 (dd, J = 2.15, 3.58 Hz), 128.41, 129.93 (t, J = 4.38 Hz), 132.35 (t, J = 2.29 Hz), 132.84, 134.22, 190.32 (dd, J = 28.92, 30.63 Hz). ^{19}F NMR ($CDCl_3$): δ 46.36 (dd, J = 15.89, 290.81 Hz), 54.81 (dd, J = 7.76, 290.81 Hz); Anal. Calcd. for $C_{12}H_{12}F_2O_2$: C, 63.71; H, 5.35. Found: C, 63.50; H, 5.39.

3.25. (E)-6-Benzyloxy-4,5-epoxy-7,7-difluorododecan-8-one

N-(3-Benzyloxy-4,5-epoxy-2,2-difluorooctanoyl)pyrrolidine. 92% yield. ^1H NMR ($CDCl_3$): δ 0.97 (3 H, t, J = 7.14 Hz), 1.42–1.66 (4 H, m), 1.72–1.88 (4 H, m), 2.93 (1 H, dt, J = 2.72, 5.22 Hz), 3.09 (1 H, dd, J = 2.20, 7.42 Hz), 3.50–3.55 (2 H, m), 3.55–3.78 (2 H, m), 3.70 (1 H, ddd, J = 7.01, 7.01, 16.76), 4.63 (1 H, d, J = 11.26 Hz), 4.87 (1 H, d, J = 11.54 Hz), 7.26–7.37 (5 H, m). ^{13}C NMR($CDCl_3$): δ 13.86, 19.04, 23.21, 26.37 (dd, J = 1.43, 3.15 Hz), 33.49, 46.81 (dd, J = 4.58, 9.45 Hz), 47.77, 54.93 (dd, J = 0.86, 2.29 Hz), 56.19 (dd, J = 2.15, 4.73 Hz), 73.44, 80.44 (dd, J = 23.48, 29.49 Hz), 115.85 (dd, J = 253.37, 261.38 Hz), 127.72, 127.81, 128.10, 137.06, 161.22 (t, J = 27.77 Hz). ^{19}F NMR ($CDCl_3$): δ 46.04 (1 F, dd, J = 16.81, 268.41 Hz), 55.40 (1 F, dd, J = 6.47, 268.41 Hz). IR (neat): 1659 cm^{-1}.

In the above reaction, *N*-(3-benzyloxy-4,5-epoxy-2,2-difluorooctanoyl)pyrrolidine (1 mmol) and *n*-BuLi (2.0 eq.) in THF were used, and then worked up similarly, giving (*E*)-6-benzyloxy-4,5-epoxy-7,7-difluorododecan-8-one in 81% yield. ^1H NMR ($CDCl_3$): δ 0.88 (3 H, t, J = 7.14 Hz), 0.97 (3 H, t, J = 7.14 Hz), 1.30 (2 H, sex, J = 7.14 Hz), 1.43–1.68 (6 H, m), 2.67 (2 H, tt, J=1.65, 7.14 Hz), 2.89 (1 H, m), 3.03 (1 H, dd, J = 2.20, 7.41 Hz), 3.52 (1 H, ddd, J = 6.32, 7.41, 16.76 Hz), 4.57 (1 H, d, J = 12.40 Hz), 4.84 (1 H, d, J = 12.40 Hz), 7.25–7.38 (5 H, m). ^{13}C NMR($CDCl_3$): δ 13.81, 13.90, 22.02, 24.44, 33.51, 37.91, 54.66 (d, J = 1.43 Hz), 55.97 (dd, J = 2.00, 4.58 Hz), 72.97, 79.80 (dd, J = 23.62, 29.63 Hz), 115.00 (dd, J = 254.80, 260.87 Hz), 127.92, 127.26, 128.23, 136.58, 201.20 (dd, J = 25.48, 30.64 Hz). ^{19}F NMR ($CDCl_3$): δ 39.59 (1 F, dd, J = 16.37, 267.11 Hz), 52.46 (1 F, dd, J = 6.03, 267.11 Hz). IR (neat): 1743 cm^{-1}. Anal. Calcd. for: C, 67.04; H, 7.70. Found: C, 66.72; H, 7.58.

3.26. General procedure for epoxide

To a solution of mCPBA (2.0 equiv., >65% assay) in CH_2Cl_2 (0.1 M), allyl alcohol (1 equiv.) was added at −10 °C under an argon atmosphere. After 72 h of stirring at −10 °C, the reaction was quenched with 10% aq. $NaHSO_3$. The separated aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were washed with saturated aq. $NaHCO_3$, twice and brine, dried over $MgSO_4$, and concentrated. The residual was purified by column chromatography (hexane/AcOEt).

3.27. (E)-5,5-Difluoro-4-hydroxy-2,3-epoxydecan-6-one

85% yield; IR (neat): 1743 cm^{-1}. Anal. Calcd. for $C_{10}H_{16}F_2O_3$: C, 54.05; H, 7.26. Found: C, 53.69; H, 7.48. Major isomer; ^1H NMR ($CDCl_3$): δ 0.93 (3 H, t, J = 7.28 Hz), 1.32–1.40 (2 H, m), 1.38 (3 H, d, J = 4.94 Hz), 1.57–1.68 (2 H, m), 2.73 (2 H, dt, J = 1.46, 7.28 Hz), 3.05 (1 H, dq, J = 2.68, 5.22 Hz), 3.08 (1 H, t, J = 2.61 Hz), 4.11 (1 H, ddd, J = 2.75, 5.77, 18.13 Hz). ^{13}C NMR($CDCl_3$): d 13.72, 16.76, 21.98, 24.40, 37.61, 51.45, 56.12 (t, J = 3.72 Hz), 69.71 (dd, J = 24.48, 28.77 Hz), 114.98 (dd, J=255.66, 260.52 Hz), 201.30 (dd, J = 25.76, 30.92 Hz). ^{19}F NMR ($CDCl_3$): δ 36.77 (dd, 1 F, J = 18.10, 274.88 Hz), 49.17 (dd, 1 F, J = 5.60, 274.88 Hz). Miner isomer; ^1H NMR ($CDCl_3$): δ 0.93 (3 H, t, J = 7.28 Hz), 1.32–1.40 (2 H, m), 1.37 (3 H, d, J = 5.50 Hz), 1.57–1.68 (2 H, m), 2.74 (2 H, dt, J = 1.65, 7.14 Hz), 3.00 (1 H, dd, J = 2.75, 6.04 Hz), 3.12 (1 H, dq, J = 2.20, 5.22 Hz), 4.27 (1 H, ddd, J = 3.44, 8.24, 14.13 Hz). ^{13}C NMR($CDCl_3$): δ 13.72, 16.76, 21.98, 24.40, 37.65, 51.55, 56.17 (t, J = 3.29 Hz), 68.90 (dd, J = 25.06, 27.63 Hz), 115.25 (dd, J = 255.51, 258.95 Hz), 201.20 (t, J = 28.06 Hz). ^{19}F NMR ($CDCl_3$): δ 40.26 (1 F, dd, J = 14.22, 273.15 Hz), 46.68 (1 F, dd, J = 7.76, 273.15 Hz).

*3.28. N-((E)-2,2-Difluoro-3-hydroxy-4,5-epoxyhexanoyl)pyrrolidine (**5a**)*

^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, d, J = 4.97 Hz), 1.84–1.93 (2 H, m), 1.95–2.04 (2 H, m), 3.05–3.11 (2 H, m), 3.40 (1 H, br), 3.55 (2 H, t, J = 7.01 Hz), 3.75 (2 H, t, J = 6.73 Hz), 4.13 (1 H, ddd, J = 3.85, 8.24, 15.38 Hz). ^{13}C NMR($CDCl_3$): δ 16.93, 23.18, 26.34 (dd, J = 1.43, 2.29 Hz), 46.91 (dd, J = 5.15, 7.44 Hz), 47.39, 51.22, 56.26 (t, J = 3.87 Hz), 70.94 (dd, J = 24.05, 27.49 Hz), 115.34 (dd, J = 257.08, 262.24 Hz), 161.34 (t, J = 28.49 Hz). ^{19}F NMR ($CDCl_3$): δ 44.78 (dd, J = 15.51, 286.93 Hz), 51.07 (dd, J = 8.19, 286.93 Hz). Anal. Calcd. for $C_{10}H_{15}F_2NO_3$: C, 51.06; H, 6.43; N, 5.95. Found: C, 51.26; H, 6.04; N, 5.67.

*3.29. N-((Z)-2,2-Difluoro-3-hydroxy-4,5-epoxyhexanoyl)pyrrolidine (**5b**)*

Major isomer:^{1}H NMR ($CDCl_3$): δ 1.38 (3 H, d, J = 5.61 Hz), 1.87–1,92 (2 H, m), 1.97–2.02 (2 H, m), 3.22 (1 H, dq, J = 4.28, 5.61 Hz), 3.28 (1 H, dd, J = 4.37, 6.83 Hz), 3.53 (1 H, br), 3.56 (2 H, t, J = 7.12 Hz), 3.76 (1 H, t, J = 7.72 Hz), 4.09 (1 H, m). ^{13}C NMR($CDCl_3$): δ 13.92 (dd, J = 0.57, 2.00 Hz), 23.20, 26.33 (dd, J = 1.14, 2.29 Hz), 46.48 (dd, J = 4.87, 7.44 Hz), 47.38, 53.01, 54.74 (dd, J=3.15, 4.87 Hz), 69.80 (dd, J = 4.05, 29.20 Hz), 115.31 (dd, J = 256.80, 262.81 Hz), 161.30 (t, J = 28.63 Hz). ^{19}F NMR ($CDCl_3$): δ 43.25 (dd, J = 15.26, 289.92 Hz), 51.44 (dd, J = 3.05, 289.92 Hz).

*3.30. N-((E)-2,2-Difluoro-3-hydroxy-4,5-epoxyoctanoyl)pyrrolidine (**5c**)*

^{1}H NMR ($CDCl_3$): δ 0.97 (3 H, t, J = 7.26 Hz), 1.43–1.53 (2 H, m), 1.55–1.60 (2 H, m), 1.86–1.91 (2 H, m), 1.96–2.02 (2 H, m), 3.01 (1 H, dt, J = 2.28, 5.61 Hz), 3.11 (1 H, dd, J = 2.38, 3.85 Hz), 3.51–3.60 (2 H, m), 3.75 (2 H, t, J = 6.60 Hz), 4.13 (1 H, ddd, J = 3.90, 7.82, 15.87 Hz). ^{13}C NMR ($CDCl_3$): δ 13.75, 19.00, 23.12, 26.28 (dd, J = 1.43, 2.29 Hz), 33.29, 46.47 (dd, J = 5.16, 7.73 Hz), 47.33, 55.04, 55.35 (t, J = 3.87 Hz), 71.14 (dd, J = 24.05, 27.49 Hz), 115.37 (dd, J = 257.59, 262.23 Hz), 161.30 (t, J = 28.49 Hz). ^{19}F NMR ($CDCl_3$): δ 44.71 (dd, J = 15.52, 286.94 Hz), 51.32 (dd, J = 7.76, 286.94 Hz). Anal. Calcd. for $C_{12}H_{19}F_2NO_3$: C, 54.74; H, 7.27; N, 5.32. Found: C, 54.62; H, 7.04; N, 4.99.

*3.31. N-((E)-2,2-Difluoro-3-hydroxy-4-ethyl-4,5-epoxyoctanoyl)pyrrolidine (**5d**)*

Major isomer:^{1}H NMR (CDCl3): δ 0.99 (3 H, t, J = 7.42 Hz), 1.06 (3 H, t, J = 7.70 Hz), 1.42–2.20 (10 H, m), 3.06–3.10 (1 H, m), 3.53 (2 H, t, J = 6.59 Hz), 3.67–3.78 (2 H, m), 3.82 (1 H, d, J = 5.50 Hz), 4.10–4.22 (1 H, m). ^{13}C NMR($CDCl_3$): δ 9.58, 13.93, 19.75, 21.71 (dd, J = 1.43, 4.01 Hz), 23.11, 26.37 (t, J = 2.87 Hz), 29.63, 46.60 (dd, J = 4.29, 9.02 Hz), 47.47, 60.18 (d, J = 2.86 Hz), 62.49, 74.28 (dd, J = 23.05, 27.06 Hz), 115.80 (dd, J = 256.38, 264.39 Hz), 162.09 (t, J = 28.77 Hz). ^{19}F NMR ($CDCl_3$): δ 44.39 (dd, J = 19.82, 282.63 Hz), 54.91 (dd, J = 5.60, 282.63 Hz). IR: 1652 cm^{-1}. Anal. Calcd. for $C_{14}H_{23}F_2NO_3$: C, 57.72; H, 7.96; N, 4.81. Found: C, 57.96; H, 8.21; N, 5.12. Minor isomer: ^{1}H NMR ($CDCl_3$): δ 0.99 (3 H, t, J = 7.42 Hz), 1.07 (3 H, t, J = 7.41 Hz), 1.42–2.20 (10 H, m), 2.96 (1 H, br), 3.17 (1 H, dt, J = 1.37, 6.05 Hz), 3.51–3.59 (2 H, m), 3.67–3.78 (2 H, m), 4.43 (1 H, dd, J = 4.40, 19.23 Hz). ^{13}C NMR($CDCl_3$): δ 8.62, 13.88, 19.56, 21.61 (dd, J = 1.72, 2.29 Hz), 23.17, 26.39 (t, J = 2.86 Hz), 29.67, 46.60 (dd, J = 4.01, 9.02 Hz), 47.60, 60.02 (d, J = 3.15 Hz), 61.37 (d, J = 1.72 Hz), 69.05 (dd, J = 24.34, 29.49 Hz), 116.39 (dd, J = 252.51, 263.39 Hz), 161.60 (t, J = 28.34 Hz). ^{19}F NMR ($CDCl_3$): δ 44.28 (dd, J = 18.96, 270.57 Hz), 54.15 (d, J = 269.70 Hz).

*3.32. (E)-5,5-Difluoro-4-hydroxy-2,3-epoxydecan-6-one (**5e**)*

Major isomer; ^{1}H NMR ($CDCl_3$): δ 0.93 (3 H, t, J = 7.28 Hz), 1.32–1.40 (2 H, m), 1.38 (3 H, d, J = 4.94 Hz), 1.57–1.68 (2 H, m), 2.73 (2 H, dt, J = 1.46, 7.28 Hz), 3.05 (1 H, dq, J = 2.68, 5.22 Hz), 3.08 (1 H, t, J = 2.61 Hz), 4.11 (1 H, ddd, J = 2.75, 5.77, 18.13 Hz). ^{13}C NMDCl_3): δ 13.72, 16.76, 21.98, 24.40, 37.61, 51.45, 56.12 (t, J = 3.72 Hz), 69.71 (dd, J = 24.48, 28.77 Hz), 114.98 (dd, J = 255.66, 260.52 Hz), 201.30 (dd, J = 25.76, 30.92 Hz). ^{19}F NMR ($CDCl_3$): δ 36.77 (dd, J = 18.10, 274.88 Hz), 49.17 (dd, J = 5.60, 274.88 Hz). Anal. Calcd. for $C_{10}H_{16}F_2O_3$: C, 54.05; H, 7.26. Found: C, 53.69; H, 7.48.

Miner isomer; ^{1}H NMR ($CDCl_3$): δ 0.93 (3 H, t, J = 7.28 Hz), 1.32–1.40 (2 H, m), 1.37 (3 H, d, J = 5.50 Hz), 1.57–1.68 (2 H, m), 2.74 (2 H, dt, J = 1.65, 7.14 Hz), 3.00 (1 H, dd, J = 2.75, 6.04 Hz), 3.12 (1 H, dq, J = 2.20, 5.22 Hz), 4.27 (1 H, ddd, J = 3.44, 8.24, 14.13 Hz). ^{13}C NMR ($CDCl_3$): δ 13.72, 16.76, 21.98, 24.40, 37.65, 51.55, 56.17 (t, J = 3.29 Hz), 68.90 (dd, J = 25.06, 27.63 Hz), 115.25 (dd, J = 255.51, 258.95 Hz), 201.20 (t, J = 28.06 Hz). ^{19}F NMR ($CDCl_3$): δ 40.26 (dd, J = 14.22, 273.15 Hz), 46.68 (dd, J = 7.76, 273.15 Hz).

*3.33. (E)-2,2-Difluoro-3-hydroxy-1-phenyl-4,5-epoxyhexan-1-one (**5f**)*

82% yield. IR (neat): 1699 cm^{-1}. major isomer; ^{1}H NMR ($CDCl_3$): δ 1.38 (3 H, d, J = 5.22 Hz), 2.78 (1 H, d, J = 7.96 Hz), 3.06–3.21 (2 H, m), 4.25–4.37 (1 H, m), 7.48–7.54 (2 H, m), 7.62–7.69 (1 H, m), 8.09–8.14 (2 H, m); ^{13}C NMR($CDCl_3$): δ 16.65, 16.67, 51.37, 51.55, 56.20, 56.25, 69.37 (t, J = 25.48 Hz), 70.26 (dd, J = 24.05, 27.20 Hz), 116.41 (dd, J = 257.37, 261.67 Hz), 116.62 (t, J = 258.66 Hz), 128.36, 128.43, 129.80, 129.85, 129.89,

129.94, 134.20, 134.28, 189.37 (dd, J = 28.06, 29.48 Hz), 189.50 (t, J = 28.49 Hz). ^{19}F NMR ($CDCl_3$): δ 47.23 (dd, J = 16.37, 292.11 Hz), 54.44 (dd, J = 7.75, 292.11 Hz); Anal. Calcd. for $C_{12}H_{12}F_2O_3$: C, 59.50; H, 4.99. Found: C, 59.26; H, 5.15.

Miner isomer; ^{1}H NMR (CDCl3): d 1.37 (3 H, d, J = 5.22 Hz), 2.71 (1 H, br), 3.06–3.21 (2 H, m), 4.40–4.51 (1 H, m), 7.48–7.54 (2 H, m), 7.62–7.69 (1 H, m), 8.09–8.14 (2 H, m). ^{19}F NMR ($CDCl_3$): δ 47.85 (dd, J = 15.89, 291.24 Hz), 53.48 (dd, J = 7.75, 291.24 Hz).

*3.34. (E)-Ethyl 5,5-difluoro-4-hydroxy-2,3-epoxyhexanate (**5g**)*

79% yield, major isomer: ^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, t, J = 7.14 Hz), 1.38 (3 H, d, J = 5.22 Hz), 2.65 (1 H, br), 3.06 (1 H, dq, J = 2.20, 5.22 Hz), 3.10 (1 H, t, J = 2.20 Hz), 4.08–4.21 (1 H, m), 4.38 (2 H, q, J = 7.14 Hz). ^{13}C NMR ($CDCl_3$): δ 13.74, 16.62, 51.21, 55.96 (t, J = 3.87 Hz), 63.21, 70.01 (t, J = 26.63 Hz), 113.73 (dd, J = 253.93, 257.97 Hz), 162.29 (dd, J = 30.35, 32.06 Hz). ^{19}F NMR ($CDCl_3$): δ 39.05 (ddd, J = 6.03, 16.94, 267.12 Hz), 48.67 (dd, J = 6.03, 267.12 Hz). IR: 1762 cm^{-1}. Anal. Calcd. for $C_8H_{12}F_2O_4$: C, 45.72; H, 5.75. Found: C, 45.54; H, 6.15.

minor isomer: ^{1}H NMR ($CDCl_3$): δ 1.371 (3 H, d, J = 5.22 Hz), 1.374 (3 H, t, J = 7.14 Hz), 2.56 (1 H, br), 3.02 (1 H, dd, J = 2.48, 3.57 Hz), 3.18 (1 H, dq, J = 2.20, 5.22 Hz), 4.27 (1 H, ddd, J = 3.58, 8.52, 13.46 Hz), 4.38 (2 H, q, J = 7.14 Hz). ^{13}C NMR ($CDCl_3$): δ 13.74, 16.65, 51.59, 55.80 (t, J = 3.44 Hz), 63.16, 69.61 (t, J = 25.91 Hz), 113.90 (t, J = 254.94 Hz), 162.29 (dd, J = 30.35, 32.06 Hz). ^{19}F NMR ($CDCl_3$): δ 41.75 (dd, J = 13.79, 266.26 Hz), 46.71 (dd, J = 8.62, 266.26 Hz).

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