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# THE SYNTHESIS OF OPTICALLY ACTIVE BUILDING BLOCKS CARRYING A MONOFLUOROMETHYL GROUP

Tomoya KITAZUME*, Masatomo ASAI, Jenq Tain LIN
and Takashi YAMAZAKI

Department of Bioengineering, Tokyo Institute of Technology,
Meguro-ku, Ookayama, Tokyo 152 (Japan)

## SUMMARY

Studies on synthetic tools for optically active molecules with monofluoromethyl groups prepared by the microbial hydrolysis of the corresponding acetates have been undertaken. The absolute configuration of these monofluoromethylated chiral compounds is determined.

## INTRODUCTION

The control of absolute stereochemistry of molecules in fluorine chemistry is of fundamental importance for molecular design concerned with optimizing their biological activities [1-5]. Recently, we have reported examples of stereocontrolled synthesis of fluorinated compounds with known absolute configuration.

In our continuing study of stereocontrolled synthetic tools for fluorinated molecules, we now describe a synthetic approach to optically active molecules possessing the monofluoromethylated group, and determination of their absolute configuration.

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## RESULTS AND DISCUSSION

### Preparation of monofluoromethyl alkyl (or aryl) ketones (1)

We found a practical synthetic route to these compounds, which was the reaction of a Grignard reagent with ethyl monofluoroacetate.

$$CH_2FCO_2Et + RMgX \longrightarrow CH_2FC(O)R \quad (1)$$

This method is a simple process involving the dropwise addition of ethyl monofluoroacetate to a solution of the Grignard reagent in diethyl ether as solvent below -50°C. Details are given for the preparation of (1a) and the products are described in Table 1.

TABLE 1

Physical properties of $CH_2FC(O)R$

| Compound No | R | Yield (%) | Bp (°C/mmHg) | Analysis: Found (Calcd) C | H |
|---|---|---|---|---|---|
| (1a) (nc) | Ph | 63 | 108-110/18 | 69.71 (69.56) | 5.04 (5.11) |
| (1b) (nc) | $PhCH_2$ | 60 | 83-86/5 | 71.35 (71.04) | 6.10 (5.96) |
| (1c) (nc) | $PhCH_2CH_2$ | 43 | 112-116/10 | 77.04 (76.90) | 6.87 (7.10) |
| (1d) (nc) | $CH_3(CH_2)_5$ | 57 | 59-60/23 | 65.94 (65.72) | 10.56 (10.34) |

Reduction of monofluoromethyl alkyl (or aryl) ketones

When the reduction of the title materials with lithium aluminium hydride take place, the corresponding carbinols are not obtained because fluorine was released preferentially from the starting materials. In order to obtain carbinols possessing the monofluoromethyl group, sodium borohydride is a suitable reductive reagent (Table 2).

$$\underset{(1)}{CH_2FC(O)R} \xrightarrow[EtOH]{NaBH_4} \underset{(2)}{CH_2FCH(OH)R}$$

TABLE 2

Physical properties of $CH_2FCH(OH)R$

| Compound No | R | Yield (%) | Bp (°C/mmHg) | Analysis: Found (Calcd) C | H |
|---|---|---|---|---|---|
| (2a) (nc) | Ph | 84 | 103/12 | 68.82 | 6.59 |
| | | | | (68.56) | (6.47) |
| (2b) (nc) | $PhCH_2$ | 76 | 86-88/4 | 69.95 | 7.35 |
| | | | | (70.11) | (7.19) |
| (2c) (nc) | $PhCH_2CH_2$ | 92 | a | 76.04 | 8.04 |
| | | | | (75.92) | (8.28) |
| (2d) (nc) | $CH_3(CH_2)_5$ | 83 | a | 64.76 | 11.85 |
| | | | | (64.83) | (11.56) |

[a] The product was purified by column chromatography on silica gel.

## Asymmetric hydrolysis of 1-substituted 2-fluoroethylacetates

Asymmetric hydrolysis of prochiral compounds with enzymes of microbial or animal origin has been extensively studied up to now [6-11]. However, no practical microbial hydrolysis of monofluoromethylated compounds to give chiral building blocks has been reported. To establish practical routes to monofluoromethylated chiral synthetic tools, asymmetric hydrolysis of 1-phenyl-2-fluoroethylacetate (3a), with a variety of lipases or pig liver esterase as shown in Table 3, was examined.

$$\underset{(2)}{CH_2FCH(OH)R} \xrightarrow{AcCl} \underset{(3)}{CH_2FCH(OAc)R}$$

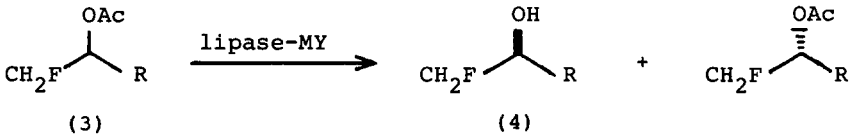
TABLE 3

Asymmetric hydrolysis of compound (3a)

| Origin of enzyme | Hydrolysis ratio (%) | Time (h) | $[\alpha]_D$/MeOH | Optical purity %ee[d] |
|---|---|---|---|---|
| lipase-My[a] | 34 | 1.5 | +20.7(c 0.94) | 26 |
| lipase-My[b] | 33 | 4.5 | +17.4(c 1.11) | 22 |
| P.L.E.[c] | 40 | 5.9 | 0 | 0 |

[a] *Candida cylindracea* (Meuto Sangyo Co. Ltd.) : Method ; lipase-MY(10 g)/substrate(20 mmol). [b] Method ; lipase-MY (5 g)/substrate(20 mmol). [c] pig liver esterase (Sigma Co. Ltd.) : Method ; P.L.E.(90 µl)/substrate(15 mmol).
[d] The optical purities were determined by $^{19}F$ NMR after conversion of the alcohol to its diastereomeric ester by optically active (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride.

The results shown in Table 3 suggest that the lipase-MY (*Candida cylindracea* ) is adequate for the optical resolution of title materials. Therefore, the next step was the optical resolution of title materials with lipase-MY.




(3) (4)

The results shown in Table 4 clearly demonstrate that optical resolution by asymmetric hydrolysis is a practical method for the synthesis of monofluoromethylated chiral materials.

TABLE 4

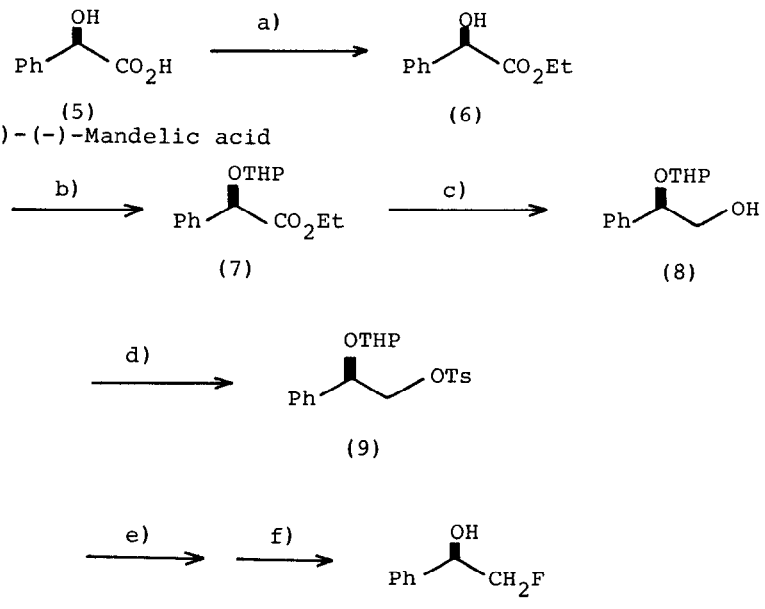
Asymmetric hydrolysis of $CH_2FCH(OAc)R$ (3) with lipase-MY

| Compound No | R | Hydrolysis[a] ratio (%) | Time (h) | $[\alpha]_D$/MeOH | Optical[b] purity %ee |
|---|---|---|---|---|---|
| (3a) | Ph | 34 | 1.5 | +20.7 (c 0.94) | 26 |
| (3b) | $PhCH_2$ | 50 | 2.0 | +3.91 (c 1.03) | 16 |
| (3c) | $PhCH_2CH_2$ | 34 | 2.5 | +22.1 (c 1.85) | 81 |
| (3d) | $CH_3(CH_2)_5$ | 34 | 2.5 | +3.67 (c 1.08) | 24 |

[a] The hydrolysis ratio was determined by $^{19}F$ NMR signal intensities. [b] The optical purities were determined by $^{19}F$ NMR after conversion of the alcohols to their diastereomeric esters by optically active (R)-α-methoxy-α-trifluoromethylphenylacetic acid chloride.

## Determination of absolute configuration

Our continuing studies on the chiral fluorinated materials developed by microorganisms have shown their synthetic potential. To apply this methodology, we first investigated the absolute configuration of an optically active carbinol possessing the monofluoromethyl group. To achieve the desired structure to determine the absolute configuration, a brief outline of the conversions operated defining the synthetic strategies employed is shown in Scheme I.




(R)-(-)-(10) : 85 %ee

$[\alpha]_D$/MeOH -67.3 (c o.94)

a) EtOH/$H^+$ b) dihydropyran/$CH_2Cl_2$ c) $LiAlH_4/Et_2O$ d) TsCl/pyridine e) CsF/triethyleneglycol f) $H^+$

Scheme I

TABLE V

$^{1}H$ and $^{19}F$ NMR spectral data

| Compound No | $^{19}F$ NMR | $^{1}H$ NMR |
|---|---|---|
| (1a) | 150(t)<br>$J_{F-CH_2}$ = 41 Hz | 5.3($CH_2$, d), 7.2-8.0(Ar-H) |
| (1b) | 145(t.t)<br>$J_{F-CH_2}$ = 45 Hz<br>$J_{F-COCH_2}$ = 2.8 Hz | 3.7($COCH_2$, d), 4.6($CH_2F$, d), 7.2(Ar-H) |
| (1c) | 133(t)<br>$J_{F-CH_2}$ = 45 Hz | 2.67(4xH, m), 4.53($CH_2F$, d), 7.1(Ar-H) |
| (1d) | 146(t.t)<br>$J_{F-CH_2}$ = 46 Hz<br>$J_{F-COCH_2}$ = 2.8 Hz | 0.72-1.75(11xH, m), 2.53(CH, $J_{CH_2-CH_2}$ = 6.8 Hz), 4.63($CH_2F$, d) |
| (2a) | 138(d.t)<br>$J_{F-CH_2}$ = 45 Hz<br>$J_{F-CH}$ = 15 Hz | 3.2(1H, br), 4.2($CH_AF$, d.d.d : $J_{H_A-H_B}$ = 9, $J_{H_A-CH}$ = 6.8 Hz) 4.3($H_B$, d.d.d: $J_{H_B-CH}$ = 3.7 Hz), 4.9(CH, d.d.d), 7.3(Ar-H) |
| (2b) | 147(t.d)<br>$J_{F-CH_2}$ = 41 Hz<br>$J_{F-CH}$ = 17 Hz | 2.6(OH, br), 2.7($CH_2$, d : $J_{CH_2-CH}$ = 6.5 Hz), 3.6-4.1(CH , m), 4.1($CH_A$, d.d.d : $J_{H_A-CH}$ = 5.4 Hz), 7.2(Ar-H) |
| (2c) | 145(t.d)<br>$J_{F-CH_2}$ = 45 Hz<br>$J_{F-CH}$ = 18 Hz | 1.67(2xH, m), 2.67(3xH, m), 3.67(CH, m), 4.20($CH_2F$, d.d) , 6.9(Ar-H) |
| (2d) | 145(d.t)<br>$J_{F-CH_2}$ = 46 Hz<br>$J_{F-CH}$ = 17 Hz | 0.67-1.67(13xH), 3.23(OH, br), 3.67(CH, m), 4.27($CH_2F$, d.d) |

In the Scheme I, the starting point is optically active (R)-(-)-mandelic acid. The protected (R)-ester (7) was selectively reduced with lithium alminium hydride to give good yield of the optically pure compound (8), which was reacted with tosyl chloride to give the tosylate (9). This was treated with cesium fluoride in triethyleneglycol for 5h at 110°C, and then the reaction mixture was hydrolysed with HCl. (R)-(-)-1-phenyl-2-fluoroethanol (10) with the desired absolute configuration, was obtained in the above system.

The present results offer a possibility for the microbial transformation of ethyl fluoroacetate to versatile chiral building blocks possessing the monofluoromethyl group.

## EXPERIMENTAL

### Fluoromethyl phenyl ketone (1a)(nc)

Into a mixture solution of ethyl fluoroacetate (10.6 g, 100 mmol) and freshly dried diethyl ether (100 ml), phenyl magnesium bromide (150 mmol) was added dropwise at a temperature below -78°C. After a further 7h of stirring below -60°C, the reaction mixture was quenched with saturated $NH_4Cl$. The oily material was extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave fluoromethyl phenyl ketone in a yield of 63 %, bp 108-110°C/18 mmHg.

### 1-Phenyl-2-fluoroethanol (2a)

Into a solution of sodium borohydride (25 mmol) and ethanol (50 ml), fluoromethyl phenyl ketone (1a)(2.76 g, 20 mmol) was added dropwise at room temperature. After 4h of stirring, the reaction mixture was quenched with saturated $NH_4Cl$. The oily layer material was extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave 1-phenyl-2-fluoroethanol in a yield of 84 %, bp 103°C/12 mmHg.

## Preparation of acetate esters

A mixture of 1-fluoro-3-phenyl-2-propanol (2b)(3.6 g, 23 mmol), acetyl chloride (28 mmol) and pyridine (4 ml) in dichloromethane (50 ml) was stirred at room temperature. After 8h of stirring, the mixture was quenched with 1N HCl. Oily materials were extracted with diethyl ether, and then the organic layer was washed with 5% aqueous $NaHCO_3$, water and brine. On removal of the solvent, acetate was purified by column chromatography on silica gel using n-hexane-ethyl acetate (2:1) as eluent, in 82% yield.

$^{19}F$ NMR ($CDCl_3$ from ext. $CF_3CO_2H$): $\delta$ 150(t.d, $J_{F-CH_a}$ = 44 Hz, $J_{F-CH}$ = 21.4 Hz) ppm.

$^1H$ NMR ($CDCl_3$): $\delta$ 2.0($CH_3$, s), 3.0($CH_2$, d, $J_{CH_2-CH}$ = 6.8 Hz), 4.3($CH_aH_bF$, d.d.d, $J_{H_a-H_b}$ =9.3 Hz, $J_{H_a-CH}$ = 3.7 Hz), 4.4($CH_b$, d.d.d, $J_{H_b-CH}$ = 3.1 Hz), 5.1(CH, t.d.d.d, $J_{CH-CH_2}$ = 6.4 Hz), 7.3(Ar-H).

Other acetate esters were prepared in the same manner.

## Asymmetric hydrolysis

A suspension of lipase-MY (*Candida cylindracea* , Meito Sangyo Co. Ltd., 5 g) in distilled water (75 ml), was stirred for 15 min at 40-41 °C in the round bottom flask (200 ml). Into the mixture, the acetate ester of 1-phenyl-2-fluoroethanol (10 mmol) was added, and then the whole mixture was stirred at 40-41 °C. After 1.5h of stirring, the flocculant (200 ppm solution prepared fromp-713, Dai-ichi Kogyo Seiyaku, 10 ml) was added into the stirred mixture for a few minutes. After 1h of stirring, the mixture was acidified with 1N HCl and then the precipitates were separated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent was removed. After determining the hydrolysis ratio by $^{19}F$ NMR signal intensities using $C_6H_5CF_3$ as an internal standard, the products were separated by column chromatography using the mixture of n-hexane-diethyl ether (5:1) as eluent.

Other asymmetric hydrolysis of acetate derivatives were carried out the same scale and manner.

## Determination of optical purity

A mixture solution of (R)- -methoxy- -trifluoromethyl-phenylacetic acid chloride (MTPA-Cl)(1.1 mmol), (+)-1-phenyl-2-fluoroethanol (1 mmol) in pyridine (1 ml) was stirred at room temperature. After 24h of stirring, the whole mixture was poured into water, and then oily materials were extracted with diethyl ether. The ethereal layer was washed with 1N HCl, 5% $NaHSO_4$, sat. $Na_2S_2O_3$ solution and then brine. Removal of the solvent, the diastereomeric ratio was determined by $^{19}F$ NMR signal intensities

## Synthesis of (R)-(-)-1-Phenyl-2-fluoroethanol

### (R)-(-)-Ethyl mandelate (6)

A mixture of (R)-(-)-mandelic acid (5.1 g, 33.8 mmol), ethanol (20 ml) and p-toluenesulfonic acid (50 mg) in benzene (100 ml) was azeotropped for 19h, and then the mixture was washed with 5% aqueous $NaHCO_3$, water and brine. On removal of the solvent, distillation gave (R)-(-)-ethyl mandelate in 91 % yield: bp 101-103°C/2 mmHg [lit.[12] 103-105°C/2 mmHg]. $[\alpha]_D/CHCl_3$ -116 [lit.[13] -136 in $CHCl_3$]. >85 %ee.

### Preparation of compound (7)

A mixture of (R)-(-)-ethyl mandelate (1.7 g, 10 mmol), dihydropyran (31 mmol), p-toluenesulfonic acid (50 mg) in dichloromethane (25 ml) was stirred at room temperature. After 3 days of stirring, a mixture was washed with 5% aqueous $NaHCO_3$, water and brine. On removal of the solvent, distillation gave compound (7)(1.9 g) in a yield of 74 %: bp 105-107°C/2 mmHg.
$^1H$ NMR ($CDCl_3$): $\delta$ 1.20($CH_3$, t, $J_{CH_3-CH_2}$ = 7.5 Hz), 1.33-2.10(m, 6xH), 3.20-3.60(m, 4xH), 3.83(m, 1xH), 4.17(q, $CH_2$), 5.0(m, 1xH), 7.30(Ar-H).
IR ($cm^{-1}$): 1725 (C=O).

Reduction of (7) with lithium aluminium hydride

Into the reaction vessel placed lithium aluminium hydride (0.92 g, 25 mmol), freshly dried diethyl ether (100 ml) was added with a syringe under atmosphere of argon, and then the compound (7) (6.2 g, 24 mmol) was added at room temperature. After adding the reagent, the mixture was refluxed for 3h, and then the mixture was quenched with sat. $Na_2SO_4$ solution. Oily materials were extracted with diethyl ether, and then worked up as usual. The product was purified by column chromatography on silica gel using n-hexane-ethyl acetate (10:1) as eluent, in 65 % yield.
IR ($cm^{-1}$): 3405 (OH).

Tosylate (9) of compound (8)

A mixture of compound (8)(2.67 g, 12 mmol), tosyl chloride (2.76 g, 14 mmol), triethylamine (2.2 g) in dichloromethane (40 ml) was stirred at room temperature. After 1 day of stirring, the mixture was washed with water, and then the organic layer was dried over anhydrous magnesium sulfate. Tosylate was purified by column chromatography on silica gel using n-hexane-diethyl ether (5:1) as eluent, in 91 % yield.
$^1H$ NMR ($CDCl_3$): $\delta$ 1.40-2.10(m, 6xH), 2.43($CH_3$, s), 3.10-3.53(m, 4xH), 3.73-4.10(m, 6xH), 4.90(m, 1xH), 7.3(Ar-H).

(R)-(-)-1-Phenyl-2-fluoroethanol (10)

To a solution of cesium fluoride (1.82 g, 12 mmol) and triethyleneglycol (5 ml) heated at 110°C, (R)-tosylate (9)(10 mmol) was added, and then the mixture was heated at that temperature. After 5h of heating, the reaction mixture was acidified with conc. HCl, and then the whole was stirred for 5h. Oily materials were extracted with diethyl ether. The products were separated by column chromatography on silica gel using n-hexane-ethyl acetate (3:1) as eluent, in 24 % yield.
$[\alpha]_D$/MeOH -67.3 (c 0.94) >85 %ee.
Analysis : Found: C, 68.35 ; H, 6.53 %.
Calcd for $C_8H_9OF$: C, 68.56 ; H, 6.47 %.

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