Journal of Fluorine Chemistry, *35* (1987) 537–553

Received: July 8, 1986; accepted: November 17, 1986

MICROBIAL APPROACHES TO OPTICALLY ACTIVE SULFUR-CONTAINING FLUORINATED COMPOUNDS

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SUMMARY

A number of sulfur-containing compounds with a trifluoromethyl or a monofluoromethyl group was prepared. Studies on the microbial transformation of them have been undertaken, and possible routes to optically active bifunctional fluorinated compounds were examined.

INTRODUCTION

The importance of microbial transformation in asymmetric induction has been recognized. It provides a practical method of approach to an enantiomer with high optical purity [1-7]. As far as fluorine compounds are concerned, we have recently reported synthetic routes to optically active compounds with a fluorine or perfluoroalkyl group on the asymmetric carbon [8-15].

In our continuing study of the microbial behavior of fluorinated compounds, we describe herein syntheses of

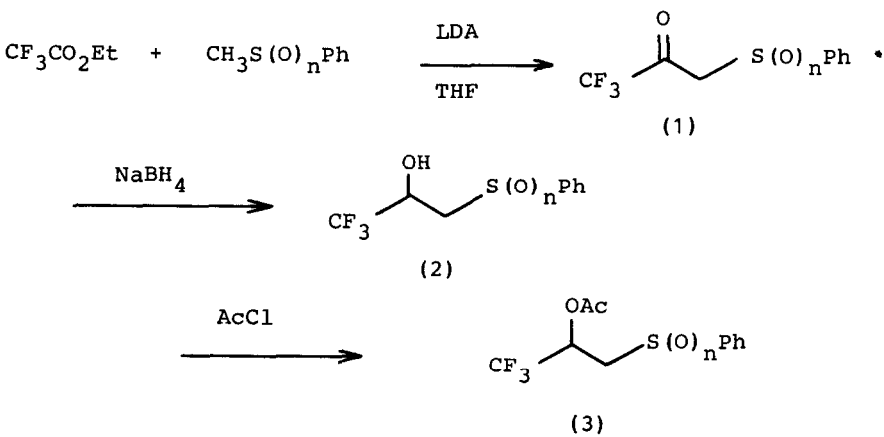
0022-1139/87/$3.50

optically active sulfur-containing fluorinated compounds, via asymmetric reduction of carbonyl group with baker's yeast and asymmetric hydrolysis with hydrolytic enzymes, and determination of their absolute configuration.

RESULTS AND DISCUSSION

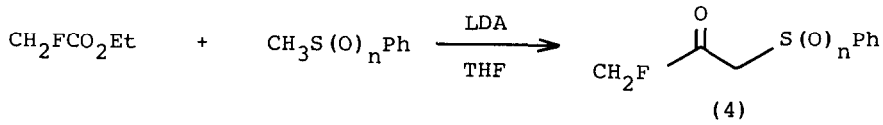
Preparation of sulfur-containing derivatives of 1,1,1-trifluoro-2-propanones (1a,1b), the corresponding 2-propanols (2a,2b) and their acetates (3a,3b)

1,1,1-Trifluoro-2-propanones (1) were prepared by the reaction of ethyl trifluoroacetate with an aryllithium compound. This method is a simple process involving the dropwise addition of ethyl trifluoroacetate to a solution of the lithium derivative in tetrahydrofuran as solvent below -50°C. These ketones were reduced with sodium borohydride to proceed the corresponding carbinol (2), and then the resulting carbinol were converted to the title materials with acetyl chloride.



Preparation of the analogous 1-fluoro-derivatives

Instead of ethyl trifluoroacetate, when ethyl fluoroacetate was used in the above mentioned system, the corresponding title materials were obtained, as shown below.



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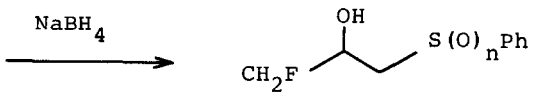

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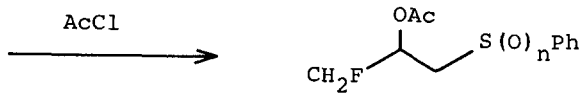
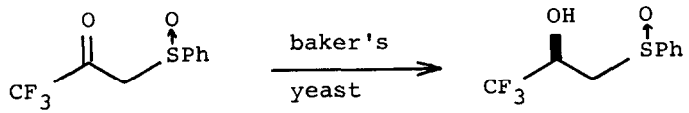


(6)

Microbial reduction of the β-ketosulfoxide with a trifluoromethyl group

When microbial transformation with active fermenting baker's yeast takes place, the corresponding diastereomer (87:13) is mainly obtained from the title material. However, β-ketosulfide and β-ketosulfone with a trifluoromethyl group were not transformed with baker's yeast.



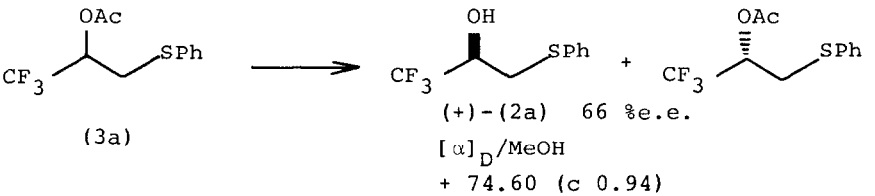
(1b) (2b)

$[\alpha]_D$/MeOH

+ 4.27 (c 1.06)

Asymmetric hydrolysis of acetate derivatives of β-hydroxysulfide and β-hydroxysulfone with trifluoromethyl group

The previously reported asymmetric hydrolyses of prochiral compounds using microorganisms suggest that the lipase-MY is adequate for the optical resolution of trifluoromethylated compounds. Therefore, the next step was the optical resolution of title materials with lipase-MY.

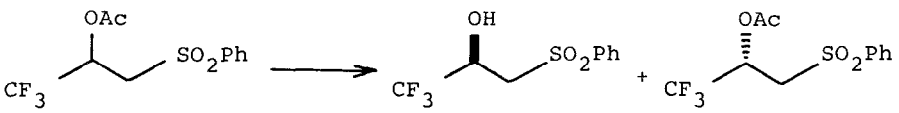


(3a)

(+)-(2a) 66 %e.e.

$[\alpha]_D$/MeOH

+ 74.60 (c 0.94)



(3c)

(+)-(2c) 58 %e.e.

$[\alpha]_D$/MeOH

+ 8.88 (c 0.74)

Determination of the absolute configuration of sulfur-containing derivatives of 1,1,1-trifluoropropanol

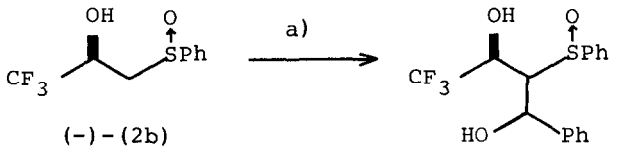
We have attempted to determine the absolute configuration and the optical purity at the asymmetric carbon. An outline of the synthetic strategies to achieve the desired structure through which to determine the absolute configuration, is shown in Scheme I.

The optically active (+)-β-hydroxysulfoxide (2b) was converted to (-)-4,4,4-trifluoro-3-hydroxy-1-phenylbutane (7) in Scheme I. While, the standard sample was synthesized as follow.

The synthetic intermediate was the optically pure (S)-(-)-ethyl 4,4,4-trifluoro-3-hydroxybutyrate (8), which was selectively reduced with lithium aluminium hydride and then treated with tosyl chloride to give the tosylate (9) as a potential synthon. Treatment of tosylate (9) with phenyl cuprate in diethyl ether gave (S)-(-)-4,4,4-trifluoro-3-hydroxy-1-phenylbutane, $[\alpha]_D$ -68.6 (c 1.75, MeOH), >96 %e.e. [9]. Furthermore, (+)-(2a) produced from the acetate derivative of β-hydroxysulfide by mean of microbial hydrolysis was converted to the corresponding (+)-β-hydroxysulfone by m-chloroperbenzoic acid.

The absolute configuration was determined by the specific rotation after conversion of the obtained (2a) to (R)-(+)-(2c) by m-chloroperbenzoic acid.

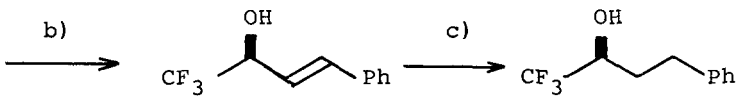
The result shown in Scheme II clearly demonstrate that the optical resolution with the asymmetric hydrolysis is useful for the design of the desired trifluoromethylated chiral materials.



(-)-(2b)

$[\alpha]_D$/MeOH

+ 4.27 (c 1.06)



(S)-(-)-(7)

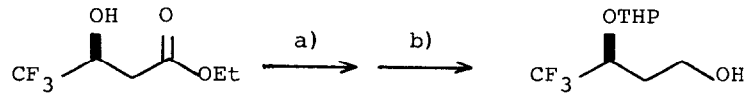
$[\alpha]_D$/MeOH

- 20.0 (c 1.18)

28 %e.e.

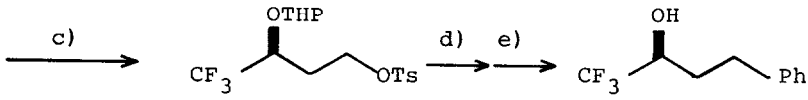
a) 2eq. $(i\text{-}Pr)_2NLi/THF/PhCH_2Br$ b) Raney Ni c) PtO_2/H_2

Scheme I



(S)-(-)-(8)

96 %e.e.



(S)-(-)-(7)

$[\alpha]_D$/MeOH

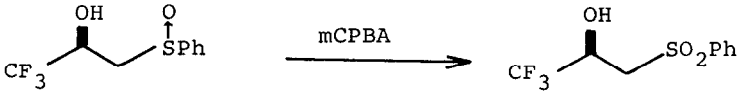
- 68.6 (c 1.87)

96 %e.e.

a) dihydropyran(DHP)/CH_2Cl_2/Pyridine

b) $LiAlH_4/Et_2O$ c) TsCl/CH_2Cl_2/Pyridine

d) Ph_2Cu/Et_2O e) H^+



(R)-(+)-(2b)

$[\alpha]_D$/MeOH

+ 4.27 (c 1.06)

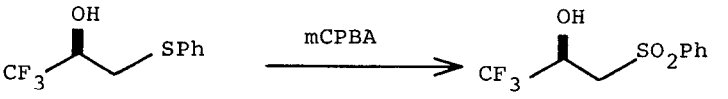
28 %e.e.

(R)-(+)-(2c)

$[\alpha]_D$/MeOH

+ 4.27 (c 1.40)

28 %e.e.



(+)-(2a)

$[\alpha]_D$/MeOH

+ 74.60 (c 0.94)

(R)-(+)-(2c)

$[\alpha]_D$/MeOH

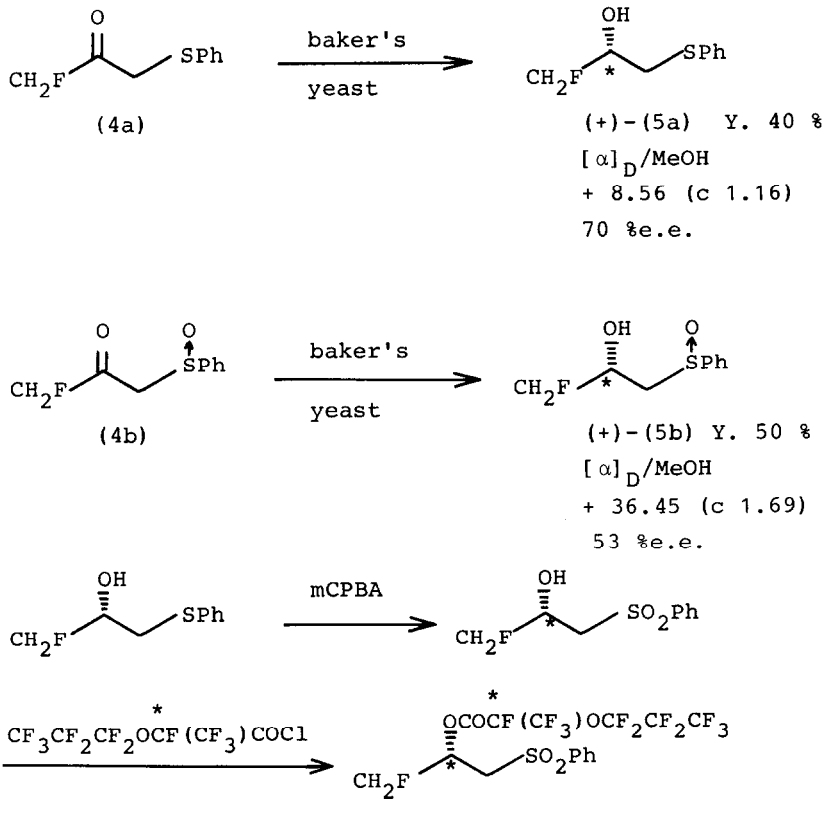
+ 10.7 (c 1.08)

70 %e.e.

Scheme II

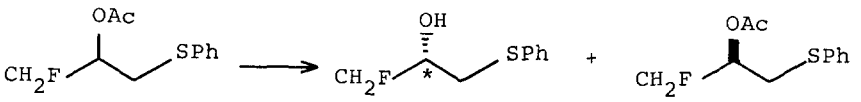
Route to optically active sulfur-containing compounds with a fluoromethyl group

The sulfur-containing fluoromethylated ketones, (4a) and (4b), were also transformed to optically active carbinols with fermenting baker's yeast. The optical purities of the corresponding carbinols, (+)-(5a) and (+)-(5b), were determined by ^{19}F NMR after conversion of the carbinols with a sulfone group at the β-position to their diastereomeric ester, as shown in Scheme III.



Scheme III

Furthermore, the microbial behavior of acetate derivatives (6a) with sulfur-containing groups attached to the β-position were examined using lipase-MY as a hydrolase. However, the optical purity of the carbinols obtained was not sufficiently high for them to be used as practical chiral building blocks of fluoromethylated materials.



(6a)

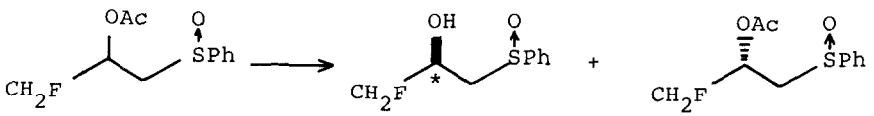
(+)-(5a)

Y. 34 %

$[\alpha]_D$/MeOH

+ 0.84 (c 1.04)

6 % e.e.



(6b)

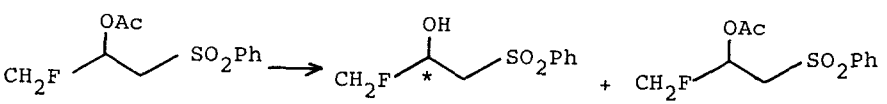
(-)-(5b)

Y. 22 %

$[\alpha]_D$/MeOH

- 0.85 (c 1.00)

10 %e.e.



(6c)

(5c)

racemic

Determination of absolute configuration of sulfur-containing compounds with a fluoromethyl group

The absolute configuration of (+)-(5a) and (+)-(5b) was determined by the specific rotation after conversion of the obtained (+)-(5a) to 1-phenylthio-2-propanol by lithium aluminium hydride. The optically active (+)-(5a) was reduced with lithium aluminium hydride in tetrahydrofuran at room temperature to give (S)-(+)-1-phenylthio-2-propanol (10), $[\alpha]_D$ +5.79 (c 1.73, MeOH), (lit.[16] (S)-(+)-(10) $[\alpha]_D$ +8.59 (c 0.78, MeOH), >99 %e.e.). Furthermore, (S)-(+)-(5a) and (+)-(5b) were converted to the corresponding β-hydroxysulfone, (+)-(5c).

This result shows that (+)-(5b) prepared from the β-ketoester (4b) by mean of the microbial reduction is the (S)-configuration at the asymmetric carbon.

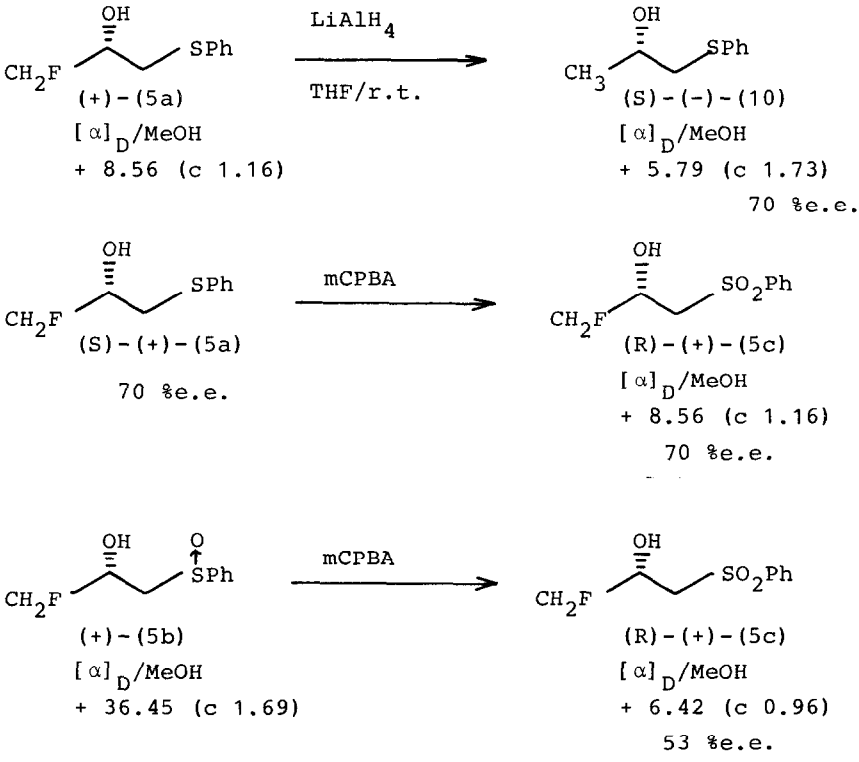


TABLE 1

Yields and Properties of Compounds (1) and (4)

Compound No	Yield (%)	Bp (°C/mmHg) (mp °C)	^{19}F NMR[b] δ ppm	^{1}H NMR δ ppm
(1a)	66	*[a]	1.6(CF_3, s)	3.80(CH_2, s), 7.33(Ar-H)
(1b)	84	108-109.5	8.7(CF_3, s)	3.10(CH_2, s), 7.63(Ar-H)
(4a)	77	120-121/7	146($CH_2\underline{F}$, t.t) $J_{CF-C\underline{H}_2F}$= 46 Hz	3.70(CH_2CO, d ; J_{CH_2-CF}= 3.3 Hz), 4.50(CH_2F, d), 7.1-7.5(Ar-H)
(4b)	76	*[a)]	146($CH_2\underline{F}$, t.t) $J_{CF-C\underline{H}_2F}$= 47 Hz	3.93(CH_2CO, d ; J_{CH_2-CF}= 3.3 Hz), 4.48(CH_2F, d), 7.65(Ar-H)

[a] The product was purified by column chromatography. [b] From ext. CF_3CO_2H in $CDCl_3$.

TABLE 2

Yields and Properties of Compounds (2) and (5)

Compound No	Yield (%)	Bp (°C/mmHg) (mp °C)	^{19}F NMR[b] δ ppm	^{1}H NMR δ ppm
(2a)	99	*[a]	1.0(CF_3,d) J_{CF_3-CH} = 6.6 Hz	3.01(CH_2,m), 3.90-4.30(2xH,m), 7.34(Ar-H)
(2b)	90	(97-98)	0.22(CF_3,d) J_{CF_3-CH} = 6.2 Hz	3.06(CH_2,m), 4.61(CH,m), 6.15(OH), 7.66(Ar-H)
			0.83(CF_3,d) J_{CF_3-CH} = 6.6 Hz	3.03(CH_2,m), 4.60(CH,m), 6.14(OH), 7.63(Ar-H)
(5a)	85	117-118/5	147($CH_2\underline{F}$,d.t) J_{CF-CH_2} = 41 Hz J_{CF-CH} = 19 Hz	3.00(CH_2,m), 3.80(CH,m), 4.4($C\underline{H}_2F$, d.d ; J_{CH_2-CH} = 4.8 Hz), 7.20 (Ar-H)
(5b)	80	*[a]	147($CH_2\underline{F}$,d.t) J_{CF-CH_2} = 40 Hz J_{CF-CH} = 19 Hz	3.20(CH_2,m), 4.00-4.50(2xH,m) 4.33($C\underline{H}_2F$,m), 7.50-8.00(Ar-H)

[a] The product was purified by column chromatography. [b] From ext. CF_3CO_2H in $CDCl_3$.

EXPERIMENTAL

Synthesis of compound (1a)(nc)

Into a solution of lithium diisopropylamine (30 mmol) in freshly dried tetrahydrofuran (30 ml), thioanisole (2.5 g, 20 mmol) in tetrahydrofuran (10 ml) was added at a temperature below -50°C. After 1 h of stirring, ethyl trifluoroacetate (2.8 g, 20 mmol) was added dropwise at that temperature. After a further 3 h of stirring below -50°C, the reaction mixture was quenched with saturated NH_4Cl. An oily material was extracted with diethyl ether, and then worked up similarly. The products were separated by column chromatography on silica gel using the n-hexane.

Analysis. Found : C, 49.31 ; H, 3.15 %.
Calcd for $C_9H_7OSF_3$: C, 49.09 ; H, 3.20 %.

Compound (2a)(nc) derived from the reduction of compound (1a)

Into a solution of sodium borohydride (25 mmol) and ethanol (50 ml), compound (1a)(4.4 g, 20 mmol) was added dropwise at room temperature. After 4 h of stirring, the reaction mixture was quenched with saturated NH_4Cl. An oily material was extracted with diethyl ether and then dried over magnesium sulfate.

Analysis. Found : C, 48.47 ; H, 4.35 %.
Calcd for $C_9H_9OSF_3$: C, 48.64 ; H, 4.08 %.

Synthesis of compound (1b)(nc)

Methyl phenyl sulfoxide (2.8 g, 20 mmol), ethyl trifluoroacetate (2.8 g, 20 mmol) and lithium diisopropylamine (30 mmol) were used in the same manner, and worked up similarly.

Analysis. Found : C, 45.67 ; H, 3.12 %.
Calcd for $C_9H_7O_2SF_3$: C, 45.76 ; H, 2.99 %.

Compound (2b)(nc) derived from the reduction of compound (1b)

Compound (1b)(4.6 g, 20 mmol) and sodium borohydride (25 mmol) in ethanol (50 ml) were used in the same manner, and worked up similarly.

Analysis. Found : C, 45.24 ; H, 3.98 %.
Calcd for $C_9H_9O_2SF_3$: C, 45.38 ; H, 3.81 %.

Compound (2c)(nc) derived from the oxidation of compound (2b)

A mixture of compound (2b)(20 mmol) and m-chloroperbenzoic acid (30 mmol) in dichloromethane (20 ml) were stirred for 5 h at 0-5°C, and then worked up as usual. The products were separated by column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5 : 1).

^{19}F NMR ($CDCl_3$) : δ 0.8 ppm(CF_3, d, J_{CF_3} = 6 Hz).

^{1}H NMR ($CDCl_3$) : δ 3.04(CH_3, m), 4.58(CH_2, m), 6.46(OH), 7.62(Ar-H).

Analysis. Found : C, 42.74 ; H, 3.47 %.
Calcd for $C_9H_9O_3SF_3$: C, 42.52 ; H, 3.57 %.

Synthesis of compound (4a)(nc)

Thioanisole (2.5 g, 20 mmol), ethyl fluoroacetate (2.1 g, 20 mmol) and lithium diisopropylamine (30 mmol) were used in the same manner, and worked up similarly. The products were separated by column chromatography on silica gel using the n-hexane as an eluent.

Analysis. Found : C, 59.25 ; H, 4.76 %.
Calcd for C_9H_9OSF : C, 59.00 ; H, 4.95 %.

Compound (5a)(nc) derived from the reduction of compound (4a)

Compound (4a)(3.6 g, 20 mmol) and sodium borohydride (25 mmol) in ethanol (50 ml) were used in the same manner, and worked up similarly. The products were separated by column chromatography on silica gel using the n-hexane as an eluent.

Analysis. Found : C, 58.26 ; H, 6.15 %.
Calcd for $C_9H_{11}OSF$: C, 58.35 ; 5.99 %.

Synthesis of compound (4b)(nc)

Methyl phenyl sulfoxide (2.8 g, 20 mmol), ethyl fluoroacetate (2.1 g, 20 mmol) and lithium diisopropylamine (30 mmol) were used in the same manner, and worked up similarly. The products were separated by column chromatography on silica gel using the n-hexane as an eluent.

Analysis. Found : C, 54.43 ; H, 4.27 %.
Calcd for $C_9H_9O_2SF$: C, 54.26 ; H, 4.55 %.

Compound (5b)(nc) derived from the reduction of compound (4b)

Compound (4b)(3.8 g, 20 mmol) and sodium borohydride (25 mmol) in ethanol (50 ml) were used in the same manner, and worked up similarly. The products were separated by column chromatography on silica gel using the n-hexane as an eluent.

Analysis. Found : C, 53.35 ; H, 5.58 %.
Calcd for $C_9H_{11}O_2SF$: C, 53.45 ; H, 5.48 %.

Compound (5c)(nc) derived from the oxidation of compound (5b)

A mixture of compound (5b)(20 mmol) and m-chloroperbenzoic acid (30 mmol) in dichloromethane (20 ml) were stirred for 5 h at 0-5°C, and then worked up as usual. The products were separated b column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5 : 1).

^{19}F NMR ($CDCl_3$) : δ 148 ppm(CH_2F, d.t, J_{CF-CH_2} = 45, J_{CF-CH} = 18 Hz).

^{1}H NMR ($CDCl_3$) : δ 3.23(CH,m), 4.05-4.45(2xH,m), 4.35(CH_2F,m), 7.50-7.95(Ar-H).

Analysis. Found : C, 42.36 ; H, 4.57 %.
Calcd for $C_9H_{11}O_3SF_3$: C, 42.19 ; H, 4.33 %.

Compound (1c)(nc) derived from the oxidation of compound (1b)

A mixture of compound (1b)(2.6 g, 10 mmol) and m-chloroperbenzoic acid (3.2 g, 20 mmol) in dichloromethane were stirred for 5 h at 0-5°C, and then worked up as usual. The products were separated by column chromatography on silica gel using the mixture solution of n-hexane-diethyl ether (5 : 1) as an eluent.

Analysis. Found : C, 42.64 ; H, 2.57 %.
Calcd for $C_9H_7O_3SF_3$: C, 42.86 ; H, 2.80 %.

Compound (4c)(nc) derived from the oxidation of compound (4b)

Compound (4b)(2.2 g, 10 mmol) and m-chloroperbenzoic acid (3.2 g, 20 mmol) were used in the above reaction, and then worked up similarly.

Analysis. Found : C, 49.75 ; H, 5.24 %.
Calcd for $C_9H_{11}O_3SF$: C, 49.53 ; H, 5.08 %.

Microbial transformation of compound (1b)

A suspension of baker's yeast (50 g), starch (75 g) in buffer solution (600 ml, pH 7.3), which is prepared from 1/15 M aq. KH_2PO_4 solution (139.2 ml) and 1/15 M aq. Na_2HPO_4 solution (460.8 ml), was stirred for 1h at 35-36°C in Jarfermentor (M-100, Tokyo Rikakikai Co. Ltd.). Into the mixture, compound (1b)(5 g) was added, and then the whole mixture was stirred at 35-36°C. After 24 hrs of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ichi Kogyo Seiyaku, 100 ml) was added into the stirring mixture for a few minutes. After 1h of stirring, the mixture was acidified with 1N HCl and then the precipitates were seperated by filtration. The oily materials were extracted with diethyl ether. The ethereal extract was dried over anhydrous magnesium sulfate and then the solvent removed. The products were separated by column chromatography on silica gel using n-hexane as an eluent.

Synthesis of acetate (3a)(nc)

A mixture solution of compound (2a)(4.4 g, 20 mmol) and acetyl chloride (2 g, 25 mmol) in pyridine (10 ml) was stirred at room temperature. After 5 h of stirring, the reaction mixture was poured into water. The oily materials were extracted with diethyl ether and then dried over magnesium sulfate. Acetate (3a) was separated by column chromatography on silica gel using n-hexane-diethyl ether (5 : 1).

^{19}F NMR ($CDCl_3$) : δ 2.5 ppm(CF_3, d, J_{CF_3-CH} = 6 Hz).

^{1}H NMR ($CDCl_3$) : δ 1.94($COCH_3$,s), 3.05(CH_2,m), 4.58(CH,m), 7.58(Ar-H).

Analysis. Found : C, 49.85 ; H, 4.35 %.

Calcd for $C_{11}H_{11}O_2SF_3$: C, 50.00 ; H, 4.20 %.

Synthesis of acetate (6a)(nc)

Compound (5a)(20 mmol) and acetyl chloride (25 mmol) were used in the same manner, and worked up similarly.

^{19}F NMR ($CDCl_3$) : δ 150 ppm(CH_2F, t.t, J_{CF-CH_2} = 46, J_{CF-CH} = 18 Hz).

^{1}H NMR (CDCl) : δ 1.93($COCH_3$,s), 3.47(CH,d), 4.53(CH_2F,d.m), 7.33(Ar-H).

Analysis. Found : C, 57.58 ; H, 5.84 %.

Cacld for $C_{11}H_{13}O_2SF$: C, 57.88 ; H, 5.74 %.

Other acetates (3c), (6b) and (6c) were prepared in the same manner.

Microbial transformation of compound (4b)

In the above reaction, baker's yeast (50 g), starch (75 g) and compound (4b)(5 g) were used , and worked up similarly. The products were separated by column chromatography on silica gel.

Asymmetric hydrolysis of compound (3)

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, compound (2a)(20 mmol) was added, and then the whole mixture was stirred at 40-41°C. After 6h of stirring, the flocculant (200 ppm solution prepared from p-713, Dai-ich Kogyo Seiyaku, 10 ppm) was added into the stirring 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 an eluent.

Asymmetric hydrolysis of compound (3b)

In the above reaction, compound (3b)(5.6 g, 20 mmol) and lipase-MY (5 g) were used, and then worked up as usual. The products were separated by column chromatography on silica gel.

Asymmetric hydrolysis of compound (6c)

Lipase-MY (5 g) and compound (6c)(5.2 g, 20 mmol) were used in the above reaction, and then worked up similarly. The products were separated by column chromatography on silica gel.

Determination of optical purity

A mixture of 1-phenyl-2-fluoroethanol (1.2 mmol), (+)-perfluoro-2-propoxypropionic acid chloride (1.0 mmol)[17] and triethylamine (1.0 mmol) in diethyl ether (10 ml) was stirred at room temperature. After 24 hrs of stirring, the mixture was poured into water, and then the ethereal layer was washed with 1N HCl solution, 5% aq. $NaHSO_4$, sat. $Na_2S_2O_3$ solution and brine. After removing the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities.

(S)-(-)-4,4,4-Trifluoro-3-hydroxy-1-phenylbutane (7) derived from (-)-(2b)

a) Into a solution of lithium diisopropylamine (30 mmol) in freshly dried tetrahydrofuran (30 ml), (-)-(2b)(20 mmol, $[\alpha]_D$ + 4.27 (c 1.06, MeOH)) was added slowly at -50 °C. After 30 min of stirring at that temperature, benzyl bromide (20 mmol) was added into the above solution. After 3 h of stirring at -30 °C, the mixture was poured into water, and then oily materials were extracted with diethyl ether. After removing the solvent, 1,3-diol was obtained as a crude intermediate.

b) Crude 1,3-diol (10 mmol) and Raney Ni (1 g) in benzene (20 ml) was refluxed for 5 h, and then Raney Ni was filtered. After removing the benzene, crude (E)-4,4,4-trifluoro-3-hydroxy-1-phenyl-1-butene was obtained. This product was reduced by PtO_2-diethyl ether system under atmospheric hydrogen to give the compound (7).
(S)-(-)-(7) was purified by column chromatography on silica gel using n-hexane-diethyl ether (10 : 1).
$[\alpha]_D$ -20.0 (c 1.18, MeOH), 28 %e.e.

(S)-(-)-1-Phenylthio-2-propanol (10) derived from (+)-(5a)

(+)-(5a)(20 mmol, $[\alpha]_D$ +8.56 (c 1.16, MeOH)) and lithium aluminium hydride (1 g) in freshly dried tetrahydrofuran (30 ml) was stirred at room temperature. After 48 h of stirring, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether, and then worked up similarly. (S)-(-)-1-phenylthio-2-propanol (10) was purified by column chromatography on silica gel using n-hexane-diethyl ether (5 : 1).
$[\alpha]_D$ -5.79 (c 1.73, MeOH), 70 % e.e.

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