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Stereo- and Regiocontrolled Synthesis of Fluorohydrins from Optically Active Epoxides

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Abstract: The hydrofluorination of optically active terminal epoxides, which were produced by a microbial reaction, with HF-amine reagents were studied. 1,2-Epoxyoctane and glycidyl hexyl ether gave the corresponding 2-fluoro-1-alkanol derivatives with inversion of the asymmetric center with high stereospecificity, while in the hydrofluorination of pentafluorostyrene oxide and 2-methyl-1,2-epoxyhexane, partial racemization occurred. The basicity of the amine used, the HF/amine ratio in the HF-amine reagent, and the substituent on the epoxide affected the stereospecificity and regioselectivity of the hydrofluorination of the epoxides.

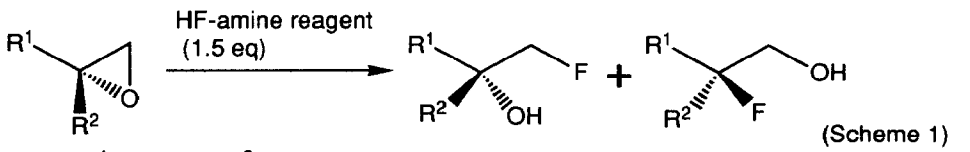
Introduction

The regioselective synthesis of fluorohydrins from various epoxides has been extensively investigated because of their increasing importance of the compounds in the synthesis of biologically active molecules such as steroids,[1] amino acids,[2] and carbohydrates,[3] and in the synthesis of ferroelectric liquid crystals.[4] Hydrogen fluorides modified with Lewis acids or bases have been applied in the ring-opening of various epoxides,[5] and some modified hydrogen fluorides have been shown to give fluorohydrins reigioselectively. Recently, one of the authors found that ferroelectric liquid crystals having optically active 2-fluoro-1-alkanols as chiral synthons showed interesting mesomorphic and physical properties.[4] The study concerning the stereochemistry of such chiral synthons is very important in order to clarify the relationship between the chemical structure and the properties of the new materials. However, there is no detailed systematic study on the stereochemistry of fluorohydrins obtained by the reaction of optically active terminal epoxides with modified hydrogen fluorides, although several reaction mechanisms have been proposed for the ring-opening of racemic terminal epoxides.[6~8]

In this paper, we report on the hydrofluorination of optically active terminal epoxides with hydrogen fluoride modified with amines (HF-amine reagents), and discuss the factors influencing the stereospecificity and regioselectivity of the hydrofluorination reaction, such as the basicity of the amines and the molar ratio of HF/amine in the HF-amine reagents, and the structure of the epoxides.

Results and Discussion

The optically active epoxides used in the present study were prepared by the microbial oxidation of the correponding olefins as previously reported; four types of epoxides **1a~d** had optical purities greater than 90%ee.[9~11] HF-amine reagents were prepared by adding an appropriate quantity of anhydrous hydrogen fluoride to amines. Hydrofluorination was simply performed by adding the epoxide into 1.5 equivalents of the HF-amine reagent (Scheme 1). A preliminary experiment showed that the regioselectivity of the hydrofluorination of **1a** did not change by the amount of the HF-amine reagent and also that a large excess of the HF-amine reagent increased oligomeric by-products. The reaction was quenched with ice-water after the complete consumption of the epoxide had been confirmed by GLC. Relatively high temperature and long reaction times were required in order to complete the reaction when the HF/amine ratio (n) was low (2~4), while the reaction was exothermic and cooling by an ice-water bath was required at high n values. The yield and the molar ratio of the resultant regioisomers, **2** and **3**, were calculated on the basis of the amount of the extract and the area ratio by gas chromatography. The results are listed in Table 1.



1a : R^1=n-C_6H_{13}, R^2=H
1b : R^1=n-$C_6H_{13}OCH_2$, R^2=H
1c : R^1=n-C_4H_9, R^2=CH_3
1d : R^1=C_6F_5, R^2=H

2a -d **3a -d**

(Scheme 1)

The reaction of **1a** with 4HF-diisopropylamine (Entry 3) gave **3a** without racemization, in agreement with the previous result for the reaction with 9HF-pyridine in diethyl ether.[4] The absolute configuration and optical purity of the resultant **3a** indicate that the attack of fluoride anion occurs from the back side of the asymmetric carbon with the inversion of the asymmetric center. The reaction of **1b** with 9HF-pyridine also gave **3b** without racemization (Entry 18); the result is consistent with that for **1a** and indicates that the attack of fluoride anion occurs in a similar manner. However, the optical purity decreased in the hydrofluorination of **1c** (Entry 20) and **1d** (Entries 22~24). This means that a racemization process exists in the hydrofluorination of these two epoxides. Moreover, the degree of racemization depended on the amine component in HF-amine reagents and the HF/amine ratio.

Several reaction mechanisms have been proposed for the hydrofluorination of racemic epoxides. Olah and Meidar[7] reported that the electronic character of the substituent of an epoxide influenced the regioselectivity and stereoselectivity in the hydrofluorination with polyHF-pyridine; 2-fluoro-2-phenylethanol was produced from styrene oxide in an S_N1 fashion via a secondary β-hydroxy carbenium ion, a highly stabilized benzylic cation, while in the case of 3,3,3-trichloro-1,2-epoxypropane an S_N2 reaction provided 1,1,1-trichloro-3-fluoro-2-propanol. They also suggested the competition of both mechanisms in the hydrofluorination of epihalohydrins. Muelbacher and Poulter[8] emphasized a

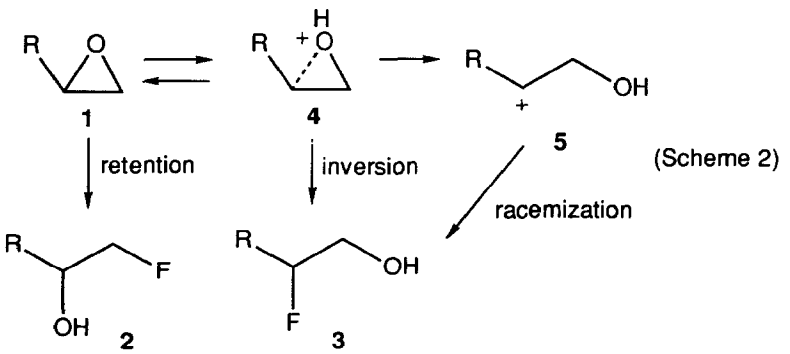
Table 1. Hydrofluorination of optically active epoxides

Entry	Epoxide	Amine	HF/amine (mol/mol)	Temp. (°C)	Time (h)	Yield [a] of 2 and 3 (%)	2 : 3 [b]	Absolute Config. [c] (optical purity)
1	**R-1a** (91%ee)	i-Pr_2NH	2	110	8	52	66:34	R-**2a** (94%ee) [d]
2			3	60	1.5	49	40:60	
3			4	rt	1	56	19:81	S-**3a** (92%ee) [e]
4			5	0	1	45	13:87	
5		n-Bu_3N	2	110	8	45	66:34	
6			3	100	7	49	59:41	
7			4	60	2.5	50	39:61	
8			5	rt	1.5	38	25:75	
9		Pyridine	2	110	5	2	46:54	
10			3	60	1.5	19	35:65	
11			4	rt	2	40	23:77	
12			5	0	1.5	37	17:83	
13			9 [f]	0	1.5	37	13:87	S-**3a** (92%ee)
14		Melamine	2	40	1	g)	30:70	
15			4	rt	1	14	25:75	
16	**R-1b** (90%ee)	i-Pr_2NH	2	110	2	52	80:20	
17			4	40	1.5	32	59:41	
18		Pyridine	9	rt	1.5	47	50:50	R-**2b** (87%ee) [h] R-**3b** (86%ee) [i]
19	**R-1c** (90%ee)	i-Pr_2NH	2	110	1	24	19:81	S-**3c** (85%ee)
20			4	rt	1	61	0:100	S-**3c** (71%ee) [j]
21		Pyridine	9	0	1	0	k)	
22	**R-1d** (97%ee)	i-Pr_2NH	3	60	17	49	0:100	S-**3d** (56%ee)
23			4	rt	69	50	0:100	S-**3d** (61%ee) [l]
24		Pyridine	9	0	1	52	0:100	S-**3d** (21%ee)

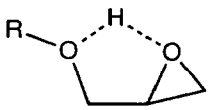
a) Calculated on the basis of the amount of the extract and the purity of these isomers determined by GLC (3 % SE-30 on Chromosorb WAW DMCS, 2 m). b) Determined by GLC (15 % DEGS on Uniport B, 2 m). c) Determined by GLC or ^{19}F-NMR analysis of their MTPA esters. d) $[\alpha]_D^{25}$ +13.8 (c 2.0, Et_2O). e) $[\alpha]_D^{25}$ -13.6 (c 2.0, Et_2O). See ref 4. f) The reaction was carried out in diethyl ether. g) Could not determined since the reaction mixture contained residual epoxide. h) $[\alpha]_D^{25}$ -7.7 (neat). i) $[\alpha]_D^{25}$ -1.8 (neat). j) $[\alpha]_D^{25}$ -0.7 (c 2.6, $CHCl_3$). k) Only oligomeric products were obtained. l) $[\alpha]_D^{25}$ +12.0 (c 0.3, $CHCl_3$).

steric effect as a major factor in determining the regioselectivity for the ring-opening of benzyl ether derivatives of simple aliphatic epoxy alcohols with 3HF-diisopropylamine.

Partial racemization observed in the formation of **3c** and **3d** in the present study indicates that the reaction partially proceeds through stabilized carbenium ions **5**, a tertialy carbenium ion and a benzylic cation, as was suggested by Olah and Meidar.[7] However, the incomplete racemization implies the participation of another reaction route; the asymmetric carbon of protonated epoxide **4** is attacked from the back side by fluoride anion in an S_N2 fashion. High n value and low basicity of the amine in an HF-amine reagent resulted in the decrease of the optical purities of **3c** and **3d**, indicating the increase of the contribution of the reaction via **5**. It is said that HF-amine reagents are in equilibrium with a small amount of free hydrogen fluoride.[12] Free proton derived from such a hydrogen fluoride would protonate on the epoxide oxygen. The concentration of free hydrogen fluoride would increase with lowering the basicity of the amine in a HF-amine reagent (i-Pr_2NH > n-Bu_3N >> pyridine > melamine[13]) and with increasing the HF/amine ratio n to give carbenium ion **5** with higher probability. Oligomerization observed in the reaction of **1c** with 9HF-pyridine (Entry 21) is also supposed to be caused by the formation of carbenium ion **5c**. In contrast, the hydrofluorination of **1a** and **1b** gave 2-fluoro-1-alkanol derivatives with high stereospecificity; this result indicates that the contribution of a carbenium ion intermediate is negligible in these cases as was suggested by Suga et al.[6]



Although the regioselectivity was almost complete in the hydrofluorination of **1c** and **1d**, the basicity of the amine and HF/amine ratio (n) in HF-amine reagents also affected the regioselectivity of the hydrofluorination of **1a** and **1b**. When the concentration of free hydrogen fluoride is low, fluoride anion tends to react with free epoxide **1** and favorably attacks at the less hindered epoxy carbon through an S_N2 fashion to give **2**. Meanwhile, once the epoxide is protonated by free proton, fluoride anion readily attacks at the more substituted epoxy carbon with low electron density, resulting in the increase of the ratio of regioisomer **3**. In the case of **1b**, the protonated epoxide could probably form five-membered chelate **6** as an intermediate in addition to other probable intermediates **1**, **4**, and **5**. The ring-opening at CH_2-O in the epoxide would occur preferentially via intermediate **6** similar to the ring-opening of 2,3-epoxy alcohol with nucleophiles in the presence of Ti(O-i-Pr)$_4$.[14] The existence of **6** tends to give **2b**, and the ratio of regioisomers shifts to **2**, compared to the hydrofluorination of **1a**.



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In summary, this paper has demonstrated that the sterospecificity and regioselectivity of the hydrofluorination of optically active terminal epoxides with HF-amine reagents are determined by the basicity of the amines, the HF/amine ratio, and the type of epoxides. A back-side attack by fluoride anion occurred on protonated epoxides to give 2-fluoro-1-alkanol derivatives with high stereospecificity, while the formation of stable carbenium ions from protonated epoxides resulted in partial racemization. The regioselectivity of the reaction of simple aliphatic epoxides, for which the formation of a carbenium ion intermediate was negligible, was strongly affected by the basicity of the amines and the HF/amine ratio of HF-amine reagents.

Experimental Part

1. General remarks

Infrared spectra were recorded on a Shimazu IR-435. ^{1}H-NMR spectra were recorded on a Varian EM360L NMR spectrometer in $CDCl_3$ at 24°C using TMS as an internal standard. ^{19}F-NMR Spectra were recorded on a JEOL JNM-GSX 270 FT-NMR spectrometer in $CDCl_3$ at 24°C using trifluoroacetic acid as an internal standard. Mass spectra were obtained at a 70 eV ionization potential on a JEOL JMS DX-300. Optical rotations were measured at 25°C by Na D-line on an Union automatic digital polarimeter PM-201.

Optically active epoxides used in the present study were prepared by the microbial oxidation of the corresponding olefins.[9~11] Diisopropylamine, tributylamine, and melamine are of commercial origins. HF-amine reagents except for the commercial 9HF-pyridine (Aldrich) were prepared by mixing liquefied anhydrous hydrogen fluoride and the corresponding amines at -78°C.

The preparation of HF-amine reagents and the hydrofluorination of epoxides were carried out under a nitrogen atmosphere in a teflon bottle.

The extracted crude product was analyzed by GLC (2m, 3 % SE-30 on Chromosorb WAW DMCS) in order to calculate the yield of the regioisomeric mixture on the basis of the peak area ratio of the isomers and oligomeric by-products. The ratio of two regioisomers in the crude product was determined by GLC (2m, 15 % DEGS on Uniport B).

In order to determine the optical purity by capillary column GLC (ϕ 0.25 mm × 25 m, PEG-20M bonded on df 0.5 μm silica gel) or ^{19}F-NMR, the fluorohydrins were converted to the corresponding MTPA esters by esterification with (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. The absolute configuration of **3a** was confirmed by comparing its optical rotaion with that of an authentic sample,[4] while those of **3b** and **3d** were determined by the recyclization of the fluorohydrins under basic conditions, which gave **1b** and **1d** via an intramolecular S_N2 reaction, respectively. Fluorohydrin **3c** was converted into the corresponding ester by oxidation and then esterification, and its optical rotation was compared with that of an authentic sample.[15]

2. Fluorohydrins

1-Fluoro-2-octanol (**2a**). To 2HF-i-Pr_2NH (n=2, 3.17 g, 23 mmol) was added drop by drop (R)-(+)-1,2-epoxyoctane (1.92 g, 15 mmol, $[\alpha]_D^{25}$ +14.4 (neat), 91%ee) under cooling with an ice-water bath, and the reaction mixture was stirred for 8 h at 110 °C under nitrogen. The reaction mixture was cooled to room temperature, poured into ice-water (30 ml), and extracted with diethyl ether (3 × 30 ml). The combined organic layers were washed successively with aqueous sodium carbonate (3 × 80 ml) and water (2 × 80 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The remaining residue (1.26 g) was found to contain 1-fluoro-2-octanol and 2-fluoro-1-octanol (66:34) in 92% purity by GLC. Silica gel column chromatography (eluent: toluene), followed by distillation, gave 0.57 g (26%) of 1-fluoro-2-octanol (**2a**) as a colorless oil: Bp 78~83°C/7mmHg; $[\alpha]_D^{25}$ +13.8 (c 2.0, Et_2O); IR 3380, 2950, 2850, 1450, 1050, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.9 (3H, t), 1.3~1.5 (10H, m), 2.4 (1H, d), 3.8~3.9 (1H, m), 4.2~4.5 (2H, m). Trimethylsilylated **2a**: MS (70 eV) m/z (relative intensities) 69 (100), 135 (21), 187 (41), 205 (0.7) [M-15].

2-Fluoro-1-octanol (**3a**). To 4HF-i-Pr_2NH (n=4, 272 g, 1.5 mol) was added drop by drop (R)-(+)-1,2-epoxyoctane (128 g, 1 mol, $[\alpha]_D^{25}$ +14.4 (neat), 91%ee) under cooling with an ice-water bath (< 5 °C), and the reaction mixture was gradually warmed to room temperature and stirred continuously for 1 h under nitrogen. The reaction mixture was poured into ice-water (500 ml) and extracted with diethyl ether (2 × 700 ml). The combined organic layers were washed successively with aqueous sodium carbonate (3 × 1000 ml) and water (2 × 1000 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The remaining residue (134 g) was found to contain 1-fluoro-2-octanol and 2-fluoro-1-octanol (19:81) in 62% purity by GLC. Silica gel column chromatography (eluent: toluene), followed by distillation, gave 32 g (22%) of 2-fluoro-1-octanol (**3a**), of which the ^{1}H-NMR spectrum was identical with that previously reported,[4] as a colorless liquid: Bp 70~73°C/7mmHg; $[\alpha]_D^{25}$ -13.6 (c 2.0, Et_2O) (Cf. ref 4. $[\alpha]_D^{25}$ -10.4 (c 2.0, Et_2O)); IR 3200, 2850, 1440, 1360, 1260, 1120, 1040, 820, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.9 (3H, bt), 1.0~1.9 (10H, m), 2.2 (1H, s), 3.6 (2H, dd, J = 25 Hz, J = 5 Hz), 4.5 (1H, dm, J = 51 Hz). Trimethylsilylated **3a**: MS (70 eV) m/z (relative intensities) 69 (100), 107(87), 185 (0.7), 201 (0.2) [M-19], 205 (0.2) [M-15].

1-Fluoro-3-hexyloxy-2-propanol (**2b**) and **2-fluoro-3-hexyloxy-1-propanol** (**3b**). To 9HF-pyridine (n=9, 39.3 g, 150 mmol) was added drop by drop (R)-(+)-glicidyl hexyl ether (15.8 g, 100 mmol, $[\alpha]_D^{25}$ +9.2 (neat), 90%ee) under cooling with an ice-water bath (< 5 °C), and the reaction mixture was gradually warmed to room temperature and stirred continuously for 1.5 h under nitrogen. The reaction mixture was poured into ice-water (300 ml) and extracted with diethyl ether (2 × 300 ml). The combined organic layers were washed successively with aqueous sodium carbonate (3 × 500 ml) and water (2 × 500 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The remaining residue (15.6 g) was found to contain 1-fluoro-3-hexyloxy-2-propanol and 2-fluoro-3-hexyloxy-1-propanol (50:50) in 57% purity by GLC. Silica gel column chromotography (eluent: hexane/ethyl acetate 3/1(v/v)), followed by distillation, gave 2.35 g (13%) of 1-fluoro-3-hexyloxy-2-propanol (**2b**) and 2.13 g (12%) of 2-fluoro-3-hexyloxy-1-propanol (**3b**) as colorless liquids. **2b**: Bp 70~80°C/2mmHg (glass tube oven); $[\alpha]_D^{25}$ -7.7 (neat); IR 3350, 2850, 1460, 1380, 1080, 920 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.9 (3H, bt), 1.1~1.9 (8H, m), 2.65 (1H, s), 3.3~3.6 (4H, m), 3.7~4.3 (1H, m), 4.4 (2H, dd, J = 48 Hz, J = 5 Hz). **3b**: Bp 80~90°C/2mmHg (glass tube oven), $[\alpha]_D^{25}$ -1.8 (neat); IR

3350, 2900, 2850, 1450, 1370, 1100, 1040, 910, 830 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.9 (3H, bt), 1.0~1.9 (8H, m), 2.5 (1H, s), 3.3~3.7 (4H, m), 3.9 (2H, dd, J = 10 Hz, J = 5 Hz), 4.6 (1H, dm, J = 48 Hz).

2-Fluoro-2-methyl-1-hexanol (3c). To 4HF-i-Pr_2NH (n=4, 2.7 g, 15 mmol) was added drop by drop (R)-(-)-2-methyl-1,2-epoxyhexane (1.14 g, 10 mmol, $[\alpha]_D^{25}$ -9.3 (neat), 90%ee) under cooling with an ice-water bath (< 5 °C), and the reaction mixture was gradually warmed to room temperature and stirred continuously for 1 h under nitrogen. The reaction mixture was poured into ice-water (20 ml) and extracted with diethyl ether (2 × 30 ml). The combined organic layers were washed successively with aqueous sodium carbonate (3 × 50 ml) and water (2 × 50 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The remainig residue (1.33 g) was found to contain 2-fluoro-2-methyl-1-hexanol in 62% purity by GLC. Distillation gave 0.26 g (19%) of 2-fluoro-2-methyl-1-hexanol (**3c**), of which the ^{1}H-NMR spectrum was identical with that obtained using SiF_4 as a fluorination reagent,[16] as a colorless liquid: Bp 70°C/12mmHg (glass tube oven); $[\alpha]_D^{25}$ -0.7 (c 2.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$); 0.9 (3H, bt), 1.3 (3H, d, J = 22 Hz), 1.1~1.9 (6H, m), 2.0 (1H, s), 3.5 (2H, d, J = 20 Hz).

2-Fluoro-2-(pentafluorophenyl)ethanol (3d). To 4HF-i-Pr_2NH (n=4, 4.5 g, 22.5 mmol) was added drop by drop (R)-(+)-pentafluorostyrene oxide (3.15 g, 15 mmol, $[\alpha]_D^{25}$ +2.5 (neat), -4.4 (c 1.0, benzene), 97%ee) under cooling with an ice-water bath, and the reaction mixture was stirred for 69 h at room temperature under nitrogen. The reaction mixture was poured into ice-water (50 ml) and extracted with diethyl ether (2 × 70 ml). The combined organic layers were washed successively with aqueous sodium carbonate (3 × 100 ml) and water (2 × 100 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. The remaining residue (2.99 g) was found to contain 2-fluoro-2-(pentafluorophenyl)ethanol in 57% purity by GLC. Distillation gave 1.00 g (29%) of 2-fluoro-2-(pentafluorophenyl)ethanol (**3d**) as a colorless liquid: Bp 70~100°C/13mmHg (glass tube oven); $[\alpha]_D^{25}$ +12.0 (c 0.3, $CHCl_3$); IR 3350, 1660, 1500, 1460, 1080, 1040, 1000 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 3.1 (1H, s), 3.4~4.5 (2H, m), 5.8 (1H, dm, J = 47 Hz); ^{19}F-NMR ($CDCl_3$, CF_3COOH) 65.5 (2F), 76.0 (1F), 85.1 (2F), 114.7 (1F). MS (70 eV) m/z (relative intensities): 31 (100), 51 (5), 99 (6), 181 (11), 199 (38), 200 (20), 230 (17) [M].

3. Recyclization from fluorohydrins

Glycidyl hexyl ether from 2-fluoro-3-hexyloxy-1-propanol. A mixture of (-)-2-fluoro-3-hexyloxy-1-propanol (0.45 g, 2.5 mmol) and sodium hydride (0.2 g, 86% in parafin, 7 mmol) in tetrahydrofuran (10 ml) was refluxed for 5 h. The mixture was cooled to room temperature, neutralized with diluted hydrochloric acid, and extracted with diethyl ether (40 ml). The organic layer was washed with water (2 × 30 ml), dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Silica gel column chromatography (eluent: dichloromethane) gave 0.01 g of glycidyl hexyl ether having specific rotation of +8 (c 1, hexane), indicating that glycidyl hexyl ether derived from (-)-2-fluoro-3-hexyloxy-1-propanol had R configuration.

Pentafluorostyrene oxide from 2-fluoro-2-(pentafluorophenyl)ethanol. A mixture of (+)-2-fluoro-2-(pentafluorophenyl)ethanol (0.57 g, 2.4 mmol) and 12 M sodium hydroxide (5 ml) in hexane (5 ml) was stirred under vigorous reflux for 12 h. The mixture was cooled to room temperature and extracted with hexane (2 × 20 ml). The combined organic layers were washed with water (2 × 20 ml), dried with

anhydrous sodium sulfate, and concentrated under reduced pressure to give pentafluorostyrene oxide (0.26 g),which showed specific rotation of -5 (c 0.9, benzene), indicating that it had R configuration.

4. Ester

Methyl 2-fluoro-2-methylhexanoate. To a mixture of concd. sulfuric acid (11 g), water (100 ml), and (-)-2-fluoro-2-methyl-1-hexanol (2.14 g, 16 mmol) was added potassium permanganate (9.7 g, 61 mmol) by portions at below 30°C, and the mixture was stirred vigorously for 6 h. Sodium hydrogensulfite (7.3 g) was added slowly to the reaction mixture under cooling with an ice-water bath to reduce excess of potassium permanganate. The mixture was extracted with diethyl ether (2 × 70 ml), and then the combined organic layers were extracted with 10% sodium hydroxide (2 × 70 ml). The combined alkaline layers were acidified by adding concd. hydrochloric acid with continuous agitation. The acidic layer was extracted with chloroform (2 × 70 ml). The organic layers were combined, washed with water (2 × 70 ml), dried with anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by distillation to give 0.88 g (37%) of 2 fluoro-2-methylhexanoic acid: Bp 107~108°C/14mmHg; $[\alpha]_D^{25}$ -4.9 (c 3.0, Et_2O). To a solution of 2-fluoro-2-methylhexanoic acid (0.50 g, 3.4 mmol) in diethyl ether (1 ml) was added a solution of diazomethane in diethyl ether until the mixture showed yellow color due to a small excess of diazomethane. Excess diazomehtane and diethyl ether were removed at an atmospheric pressure to give 0.55 g (100%) of methyl 2-fluoro-2-methylhexanoate: $[\alpha]_D^{25}$ -4.2 (c 1.0, $CHCl_3$) (Cf. ref 15. $[\alpha]_D^{25}$ -4.6 ($CHCl_3$)).

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