# Fluorination of Hydroxyesters with N,N-Diethyl-1,1,2,3,3,3-Hexafluoro Propaneamine

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**The reactions of N,N-diethyl-1,1,2,3,3,3-hexafluoro propaneamine (PPDA) with β-hydroxyl esters gave their corresponding fluorides. For example, methyl (S)-(+)-3-fluorobutyrate was obtained from the reaction of methyl (R)-(-)-3-hydroxybutyrate with PPDA. The reaction of α-hydroxy esters with PPDA gave a mixture of their corresponding fluorides and 2,3,3,3-tetrafluoropropionate esters. However, γ- and δ-hydroxyesters did not give their fluorinated compounds. Hydrolysis of those racemic monofluoroesters with Lipase MY gave optical active monofluorocarboxylic acids and esters.**

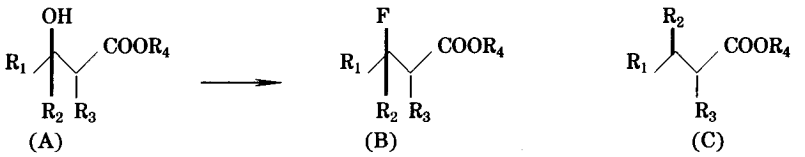
Fluorinated compounds have been widely utilized in biochemical and industrial investigations. Fluoroalkyl amino Reagent (FAR) and diethyl amino sulfur trifluoride (DAST) are useful fluorinating reagents for various alcohols. Recently, we reported that N,N-Diethyl-1,1,2,3,3,3-hexafluoro propaneamine (PPDA, *Ishikawa* reagent) is useful as a fluorinating reagent for fatty alcohols (1) and various diols (2). However, the reactions of various aliphatic hydroxyesters with PPDA have not been studied in detail. In this paper, the reactivity of hydroxyesters, chemical structures of the products and reaction conditions of the fluorination reaction were studied systematically. Hydrolysis of these mnofluoroesters with Lipase MY (*Candida cyclindracea*, Meito Sangyo Co. Ltd.) gave optical active monofluorocarboxylic acids.

## EXPERIMENTAL

The reaction products were analyzed by gas-liquid chromatography (GLC) on a Shimadzu Model GC-3BF Chromatograph using a 3 m × 3 mm column of 15% Silicone DC 200 on 60-80 mesh Celite 545. $^1$H NMR and $^{19}$F NMR spec-

**TABLE 1**

**Fluorination of β-Hydroxyesters with PPDA**




| Hydroxyesters(A) | | | | Reaction Time | (B) | (C) | $^{19}$F NMR of (B) | | |
|---|---|---|---|---|---|---|---|---|---|
| $R_1$ | $R_2$ | $R_3$ | $R_4$ | (hr) | Yield (%)*5 | Yield (%) | | | |
| $CH_3$ | H | H | Me*1 | 3 | 40*2 | 0 | +93.3(ddqd) | J(F-Hb)=48.0<br>J(F-$CH_3$(a))=24.0 | J(F-Hc)=22.5<br>J(F-Hd)=16.0 |
| $CH_3$ | H | H | Et | 3 | 38 | 0 | +90.3(ddqd) | J(FH)=42.3<br>J(F-$CH_3$)=20.7 | J(FH)=20.7<br>J(FH)=15.1 |
| $C_2H_5$ | H | H | Me*3 | 3 | 38*4 | 0 | +100.8(m) | | |
| $C_3H_7$ | H | H | Et | 3 | 50 | 3 | +101.3(m) | | |
| $C_4H_9$ | H | H | Et | 3 | 61 | 5 | +99.3(m) | | |
| $C_5H_{11}$ | H | H | Et | 3 | 81 | 10 | +98.7(m) | | |
| $C_7H_{15}$ | H | H | Et | 3 | 68 | 14 | +98.7(m) | | |
| $C_9H_{19}$ | H | H | Et | 3 | 56 | 17 | +98.5(m) | | |
| $C_{11}H_{23}$ | H | H | Et | 3 | 41 | 20 | +98.3(m) | | |
| $C_5H_{11}$ | H | $CH_3$ | Et | 3 | 35 | 38 | +102.3(m) | | |
| $C_7H_{15}$ | H | $CH_3$ | Et | 3 | 39 | 38 | +102.0(m) | | |
| $C_9H_{19}$ | H | $CH_3$ | Et | 3 | 43 | 58 | +101.0(m) | | |
| $C_{11}H_{23}$ | H | $CH_3$ | Et | 3 | 38 | 50 | +101.7(m) | | |
| $C_4H_9$ | $CH_3$ | H | Et | 10 | 63 | 0 | +68.5(qm) | J(FH)=16.9 | |
| $C_5H_{11}$ | $CH_3$ | H | Et | 10 | 66 | 0 | +75.3(qm) | J(FH)=16.5 | |
| $C_6H_{13}$ | $CH_3$ | H | Et | 10 | 74 | 0 | +75.1(qm) | J(FH)=16.2 | |
| $C_7H_{15}$ | $CH_3$ | H | Et | 10 | 65 | 0 | +69.7(qm) | J(FH)=16.0 | |

*1R(-)-form $[\alpha]_D^{18}$=-23.23
*2S(+)-form $[\alpha]_D^{18}$=+6.65
*3R(-)-form $[\alpha]_D^{18}$=-13.9
*4S(+)-form $[\alpha]_D^{18}$=+2.20
*5The yield was calculated as isolated yields.

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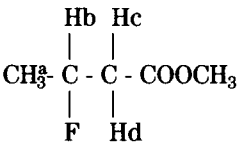
tra were obtained using $CDCl_3$ as a solvent on a Hitachi Model R-24 spectometer. The chemical shift values are expressed in $\delta$ value (ppm) relative to a TMS internal standard ($^1H$ NMR), and ppm values relative to an external $CF_3COOH$ ($^{19}F$ NMR, positive values upfield). IR spectra were obtained on a JASCO Model IR-G infrared spectrophotometer. Hydroxyesters were prepared by Reformatsky reaction or reduction of corresponding ketones.

*Fluorination of β-Hydroxyesters with PPDA.* As a typical method using fractional distillation, fluorination of methyl (R)-(-)-3-hydroxybutyrate (I) is shown in the following pages. A solution of PPDA (10.0 g, 44.8 mmol) in $CH_2CL_2$ (20 cc) was added dropwise into a solution of I (2.05 g, 17.4 mmol) ($[\alpha]_D^{28}$ = -23.23) in $CH_2CL_2$ (10 ml) at room temperature. The reaction mixture was treated as reported previously (1) to give 1.02 g of methyl (S)-(+)-3-fluorobutyrate (II) boiling at 71-79C at 200 mmHg. It showed the following properties: $[\alpha]_D^{28}$ = +6.65; IR ($cm^{-1}$): 1730; $^1H$ NMR ($\delta$, ppm): 1.37 (3H,dd,J ($CH_3$-F)=24.0 Hz, J($CH_3$-H)=6.75 Hz, $CH_3$(a)), 2.35 (1H,ddd,J(Hc-F)=22.5 Hz, J(Hc-Hd)=16.0 Hz, J(Hc-Hb)=6.0 Hz, Hc), 2.65(1H, ddd,J(Hd-F)=16.0 Hz, J(Hd-Hc)=16.0 Hz, J(Hd-Hb)=6.0 Hz, Hd), 3.40(3H, s, -COOC$\underline{H_3}$), 5.00 (1H, dq, J(Hb-F)=48.0 Hz, J(Hb-$CH_3$(a))=6.75 Hz, Hb); $^{19}F$ NMR




(II)

**TABLE 2**

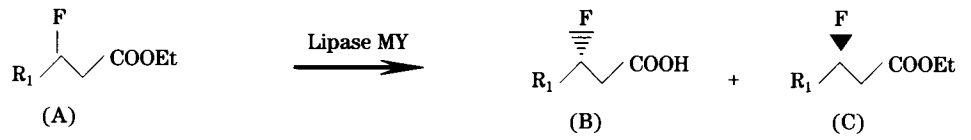
**Fluorination of α-Hydroxyesters and Other Hydroxyesters with PPDA**

| Hydroxyester | Product | Yield[a] (%) | $^{19}F$ NMR ($\delta$,ppm) $CF_3$ | CHF | J(Hz) | |
|---|---|---|---|---|---|---|
| α-Hydroxyesters | | | | | | |
| Ethyl 2-Hydroxybutyrate | Ethyl 2-(2,3,3,3-tetra-fluoropropyloxy)-butyrate | 31 | -1.67(dd) | +126.0(dq) | J(HF)=6.6<br>J(HF)=41.4 | J(FF)=10.5<br>J(FF)=10.5 |
| | Ethyl 2-Fluorobutyrate | 10 | | +125.7(dddq) | J(FH)=38.5<br>J(FH)=18.8 | J(FH)=19.7<br>J(FH)=9.4 |
| Ethyl 2-Hydroxypentanate | Ethyl 2-(2,3,3,3-tetra-fluoropropyloxy)-pentanate | 42.1 | -1.63(dd) | +126.(dq) | J(FH)=6.2<br>J(HF)=41.1 | J(FF)=10.2<br>J(FF)=10.1 |
| | Ethyl 2-Fluoropentanate | 13.4 | | +125.7(m) | | |
| Methyl 2-Hydroxy-4-methylpentanate | Methyl 2-(2,3,3,3-tetra-fluoropropyloxy)-pentanate | 43 | -1.65(dd) | +126.0(dq) | J(FH)=6.1<br>J(FH)=41.0 | J(FF)=10.0<br>J(FF)=10.3 |
| | Methyl 2-Fluoro-4-methylpentanate | 15 | | +126.0(m) | | |
| Ethyl 2-Hydroxy-octanoate | Ethyl 2-(2,3,3,3-tetra-fluoropropyloxy)-octanoate | 10 | -1.64(dd) | +126.0(dq) | J(FH)=6.4<br>J(FH)=41.1 | J(FF)=10.3<br>J(FF)=10.0 |
| | Ethyl 2-Fluorooctanoate | 3 | | +125.9(m) | | |
| Ethyl 2-Hydroxy-decanoate | Ethyl 2-(2,3,3,3-tetrafluoro-propyloxy)-decanoate | 3 | | | | |
| | Ethyl 2-Fluorodecanoate | 1 | | | | |
| Methyl 2-Hydroxy-palmitate | — | | | | | |
| Methyl 2-Hydroxy-stearate | — | | | | | |
| Other Type Hydroxyesters | | | | | | |
| Methyl (S)-(+)-3-Hydroxy-2-methylpropionate $[\alpha]_D^{15}$ =+26.8 | Methyl (S)-(+)-3-fluoro-2-methylpropionate $[\alpha]_D^{15}$ =+3.12 | 20 | | +141.2(td) | J(F-$CH_2$)=41.4<br>J(F-CH)=16.9 | |
| Methyl 4,4,4-Trichloro-3-hydroxybutyrate | Methyl 4,4,4-Trichloro-3-(2,3,3,3-terafluro-propionyl)-butyrate | 45 | -2.33(dd) | +123.7(dg) | J(FF)=12.4<br>J(FH)=39.5 | J(FH)=7.5<br>J(FF)=12.4 |
| Ethyl 4-Hydroxypentanate | — | | | | | |
| Ethyl 5-Hydroxyheptanate | — | | | | | |
| Ethyl 10-Hydroxyundecanoate | — | | | | | |
| Methyl 12-Hydroxystearate | — | | | | | |

[a]The yield was calculated as isolated yield.

**TABLE 3**

**Hydrolysis of β-Fluoroesters**




(A) (B) (C)

| Fluoroesters(A) R | Reaction Time hr | Conversion (%) | (B) $[\alpha]_D^{22}$(EtOH, c) | (C) |
|---|---|---|---|---|
| $C_5H_{11}$ | 2.0 | 37 | +4.54(1.08) | -1.21(1.00) |
| $C_5H_{11}$ | 2.5 | 44 | +3.90(1.00) | -2.36(1.02) |
| $C_5H_{11}$ | 3.0 | 48 | +2.42(1.02) | -2.44(1.04) |
| $C_7H_{15}$ | 2.0 | 34 | +3.78(1.02) | -2.00(1.00) |
| $C_7H_{15}$ | 3.0 | 45 | +2.54(1.04) | -3.04(1.00) |
| $C_7H_{15}$ | 4.0 | 50 | +2.65(1.00) | -3.13(1.04) |

(δ, ppm): +93.3, ddqd J(F-Hb)=48.0 Hz, J(F-Hc)=22.5 Hz, J(F-$CH_3$(a))=24.0 Hz, J(F-Hd)=16.0 Hz, -CHF-).

As a typical method using liquid chromatography, fluorination of ethyl 3-hydroxydecanoate is shown as follows. A solution of PPDA (4.5g, 20.0 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise into a solution of the hydroxyester (2.2 g,10 mmol) in $CH_2Cl_2$ (25 ml) at room temperature. The reaction mixture was treated in the same manner to give the residous oil. The crude product was chromatographed with silica gel using n-hexane (90 volume), containing ethyl acetate (10 volume), to give ethyl 3-fluorodecanoate (1.3 g, yield 58%) and ethyl 2-decenoate (0.37 g, yield 14%). Ethyl 3-fluorodecanoate showed the following spectral data: IR($cm^{-1}$): 1728; $^1H$ NMR (δ,ppm): 0.88 (3H,t, J=4.8 Hz, -$CH_2CH_3$), 1.21 (3H,t, J=7.0 Hz, -$OCH_2CH_3$), 1.2 - 1.6 [10H, m,-$(CH_2)_5$ -], 1.6 - 1.9 (2H,m,-$CH_2CHF$), 2.2 - 2.7 (2H,m,-$CH_2CO$), 4.04 (2H, q,J=7.0 Hz,-$OCH_2CH_3$), 4.1 - 5.4 [1H,m,-CHF);$^{19}F$ NMR (δ, ppm): +98.7 (m, -CHF-). Ethyl 2-decenoate was confirmed by comparing with its authentic sample.

Other hydroxyesters were treated with PPDA in the same manners, and the results are listed in Tables 1 and 2.

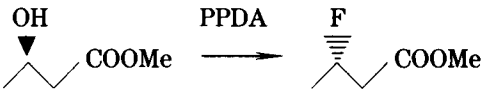
*Hydrolysis of Ethyl 3-Fluorodecanoate with Lipase MY.* Lipase MY (*Candida cyclindracea*, Meito Sangyo Co. Ltd.) (2.0g) was dispersed in a mixture of 1/15 Molar/l solution of sodium hydrogen phosphate (18 ml) and 1/15 Molar/l solution of potassium dihydrogen phosphate (7 ml). Ethyl 3-fluorodecanoate (1.4 g, 6.4 mmol) was added to this solution. The mixture was agitated for 4 hours at 38 C. After adding diluted hydrochloric acid to pH 3, the mixture was extracted with diisopropyl ether. The ether extract was washed with saturated sodium chloride solution several times, dried over anhydrous sodium sulfate, filtered and then evaporated to remove the solvent. The residue was chromatographed over a column of silica gel eluting with n-hexane which contained increasing amounts of ethyl acetate; each 10 ml fraction was collected. Elution with n-hexane/ethyl acetate (100:50 v/v) gave pure 3-fluorodecanoic acid (0.59 g, yield 42%), and elution with n-hexane/ethyl acetate (100:10 v/v) gave ethyl 3-fluoro decanoate (0.58 g, yield 41%). 3-Flourodecanoic acid showed the following data: IR($cm^{-1}$): 1708; $^1H$ NMR (δ, ppm): 0.87 (3H,t, J=5.0 Hz, $CH_3$-), 1.1-1.7 [10H,m,-$(CH_2)_5$-], 1.7-2.1 [2H,m,-$CH_2CHF$-), 2.4-3.0 [2H,m,-$CH_2CO$-), 4.3-5.5 [1H,m,-CHF), 11.54 (1H,s,-COOH); $^{19}F$ NMR (δ,ppm): +100.0 (m,-CHF-); $[\alpha]_D^{22}$ =+2.65 (c=1..00, EtOH). The angle of rotation of ethyl 3-fluorodecanoate was $[\alpha]_D^{22}$ =-3.13 (c=1.04, EtOH)).

Other 3-fluoroesters were treated with Lipase MY in the same way, and the results are listed in Table 3.

## RESULTS AND DISCUSSION

It is known that PPDA is a useful fluorination reagent for saturated primary alcohols (1) and various diols (2). However, the reactions of most secondary alcohols with PPDA give the corresponding fluoride, or 2,3,3,3-tetrafluoropropionate, in only low yields. Undesirable side reactions such as dehydration, isomerization and dimerization of alcohols are often present in higher yields. The present paper describes the reactions of a variety of types of aliphatic hydroxyesters with PPDA.

The reactions of β-hydroxyesters with PPDA gave their corresponding fluorides. For example, methyl (S)-(+)-3-fluoro-butyrate (II)($[\alpha]_D^{28}$ =+6.65) was obtained from the reaction of PPDA with methyl (R)-(-)-3-hydroxybutyrate (I) ($[\alpha]_D^{28}$ =-23.33). As is similar with aromatic hydroxyester containing a PhC(H)(OH)-group (3), it is suggested that fluorination of aliphatic hydoxyesters by PPDA involves an $S_N2$ reaction pathway. From other 3-hydroxyesters, corresponding fluorides were obtained as their main product. The reaction of α-alkyl-substituted-

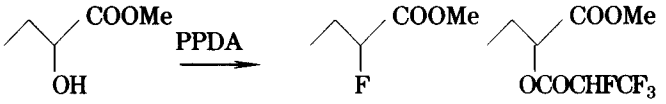



(I) (II)

β-hydroxyesters with PPDA gave mixtures of their corresponding fluorides and their dehydrofluorided esters as shown in Table 1. Fluorination of higher 3-hydroxyes-

ters such as 3-hydroxystearic acid did not give a fluorine compound.

From the reactions of lower $\alpha$-hydroxyesters with PPDA a mixture of fluoride and tetrafluoropropinate ester was obtained. For example, a mixture of methyl 2-fluorobutyrate (IV) and methyl 2-(2,3,3,3-tetrafluoropropionyloxy)-butyrate (V) was obtained from the reaction of PPDA with methyl $\alpha$-hydroxybutyrate (III). From the reaction of higher $\alpha$-hydroxyesters such as methyl $\alpha$-hydroxypalmitate, their corresponding fluorides or tetrafluoropropionyl esters were not obtained.




(III) (IV) (V)

From the reaction of $\gamma$-hydroxyesters such as ethyl 4-hydroxy-pentanoate with PPDA, fluoride or tetrafluoropropionate were not obtained. The reaction of ethyl 10-hydroxyundecanoate with PPDA gave a dehydration product. These results are listed in Table 2. As reported previously (4), $\omega$-hydroxyesters can be fluorinated.

The hydrolysis of monofluoroesters with enzyme (lipase MY) was examined. The use of an excess of water at 38-40C as a solvent was the best condition for the preparation of the monofluorocarboxylic acid. Interestingly, we have found that racemic 3-fluoresters can be optically separated into (+)-acid and (-)-esters. For example, 3-fluorodecanoic acid ($[\alpha]_D^{22}$ =+2.65) and ethyl 3-fluorodecanoate ($[\alpha]_D^{22}$ =-3.13) were obtained from racemic ethyl 3-fluorodecanoate by the action of enzyme (lipase MY). These results are shown in Table 3.

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