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A convenient method for the preparation of α,α-difluoro-β-ketoesters and α,α-difluoroamides from terpenic and perfumery aldehydes

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Abstract

Reformatsky reactions with ethyl bromodifluoroacetate gave α,α-difluoro-β-hydroxyesters in good yield from the corresponding terpenic and perfumery aldehydes. α,α-Difluoro-β-ketoesters were prepared by Swern oxidation of the α,α-difluoro-β-hydroxyesters. The reaction of hydroxyesters with amines in the presence of lipase MY, lipase PS or Novozym 435 gave α,α-difluoroamides.

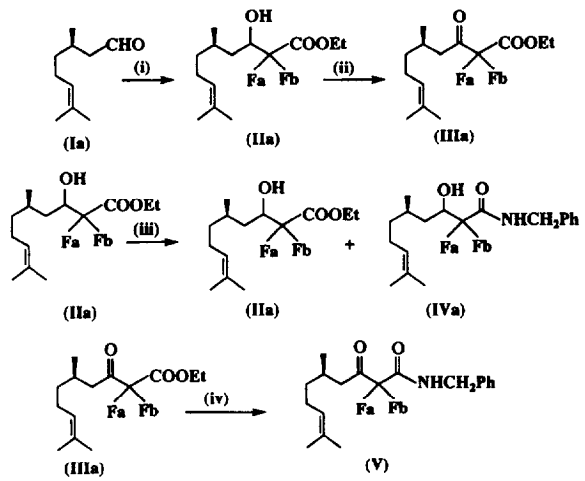
Keywords: α,α-Difluoro-β-hydroxyamide; α,α-Difluoro-β-hydroxyester; α,α-Difluoro-β-ketoester; Lipase MY; Lipase PS; Novozym 435; Swern oxidation; Terpenic aldehyde

1. Introduction

Fluorinated derivatives of terpenic and perfumery carbonyl compounds have not been examined in detail. Recently, we reported the trifluoromethylation and pentafluoroethylation of terpenic carbonyl compounds using the Olah reagent [1]. In the present study, various α,α-difluoro-β-ketoesters were prepared by Swern oxidation [2,3] of α,α-difluoro-β-hydroxyesters [4,5], obtained from the reaction of aldehydes with bromodifluoroacetate. The reaction of these hydroxyesters with amines to give the corresponding α,α-difluoro-β-hydroxyamides was examined.

2. Results and discussion

The Reformatsky reactions of ethyl bromodifluoroacetate with various carbonyl compounds have been described [4]. However, the reactions with terpenic and perfumery aldehydes have not been examined. In this work, we prepared α,α-difluoro-β-hydroxyesters by the Reformatsky reactions of ethyl bromodifluoroacetate with various terpenic and perfumery aldehydes (Scheme 1). For example, the reaction of citronellal (**Ia**) and ethyl bromodifluoroacetate gave ethyl 2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenoate (**IIa**). Other results are shown in Table 1.



Scheme 1. (i) $BrCF_2COOEt$, THF, Zu; (ii) $(-COCl)_2$, DMSO; (iii) $PhCH_2NH_2$, Lipase MY; (iv) $PhCH_2NH_2$, $ZnCl_2$.

It is known that the Swern oxalyl chloride procedure is effective for the conversion of β-hydroxyesters to the corresponding ketoesters in high yields [2,3]. We applied this Swern oxidation to α,α-difluoro-β-hydroxyesters, and their corresponding β-ketoesters were obtained in good yield. For example, the reaction of compound **IIa** with freshly distilled oxalyl chloride in dimethyl sulphoxide (DMSO) gave the corresponding β-ketoester, ethyl 2,2-difluoro-3-oxo-5,9-dimethyl-8-decenoate (**IIIa**), in a yield of 75% (Scheme 1). We have found that Swern oxidation is suitable for the oxi-

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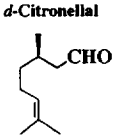
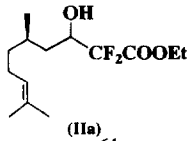
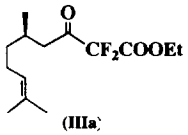
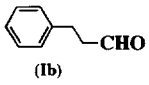
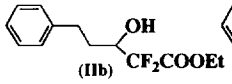
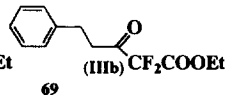
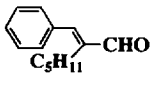
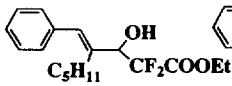
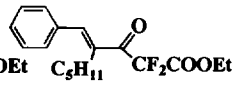
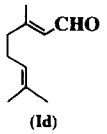
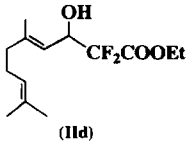
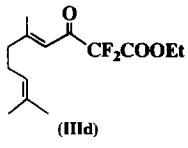
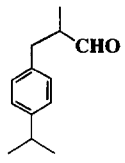
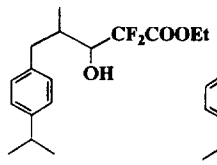
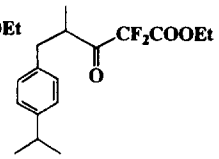
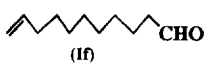
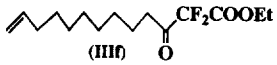
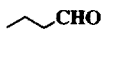
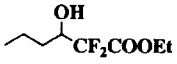
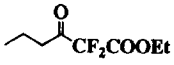
Table 1
α,α-Difluoro-β-hydroxyesters and α,α-difluoro-β-ketoesters

Carbonyl compound	β-Hydroxyester yield (%)	β-Ketoester yield (%)
d-Citronellal	 (Ia)	 (IIa) 64	 (IIIa) 75
Dihydrocinnamic aldehyde	 (Ib)	 (IIb) 63	 (IIIb) 69
Osminal	 (Ic)	 (IIc) 88	 (IIIc) 74
Citral	 (Id)	 (IId) 68	 (IIId) 75
Cyclamen aldehyde	 (Ie)	 (IIe) 77	 (IIIe) 73
10-Undecenyl aldehyde	 (If)	(IIf) 65	 (IIIf) 70
n-Butyraldehyde	 (Ig)	 (IIg) 75	 (IIIg) 72

dation of other α,α-difluoro-β-hydroxyesters. These results are shown in Table 1.

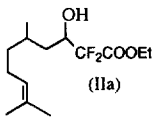
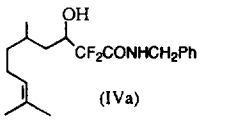
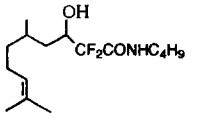
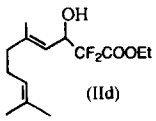
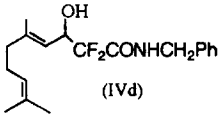
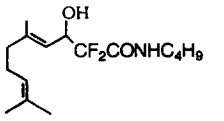
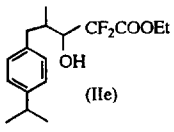
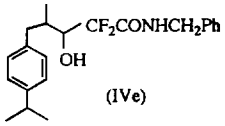
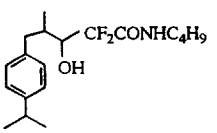
Candida antarctica lipase (CAL) is a very efficient catalyst for the enantioselective aminolysis of various racemic 3-hydroxyesters with aliphatic amines [6]. However, the reactions with terpenic derivatives containing difluoro groups have not been examined. We applied this lipase reaction to α,α-difluoro-β-hydroxyesters, and hydroxyesters and hydroxyamides with slight optical activity were obtained. For example, the reaction of compound **IIa** with benzylamine in the presence of lipase MY gave compound **IIa** ($[\alpha]_D^{20} = +13.0°$) and *N*-benzyl-2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenamide (**IVa**) ($[\alpha]_D^{20} = -1.04°$). Other results are shown in Table 2. Furthermore, the reaction of compound **IIIa** with benzylamine, catalysed by zinc dichloride, gave *N*-benzyl-2,2-difluoro-5,9-dimethyl-3-keto-8-decenamide (**V**), but in the presence of a lipase compound, **V** was not produced. At present, we are examining the biological activities of these amides.

3. Experimental details

3.1. General procedure

The reaction products were analysed by gas chromatographic methods using a 3 mm (i.d.) × 3 m column of 15% Silicone DC 200 on 60–80 mesh Celite 545. Nuclear magnetic resonance (NMR) spectra were recorded at 60 or 250 MHz for ^{1}H NMR and 56.4 or 470 MHz for ^{19}F NMR in

Table 2
α,α-Difluoro-β-hydroxyamides

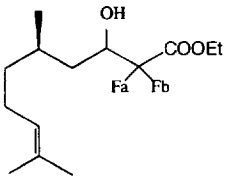
β-Hydroxyester	β-Hydroxyamide	yield (%)
 (IIa)	 (IVa)	14* 15** 17***
		19* 22**
 (IId)	 (IVd)	18* 16**
		18* 25**
 (IIe)	 (IVe)	8* 17**
		7* 35**

*Lipase PS. **Novozym. ***Lipase MY.

$CDCl_3$. ^{19}F NMR chemical shifts are reported in parts per million (ppm) relative to trifluoroacetic acid ($\delta = 0.00$) as an external standard (low field positive).

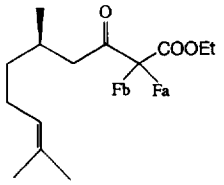
3.2. Ethyl 2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenoate (IIa)

A solution of *d*-citronellal (**Ia**) (1.54 g, 0.01 mol), zinc dust (0.85 g, 0.013 mol) and ethyl bromodifluoroacetate (2.64 g, 0.013 mol) in tetrahydrofuran (THF) (40 ml) was stirred for 7 h at 60 °C. The reaction mixture was treated with aqueous sulphuric acid (10%) and extracted with diisopropyl ether. The ether extract was washed with NaCl solution and dried over anhydrous sodium sulphate. The solvent was removed in vacuo and the residual product was chromatographed on a silica gel column with a mixture of ethylacetate and hexane (5 : 10, v/v) to give 1.78 g (64% yield) of compound **IIa**. It showed the following spectral data. IR (cm^{-1}): 3450 (OH), 1760 (>C=O). ^{19}F NMR (δ, ppm): −45.15 (1F, dd, $J_{FaFb} = 263.98$ Hz, $J_{FaH} = 15.26$ Hz, –C*Fa*FbCOOEt), −45.22 (1F, dd, $J_{FaFb} = 263.98$ Hz, $J_{FbH} = 15.26$ Hz, –CFa*Fb*COOEt), −37.79 (1F, dd, $J'_{Fa'Fb'} = 263.99$ Hz, $J_{Fa'H} = 7.63$ Hz, –C*Fa'*Fb'COOEt), −38.08 (1F, dd, $J_{Fa'Fb'} = 263.99$ Hz, $J_{Fb'H} = 7.63$ Hz, –CFa'*Fb'*COOEt). Compound **IIa** was a mixture of 50 : 50 diastereomers. ^1H NMR (δ, ppm): 0.94 (3H×1/2, d, $J = 6.59$ Hz, –CHCH_3), 0.99 (3H×1/2, d, $J = 6.59$ Hz, –CHCH_3), 1.20–1.28 (2H, m, –CH_2CH_2CH<), 1.37 (3H, t, $J = 6.96$ Hz, –OCH_2CH_3), 1.61 and 1.69 (3H and 3H, each s, –CH=C(CH_3)$_2$), 1.95–2.05 (4H, m, –CH_2–CH_2–CH- and OH), 4.11–4.15 (1H, m, –CH(OH)), 4.36 (2H, q, $J = 6.96$ Hz, –OCH_2CH$_3$), 5.10 (1H, t, $J = 6.96$ Hz, –CH=(CH$_3$)$_2$). Other α,α-difluoro-β-hydroxyesters were prepared in a similar manner, and the spectral data of the products are given in Table 3.



3.3. Ethyl 2,2-difluoro-5,9-dimethyl-3-keto-8-decenoate (IIIa)

A stirred solution of freshly distilled oxalyl chloride (0.61 g, 0.0048 mol) in dichloromethane (5 ml) was cooled to −60 °C; a solution of freshly distilled DMSO (0.69 g, 0.0088 mol) in dichloromethane (20 ml) was then added dropwise and stirring was continued for 2 min. Next, a solution of the β-hydroxyester (**IIa**) (1.11 g, 0.004 mol) in dichloromethane (5 ml) was added dropwise over 5 min and the resultant slurry was stirred for 15 min at −60 °C. After 3 h at −60 °C, triethylamine (2.04 g, 0.02 mol) was added and the resultant slurry was stirred for an additional 30 min at −60 °C. The mixture was warmed to room temperature over 5 min, water (20 ml) was added and the mixture was extracted with dichloromethane. The organic phases were washed with 1% hydrochloric acid (30 ml), 10% aqueous sodium carbonate (30 ml) and saturated sodium chloride solution (30 ml), and were then dried over anhydrous magnesium sulphate. The solvent was removed in vacuo and the residual product was purified by column chromatography with a silica gel column using a mixture of hexane and ethyl acetate (50 : 1, v/v) as solvent to give **IIIa** (0.83 g, yield 75%). The purified product showed the following spectra data. IR (cm^{-1}): 1770 (>C=O), 1730 (–COOEt). ^{19}F NMR (δ, ppm): −38.63 (2F, s, CF_2COOEt). ^1H NMR (δ, ppm): 0.94 (3H, d, $J = 6.59$ Hz, –CHCH_3), 1.20–1.28 (2H, m, –CH_2CH_2CH–), 1.34 (3H, t, $J = 7.08$ Hz, –O–CH_2CH_3), 1.59 and 1.68 (3H and 3H, each s, –CH=C(CH_3)$_2$), 1.92–2.15 (3H, m, –CH_2CH_2CH–), 2.56–2.72 (2H, m, –CHCH_2CO), 4.36 (2H, q, $J = 7.08$ Hz, –OCH_2CH$_3$), 5.07 (1H, t, $J = 7.08$ Hz, –CH=C(CH$_3$)$_2$). Other α,α-difluoro-β-ketoesters were prepared in a similar manner. The spectral data of these products are shown in Table 4.



3.4. N-Benzyl-2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenamide (IVa)

A mixture of ethyl 2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenoate (**IIa**) (1.00 g, 3.6 mmol), benzylamine (0.193 g, 1.8 mmol), lipase MY (300 mg), molecular sieves 4A 1/8 (Wako Chemical Co. Ltd.) (one piece) and 1,4-dioxan (30 ml) was stirred for 10 h at 40 °C under a nitrogen atmosphere. Lipase was filtered off and washed with diisopropyl ether. The filtrate was washed with 1 N HCl, water, 1 N NaOH and water in this order, and dried over anhydrous sodium sulphate. The solvent was removed and the residual product was purified by column chromatography with a silica gel column using a mixture of *n*-hexane and ethyl acetate (10 : 1, v/v) as solvent to give recovered compound **IIa** (0.40 g) (yield, 40%) ($[\alpha]_D^{20}$, CH_3OH, $c = 1.24$, +13.0°, 29% de) and *N*-benzyl-2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenamide (**IVa**) (0.236 g) (yield, 17%). Compound **IVa** showed the following spectral data. IR (cm^{-1}): 3325 (OH), 1690 (–CONH–). ^{19}F NMR (δ, ppm): −48.00 (1F, dd, $J_{FaFb} = 39.68$ Hz, $J_{FaH} = 18.31$ Hz, –C*Fa*FbCONH), −47.58 (1F, dd, $J_{FaFb} = 39.68$ Hz, $J_{FbH} = 18.31$ Hz, –CFa*Fb*CONH), −38.68 (1F, dd, $J_{Fa'Fb'} = 135.80$ Hz, $J_{Fa'H} = 7.63$ Hz, –C*Fa'*Fb'CONH), −38.12 (1F, dd, $J_{Fa'Fb'} = 135.80$ Hz, $J_{Fb'H} = 7.63$ Hz, –CFa'*Fb'*CONH). ^1H NMR (δ, ppm): 0.92 (3H×1/2, d, $J = 6.59$ Hz, –CHCH_3), 0.97 (3H×1/2, d, $J = 6.59$ Hz, –CHCH_3), 1.20–1.28 (2H, m, –CH_2CH_2CH–),

Table 3
Spectral data of α,α-difluoro-β-hydroxyesters

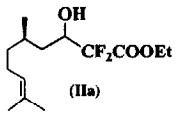
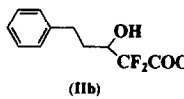
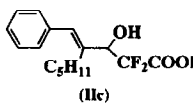
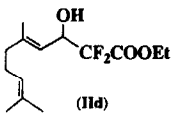
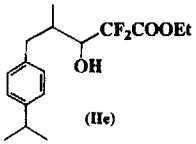
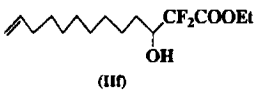
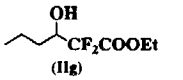
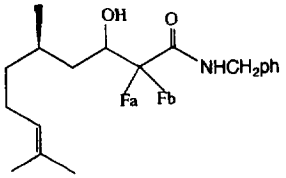
IR (cm^{-1})	^1H NMR (δ, ppm)	^{19}F NMR (δ, ppm)	Structure
See Section 3.2			 (IIa)
3450, 1760	1.34 (3H, t, J = 7.08 Hz, –O–CH_2CH_3), 1.75 (1H, broad s, O*H*), 2.69–2.77 (2H, m, ph–CH_2CH_2–) 2.90–2.97 (2H, m, ph–CH_2CH_2–), 3.99–4.07 (1H, m, >C*H*OH), 4.34 (2H, q, J = 7.08 Hz, –O–CH_2CH_3), 7.26–7.30 (5H, m, –ph)	–46.38 (1F, dd, J_{FaFb} = 265.51 Hz, J_{FaH} = 15.26 Hz, –C*Fa*Fb), –39.52 (1F, dd, J_{FaFb} = 265.51 Hz, J_{FbH} = 7.63 Hz, –CFa*Fb*)	 (IIb)
3500, 1765	0.855 (3H, t, J = 7.05 Hz, –$C_4H_8CH_3$), 1.22–1.28 (6H, m, –CH_2–$(CH_2)_3CH_3$), 1.35 (3H, t, J = 6.98 Hz, –OCH_2CH_3), 1.45–1.65 (3H, m, –$CH_2(CH_2)_3$–$(CH_2)_3$–CH_3, –O*H*), 2.42–2.50 (1H, m, ph–C*H*=C<), 4.36 (2H, q, J = 7.08 Hz, –O–CH_2–CH_3), 4.72 (1H, m, >C*H*–CF_2–), 7.24–7.37 (5H, m, –ph)	–43.31 (1F, dd, J_{FaFb} = 259.40 Hz, J_{FaH} = 15.26 Hz, –C*Fa*Fb), –37.49 (1F, dd, J_{FaFb} = 259.40 Hz, J_{FbH} = 7.63 Hz, –CFa*Fb*)	 (IIc)
3443, 1760	1.36 (3H, t, J = 7.08 Hz, –O–CH_2–CH_3), 1.60, 1.68 (3H and 3H, each s, –CH=C(CH_3)$_2$), 1.75 (3H × 1/2, s, –C(CH_3)=CH–), 1.81 (3H × 1/2, s, –C(CH_3)=CH–), 2.01–2.20 (5H, m, –CH_2–CH_2–, –O*H*), 4.34 (2H, q, J = 7.25 Hz, –CH_2–CH_3), 4.83–4.97 (1H, m, –C*H*(OH)–), 5.04–5.09 (1H, m, –C*H*=(CH_3)$_2$), 5.23–5.31 (1H, m, >C=C*H*–CH(OH)–)	–46.49 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FaH} = 15.25 Hz, –C*Fa*Fb–, cis isomer), –39.53 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FbH} = 7.63 Hz, –CFa*Fb*–, trans isomer), –45.53 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FaH} = 13.74 Hz, –C*Fa*Fb–), –35.29 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FaH} = 7.63 Hz, –CFa*Fb*–)	 (IId)
3480, 1770	0.95 (3H × 1/2, d, J = 6.60 Hz, >CH(CH_3)), 1.01 (3H × 1/2, d, J = 6.60 Hz, >CH(CH_3)), 1.19 (3H, d, J = 7.08 Hz, >CHCH_3), 1.24 (6H, d, J = 6.84 Hz, –CH(CH_3)$_2$), 1.31 (3H, t, J = 7.00 Hz, –O–CH_2–CH_3), 2.18–2.24 (1H, m, –CH(O*H*)), 2.55–2.62 (1H, m, –ph–CH_2C*H*<), 2.76–2.91 (2H, m, –ph–CH_2–), 3.02–3.08 (1H, m, >C*H*–ph–), 4.05–4.13 (1H, m, >C*H*(OH)), 4.28 (2H, q, J = 7.00 Hz, –O–CH_2–CH_3), 7.09–7.17 (4H, m, –ph–)	–42.41 (1F, dd, J_{FaFb} = 262.46 Hz, J_{FaH} = 16.79 Hz, –C*Fa*Fb–), –38.89 (1F, dd, J_{FaFb} = 262.46 Hz, J_{FbH} = 9.15 Hz, –CFa*Fb*–), –44.68 (1F, dd, $J_{Fa'Fb'}$ = 265.51 Hz, $J_{Fa'H}$ = 18.31 Hz, –C*Fa'*Fb'), –35.29 (1F, dd, $J_{Fa'Fb'}$ = 265.51 Hz, $J_{Fb'H}$ = 7.63 Hz, –CFa'*Fb'*–)	 (IIe)
3380, 1745	1.26–1.34 (10H, m, –$(CH_2)_5(CH_2)_2CO$), 1.37 (3H, t, J = 7.08 Hz, –O–CH_2CH_3), 1.65–1.70 (2H, m, –CH_2CH_2C(OH)–), 2.02–2.06 (2H, m, –CH_2–CH=CH_2), 2.83 (1H, broad s, O*H*), 3.99–4.06 (1H, m, >C*H*–OH), 4.36 (2H, q, J = 7.03 Hz, –O–CH_2CH_3), 4.92 (1H, d, J = 10.01 Hz, –CH=CH_2), 5.00 (1H, d, J = 17.09 Hz, CH=CH_2), 5.78–5.86 (1H, m, –CH_2–C*H*=CH_2)	–47.19 (1F, dd, J_{FaFb} = 263.98 Hz, J_{FaH} = 13.73 Hz, –C*Fa*Fb–), –46.76 (1F, dd, J_{FaFb} = 263.98 Hz, J_{FbH} = 7.63 Hz, –CFa*Fb*–)	 (IIf)
3400, 1740, 1100	0.95 (3H, t, J = 4.0 Hz, CH_3), 1.3 (3H, t, J = 7.0 Hz, CH_3), 1.55 (4H, m, –CH_2–), 3.16 (1H, s, –O*H*), 3.8 (1H, m, –C(OH)*H*–), 4.3 (2H, q, J = 7.0 Hz, –CH_2–)	–123.605 (1F, dd, J_{FaFb} = 265.5 Hz, J_{FaH} = 13.73 Hz, *Fa*), –116.148 (1F, dd, J_{FaFb} = 265.5 Hz, J_{FbH} = 7.63 Hz, *Fb*)	 (IIg)

Table 4
Spectral data of α,α-difluoro-β-ketoesters

IR (cm^{-1})	^1H NMR (δ, ppm)	^{19}F NMR (δ, ppm)	Structure
1780, 1755	1.32 (3H, t, J=7.08 Hz, –O–CH_2–CH_3), 2.98 (2H, t, J=7.57 Hz, phCH_2–CH_2–), 3.08 (2H, t, J=7.5 Hz, phCH_2–CH_2–), 4.33 (2H, q, J=7.08 Hz, –O–CH_2CH_3), 7.20–7.30 (5H, m, –ph)	–38.57 (2F, s, $-CF_2-$)	(IIIb)
1780, 1700	0.89 (3H, t, J=7.08 Hz, $-C_4H_8CH_3$), 1.20–1.27 (6H, m, $-CH_2(CH_2)_3CH_3$), 1.35 (3H, t, J=6.98 Hz, $-OCH_2CH_3$), 1.45–1.53 (2H, m, $-CH_2(CH_2)_3CH_3$), 2.42–2.50 (1H, m, phCH=C<), 4.40 (2H, q, J=7.08 Hz, –O–CH_2CH_3), 7.40–7.46 (5H, m, –ph)	–29.89 (2F, s, $-CF_2-$)	(IIIc)
1800, 1735	1.36 (3H, t, J=7.08 Hz, –O–CH_2CH_3), 1.58, 1.62 (3H and 3H, each s, $-CH=C(CH_3)_2$), 1.70 (3H, s, $-C(CH_3)=CH-$), 2.00–2.31 (4H, m, $-CH_2-CH_2-$), 4.37 (2H, q, J=7.08 Hz, –O–CH_2CH_3), 5.03–5.08 (1H, m, $-CH=C(CH_3)_2-$), 6.38–6.39 (1H, m, >C=CH–CO–)	–38.51 (2F, s, $-CF_2-$)	(IIId)
1780, 1740	1.18 (3H, d, J=7.08 Hz, >CHCH_3), 1.23 (6H, d, J=7.30 Hz, $-CH(CH_3)_2$), 1.28 (3H, t, J=7.08 Hz, –O–CH_2CH_3), 2.83–2.90 (2H, m, –phCH_2–), 2.98–3.10 (2H, m, >CHph–, >CH–CO–), 4.25 (2H, q, J=7.08 Hz, –O–CH_2CH_3), 7.06–7.18 (4H, m, ph–)	–38.25 (2F, s, $-CF_2-$)	(IIIe)
1790, 1750	1.24–1.32 (10 H, m, $-(CH_2)_5-(CH_2)_2-CO-$), 1.36 (3H, t, J=7.08 Hz, –O–CH_2CH_3), 1.62–1.68 (2H, m, $-CH_2CH=CH_2$), 2.01–2.06 (2H, m, $-CH_2CH=CH_2$), 2.73 (2H, t, J=7.08 Hz, $-CH_2CH_2CO-$), 4.37 (2H, q, J=7.03 Hz, $-OCH_2CH_3$), 4.93 (1H, d, J=10.25 Hz, $-CH=CH_2$), 4.99 (1H, d, J=17.09 Hz, $-CH=CH_2$), 5.77–5.85 (1H, m, $-CH_2CH=CH_2$)	–38.52 (2F, s, $-CF_2-$)	(IIIf)

1.60 and 1.68 (3H and 3H, each s, $-CH=(CH_3)_2$), 1.95–2.17 (3H, m, $-CH_2CH_2CH-$), 2.75 (1H, broad s, –OH), 4.15–4.32 (1H, m, –CH–OH), 4.51 (2H, q, J=5.94 Hz, $-NH_2CH_2ph$), 5.09 (1H, t, J=7.08 Hz, $-CH=C(CH_3)_2$), 6.80 (1H, broad s, –NH), 7.25–7.39 (5H, m, ph). $[\alpha]_D^{20}$ (CH_3OH, c=1.03) –1.04°. Other amides were prepared in a similar manner, and the spectral data are shown in Table 5.



Using lipase PS in a similar manner, a mixture of **IIa** (32% yield) and **IVa** (23% yield) was obtained. In the case of Novozym 435, a mixture of **IIa** (45% yield) and **IVa** (23% yield) was obtained. The reactions of compound **IIa** and ethyl 2,2-difluoro-3-hydroxyhexanoate with benzylamine were studied using various enzymes, and the results are shown in Table 6. The optical purities were determined by the (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA) ester method. No good optical resolution results were obtained.

A mixture of compound **IIa** (1.00 g, 3.6 mmol), *n*-butylamine (0.132 g, 1.8 mmol), lipase PS (300 mg), molecular sieves 4A 1/8 (one piece) and 1,4-dioxan (30 ml) was stirred for 10 h at 40 °C under a nitrogen atmosphere. The mixture was treated as for **IVa** to give recovered compound **IIa** (0.39 g, yield 39%) ($[\alpha]_D^{20}$, CH_3OH, c=1.24, +11.0°) and *N*-*n*-butyl-2,2-difluoro-5,9-dimethyl-3-hydroxy-8-decenamide (0.208 g, yield 19%) ($[\alpha]_D^{20}$, CH_3OH, c=1.02, –1.08). The spectral data are shown in Table 5.

3.5. *N-Benzyl-2,2-difluoro-5,9-dimethyl-3-keto-8-decenamide (V)*

A mixture of ethyl 2,2-difluoro-5,9-dimethyl-3-keto-8-decenoate (**IIIa**) (0.276 g, 1.00 mmol), benzylamine (0.321 g, 3.00 mmol), zinc chloride (0.273 g, 2.0 mmol) and benzene (30 ml) was agitated for 10 h at room temperature under nitrogen. The reaction mixture was dissolved in diisopropyl ether (200 ml). The solution was washed with 3 N HCl, 3 N NaOH and water in this order, and dried over anhydrous sodium sulphate. The solvent was removed and the residue was chromatographed over a silica gel column with a mixture

Table 5
Spectral data of reaction products of α,α-difluoro-β-hydroxyesters with benzylamine and *n*-butylamine

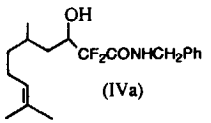
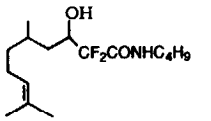
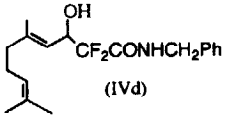
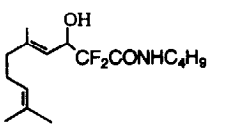
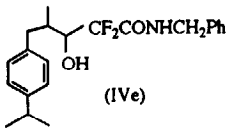
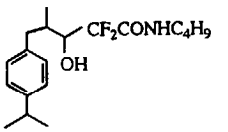
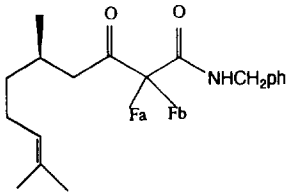
IR (cm^{-1})	^1H NMR (δ, ppm)	^{19}F NMR (δ, ppm)	Structure
See Section 3.4			 (IVa)
3330, 1680	0.93 (3H × 1/2, d, J = 6.59 Hz, >CHCH_3), 0.94 (3H, t, J = 7.31 Hz, –CH_2CH_3), 0.98 (3H × 1/2, d, J = 6.59 Hz, >CHCH_3), 1.20–1.29 (2H, m, –CH_2CH_2CH<), 1.35–1.43 (2H, m, –$CH_2CH_2CH_3$), 1.52–1.55 (2H, m, –$CH_2CH_2CH_3$), 1.60, 1.68 (3H and 3H, each s, –CH=C(CH_3)$_2$), 1.95–2.05 (3H, m, –CH_2CH_2CH<), 2.75 (1H, broad s, –OH), 3.34 (2H, q, J = 6.59 Hz, –NHCH_2–), 4.15–4.25 (1H, m, –CH(OH)–), 5.09 (1H, t, J = 6.69 Hz, –CH=C(CH_3)$_2$), 6.47 (1H, broad s, –NH–)	−45.66 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FaH} = 16.78 Hz, *Fa*), −45.558 (1F, dd, J_{FaFb} = 260.93 Hz, J_{FbH} = 15.26 Hz, *Fb*), −36.767 (1F, dd, $J_{Fa/Fb/}$ = 260.93 Hz, $J_{Fb/H}$ = 7.63 Hz, *Fa′*), −36.468 (1F, dd, $J_{Fa/Fb/}$ = 260.93 Hz, $J_{Fb/H}$ = 7.63 Hz, *Fb′*)	
3335, 1680	1.60, 1.68 (3H and 3H, each s, –CH=(CH_3)$_2$), 1.74 (3H × 1/2, s, –C(CH_3)=CH–), 1.80 (3H × 1/2, s, –C(CH_3)=CH–), 2.07–2.17 (5H, m, –CH_2CH_2–, –OH), 4.52 (2H, d, J = 5.61 Hz, –NH–CH_2–), 4.83–4.96 (1H, m, –CH(OH)–), 5.03–5.14 (1H, m, –CH=(CH_3)$_2$), 5.23–5.34 (1H, m, >C=CHCH(OH)–), 6.72 (1H, broad s, –NH), 7.27–7.35 (5H, m, –CH_2–ph)	cis form: −46.92 (1F, dd, $J_{Fa/Fb/}$ = 253.5 Hz, $J_{Fa/H}$ = 7.63 Hz, *Fa′*), −47.48 (1F, dd, $J_{Fa/Fb/}$ = 253.3 Hz, $J_{Fb/H}$ = 7.63 Hz, *Fb′*); trans form: −54.483 (1F, dd, J_{FaFb} = 257.88 Hz, J_{FaH} = 13.74 Hz, *Fa*), −54.853 (1F, dd, J_{FaFb} = 257.88 Hz, J_{FbH} = 13.74 Hz, *Fb*)	 (IVd)
3330, 1680	0.94 (3H, t, J = 7.25 Hz, –CH_2CH_3), 1.36–1.41 (2H, m, –$CH_2CH_2CH_3$), 1.53–1.57 (2H, m, –$CH_2CH_2CH_3$), 1.60, 1.68 (3H and 3H, each s, –CH=C(CH_3)$_2$), 1.74 (3H × 1/2, s, –C(CH_3)=CH–), 1.80 (3H × 1/2, s, –C(CH_3)=CH–), 2.08–2.18 (5H, m, –CH_2CH_2–, –OH), 3.30–3.37 (2H, m, –NH–CH_2), 4.79–4.94 (1H, m, –CH(OH)–), 5.03–5.14 (1H, m, –CH=(CH_3)$_2$), 5.23–5.34 (1H, m, >C=CHCH(OH)–), 6.45 (1H, broad s, –NH–)	cis form: −36.355 (1F, dd, $J_{Fa/Fb/}$ = 257.88 Hz, $J_{Fa/H}$ = 7.63 Hz, *Fa′*), −37.195 (1F, dd, $J_{Fa/Fb/}$ = 257.88 Hz, $J_{Fb/H}$ = 7.63 Hz, *Fb′*); trans form: −44.02 (1F, dd, J_{FaFb} = 248.63 Hz, J_{FaH} = 15.51 Hz, *Fa*), −44.575 (1F, J_{FaFb} = 248.63 Hz, J_{FbH} = 15.04 Hz, *Fb*)	
3340, 1700	0.98 (3H, d, J = 6.60 Hz, –CH_2CH(CH_3)–), 1.23, 1.26 (3H and 3H, each s, –CH=(CH_3)$_2$), 2.18–2.24 (1H, m, –CH(OH)), 2.53–2.65 (1H, m, –CH_2CH(CH_3)–), 2.73–2.93 (2H, m, –ph–CH_2–), 3.03–3.11 (1H, m, –CH(CH_3)$_2$), 4.05–4.18 (1H, m, –CH(OH)–), 4.51 (2H, t, J = 5.93 Hz, –NH–CH_2–), 6.70 (1H, broad s, –NH–), 7.06–7.18 (4H, m, –ph–), 7.27–7.38 (5H, m, –ph)	−34.26 (1F, dd, J_{FaFb} = 262.45 Hz, J_{FaH} = 7.63 Hz, *Fa*), −42.83 (1F, dd, J_{FaFb} = 262.46 Hz, J_{FbH} = 19.84 Hz, *Fb*), −31.26 (1F, dd, $J_{Fa/Fb/}$ = 263.98 Hz, $J_{Fa/H}$ = 7.63 Hz, *Fa′*), −43.69 (1F, dd, $J_{Fa/Fb/}$ = 263.98 Hz, $J_{Fb/H}$ = 18.31 Hz, *Fb′*)	 (IVe)
3330, 1680	0.91–1.01 (6H, m, –CH_2CH(CH_3)–, –CH_2CH_3), 1.22, 1.25 (3H and 3H, each s, –CH(CH_3)$_2$), 1.34–1.37 (2H, m, –CH_2CH_3), 1.53–1.56 (2H, m, –$CH_2CH_2CH_3$), 2.18–2.24 (1H, m, –CH(OH)–), 2.53–2.65 (1H, m, –CH_2CH(CH_3)–), 2.75–2.92 (2H, m, –ph–CH_2–), 3.02–3.12 (1H, m, –CH=(CH_3)$_2$), 3.25–3.37 (2H, m, –NHCH_2–), 4.03–4.12 (1H, m, –CH(OH)–), 6.45 (1H, broad s, –NH–), 7.06–7.18 (4H, m, –ph–)	−34.26 (1F, dd, J_{FaFb} = 262.45 Hz, J_{FaH} = 7.63 Hz, *Fa*), −42.54 (1F, dd, J_{FaFb} = 262.45 Hz, J_{FbH} = 19.83 Hz, *Fb*), −31.34 (1F, dd, $J_{Fa/Fb/}$ = 262.45 Hz, $J_{Fa/H}$ = 6.10 Hz, *Fa′*), −43.23 (1F, dd, $J_{Fa/Fb/}$ = 262.45 Hz, $J_{Fb/H}$ = 18.31 Hz, *Fb′*)	

Table 6
Reaction of α,α-difluoro-β-hydroxyesters with benzylamine. Optical purity of recovered esters

Hydroxyester	Enzyme	Recovered ester	
		$[\alpha]_D^{20}$ (c, MeOH)	Optical purity (% de)
Compound **IIa**	Lipase MY	+13.0 (1.24)	29
Compound **IIa**	Lipase PS	+11.8 (1.28)	26
Compound **IIa**	Novozym 435	+10.3 (1.28)	23
Compound **IIa**	Nothing	-	-
Ethyl 2,2-difluoro-3-hydroxy-hexanoate	Novozym 435	−6.27 (1.21)	27

of *n*-hexane and ethyl acetate (10 : 1, v/v) to give *N*-benzyl-2,2-difluoro-5,9-dimethyl-3-keto-8-decenamide (**V**) (0.285 g, yield 85%). It showed the following spectra data. IR (cm^{-1}): 3350, 1755, 1700. ^{19}F NMR (δ, ppm): −39.73 (2F, s, $-CF_2CONH$). ^1H NMR (δ, ppm): 0.93 (3H, d, $J = 6.59$ Hz, $-CHCH_3$), 1.25–1.34 (2H, m, $-CH_2CH_2CH-$), 1.59 and 1.68 (3H and 3H, each s, $-CH=C(CH_3)_2$), 1.90–2.18 (3H, m, $-CH_2CH_2CH-$), 2.56–2.78 (2H, m, $-CHCH_2CO$), 4.51 (2H, d, $J = 5.93$ Hz, $-CH_2$–ph), 5.08 (1H, t, $J = 1.32$ Hz, $-CH=C(CH_3)_2$), 6.70 (1H, broad s, –NH), 7.29–7.40 (5H, m, ph).



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References

[1] S. Watanabe, T. Fujita, M. Sakamoto, T. Mino and T. Kitazume, *J. Fluor. Chem., 73* (1995) 21.
[2] A.B. Smith III and P.A. Levenberg, *Synthesis* (1981) 567.
[3] A.J. Mancuso, D.S. Brownfain and D. Swern, *J. Org. Chem., 44* (1979) 4148.
[4] T.T. Curran, *J. Org. Chem., 58* (1993) 6360.
[5] Y. Shen and M. Qi, *J. Fluor. Chem., 67* (1994) 229.
[6] M.J. Garcia, F. Rebolledo and V. Gotor, *Tetrahedron Asymmetry, 4* (1993) 2199.