A microbially-based approach for the synthesis of chiral secondary alcohols bearing the difluoromethyl or chlorodifluoromethyl group

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Abstract

A synthetic approach to both enantiomers of the secondary alcohols $[Ph(CH_2)_nCH(OH)CXF_2$ $(n=0–2)$ $C_6H_{13}(CH_2)_nCH(OH)CFX_2$ $(n=0$ or 2) and $CXF_2CH(OH)CH_2CO_2Et$ [X = H or Cl], involving the stereoselective hydrolysis of ester derivatives, is described. The absolute configurations of these difluoromethylated or chlorodifluoromethylated molecules were determined.

Introduction

Hydrolytic enzymes are practical chiral catalysts for asymmetric synthesis [1–3]. Some chiral synthetic tools for the preparation of fluorinated bioactive materials [4–9] or ferroelectric liquid crystals [10, 11] are known. Asymmetric inductions to form chiral fluoroalkyl compounds have been reported [12–15] as microbial transformations which afforded chiral trifluorinated compounds [16] and other fluoroalkylated materials with high optical purities by the use of microorganisms [17–22]. We now describe a practical route to difluoromethylated and chlorodifluoromethylated enantiomers. The key synthetic step is based on the enantiotopic specificity of hydrolases.

Experimental

General procedure

All microbial hydrolyses were carried out in the Jarfermentor or Culstir flask. All commercially available reagents were used without further purification. Infrared spectra were obtained by using a JASCO A-102 spectrometer and KBr pellets. The ^1H (90 MHz; internal Me_4Si) and ^{19}F (56.4 MHz; external

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CF_3CO_2H) NMR spectra were recorded using Varian EM-390 and Hitachi R-24F spectrometers. Specific rotations were recorded by using a JASCO DIP-140 digital polarimeter. Yields quoted are those of the products actually isolated.

*Difluoromethyl phenyl ketone (**1a**)(nc)*

Into a solution of ethyl difluoroacetate (4.9 g, 40 mmol) in freshly dried diethyl ether (50 ml), phenyl magnesium bromide (44 mmol) was added dropwise at a temperature below −70 °C. After 4 h stirring, the mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave difluoromethyl phenyl ketone in a yield of 83%, b.p., 63–66 °C/10 Torr. Analysis: Calcd. for $C_8H_6F_2O$ (156.1): C, 60.38; H, 3.80%. Found: C, 60.17; H, 4.04%. High-resolution MS: Calcd. for $C_8H_6F_2O$: 156.1319. Found: 156.1333.

*Chlorodifluoromethyl phenyl ketone (**1f**)(nc)*

Into a solution of methyl chlorodifluoroacetate (5.8 g, 40 mmol) in freshly dried diethyl ether (50 ml), benzyl magnesium bromide (44 mmol) was added dropwise at a temperature below −70 °C. After a further 4 h stirring below −60 °C, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether. Distillation gave chlorodifluoromethyl benzyl ketone in a yield of 67%, b.p., 80 °C/10 Torr. Analysis: Calcd. for $C_8H_5F_2ClO$ (191.6): C, 50.38; H, 2.64%. Found: C, 50.21; H, 2.78%. High-resolution MS: Calcd. for $C_8H_5F_2ClO$: 191.5849. Found: 191.5837.

Other difluoromethylated or chlorodifluoromethylated ketones were prepared in the same manner.

*1-Phenyl-2,2-difluorethanol (**2a**)*(nc)

Into a solution of sodium borohydride (0.35 g, 33 mmol) and ethanol (20 ml), difluoromethyl phenyl ketone (5.1 g, 33 mmol) in ethanol (20 ml) was added dropwise at 0 °C. After 4 h stirring at room temperature, the reaction mixture was quenched with saturated NH_4Cl. Oily materials were extracted with diethyl ether and then dried over magnesium sulfate. Distillation gave 1-phenyl-2,2-difluoroethanol (**2a**) in a yield of 84%, b.p., 103 °C/12 Torr. Analysis: Calcd. for $C_8H_8F_2O$ (158.2): C, 59.61; H, 5.00%. Found: C, 59.87; H, 4.78%. High-resolution MS: Calcd. for $C_8H_8F_2O$: 158.1477. Found: 158.1464.

*1-Benzyl-2-chloro-2,2-difluoroethanol (**2g**)(nc)*

Into a solution of sodium borohydride (0.38 g, 35 mmol) and ethanol (20 ml), chlorodifluoromethyl benzyl ketone (3.9 g, 20 mmol) in ethanol (20 ml) was added dropwise at room temperature. After 5 h stirring at that temperature, the reaction mixture was worked up as usual. Distillation gave 1-benzyl-2-chloro-2,2-difluorethanol (**2g**) in a yield of 85%, b.p., 106 °C/ 9 Torr. Analysis: Calcd. for $C_{10}H_{11}F_2ClO$ (220.7): C, 59.61; H, 5.00%. Found:

C, 59.87; H, 4.78%. High-resolution MS: Calcd. for $C_{10}H_{11}F_2ClO$: 220.6466. Found: 220.6452.

Other β-fluoroalkyl carbinols were prepared in the same manner and on the same scale.

*Ethyl 4,4-difluoro-3-oxobutanoate (**3a**)(nc)*

Into the reaction vessel containing lithium diisopropylamide (200 mmol) in diethyl ether (100 ml) was added ethyl acetate (200 mmol) in diethyl ether (30 ml) via a syringe under an atmosphere of argon at −70 °C. Into this solution was added ethyl difluoroacetate (12.5 g, 100 mmol) in diethyl ether (40 ml) at −70 °C. After 4 h stirring at −70 °C, the reaction mixture was quenched with saturated NH_4Cl solution. On removal of the solvent, distillation gave ethyl 4,4-difluoro-3-oxobutanoate (**3a**) in a yield of 82%, b.p., 100 °C/100 Torr; enol/keto ratio = 14:86. Keto form: ^{19}F NMR ($CDCl_3$) δ: 46.3 (d, J_{F-H} = 50 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.32 (CH_3, t, J_{H-H} = 6.8 Hz); 4.32 (CH_2, q); 5.40 (CH_2CO, s); 6.00 (CH, t) ppm. Enol form: ^{19}F NMR ($CDCl_3$) δ: 47.8 (d, J_{F-H} = 50 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.27 (CH_3, t, J_{H-H} = 6.8 Hz); 2.67 (OH, s); 3.64 (C=CH, s); 4.18 (CH_2, q); 5.83 (CH, t) ppm. IR (cm^{-1}): 3450 (OH). Analysis: Calcd. for $C_6H_8F_2O_3$ (166.1): C, 43.38; H, 4.85%. Found: C, 43.46; H, 4.69%. High-resolution MS: Calcd. for $C_6H_8F_2O_3$: 166.1245. Found: 166.1251.

*Ethyl 4,4-difluoro-3-hydroxybutanoate (**4a**)(nc)*

Into a solution of diphenylmethylsilane (12 ml, 60 mmol) in trifluoroacetic acid (30 ml), cooled with an ice bath under an atmosphere of argon, ethyl 4,4-difluoro-3-oxobutanoate (4.97 g, 300 mmol) was added dropwise at 0 °C. After 2 h stirring at room temperature, the reaction mixture was quenched with aq. $NaHCO_3$, and oily materials were then extracted with diethyl ether. On removal of the solvent, distillation gave ethyl 4,4-difluoro-3-hydroxybutanoate (**4a**) in a yield of 74%, b.p., 95 °C/30 Torr. ^{19}F NMR ($CDCl_3$) δ: 49.0 (d.d.d, J_{F-F} = 266 Hz, J_{F-Hgem} = 52.3 Hz, J_{F-Hvic} = 10.8 Hz); 50.3 (d.d.d, J_{F-Hgem} = 52.8 Hz, J_{F-Hvic} = 12.5 Hz) ppm. ^1H NMR ($CDCl_3$) δ: 1.34 (CH_3, t, J_{H-H} = 7.2 Hz); 2.57 (CHaHb, d.d, J_{Ha-Hb} = 17.4 Hz, $J_{Ha-Hvic}$ = 7.2 Hz); 2.73 (CHaHb, d.d, $J_{Hb-Hvic}$ = 15.9 Hz); 3.74 (OH); 3.90–4.15 (CH, m); 4.22 (CH_2, q); 5.73 (CHF_2, d.t, J_{H-Hvic} = 3.9 Hz) ppm. IR (cm^{-1}): 3450 (OH); 1725 (C=O). Analysis: Calcd. for $C_6H_{10}F_2O_3$ (168.1): C, 42.86; H, 6.42%. Found: C, 42.64; H, 6.37%. High-resolution MS: Calcd. for $C_6H_{10}F_2O_3$: 168.1404. Found: 168.1417.

*Ethyl 4-chloro-4,4-difluoro-3-oxobutanoate (**3b**)(nc)*

Into the reaction vessel containing lithium diisopropylamide (200 mmol) in diethyl ether (100 ml) was added ethyl acetate (200 mmol) in diethyl ether (30 ml) via a syringe under an atmosphere of argon at −70 °C. Into the solution mixture was further added methyl chlorodifluoroacetate (16.0 g, 100 mmol) in diethyl ether (40 ml) at −70 °C. After 4 h stirring at −70 °C, the reaction mixture was quenched with saturated NH_4Cl solution.

On removal of the solvent, distillation gave ethyl 4-chloro-4,4-difluoro-3-oxobutanoate (**3b**) in a yield of 78%, b.p., 96 °C/70 Torr; enol/keto ratio = 18:32. Keto form: ^{19}F NMR ($CDCl_3$) δ: −14.3 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.32 (CH_3, t, J_{H-H} = 7.1 Hz); 4.28 (CH_2, q); 5.55 (CH_2, s) ppm. Enol form: ^{19}F NMR ($CDCl_3$) δ: −9.3 (s) ppm. ^1H NMR ($CDCl_3$) δ: 1.14 (CH_3, t, J_{H-H} = 7.1 Hz); 3.33 (OH, bd); 3.68 (C=CH, s); 5.43 (CH_2, q) ppm. IR (cm^{-1}): 3450 (OH); 1740; 1710 (C=O). Analysis: Calcd. for $C_6H_7F_2ClO_3$ (200.6): C, 35.91; H, 3.52%. Found: C, 36.04; H, 3.44%. High-resolution MS: Calcd. for $C_6H_7F_2ClO_3$: 200.5696. Found: 200.5684.

*Ethyl 4-chloro-4,4-difluoro-3-hydroxybutanoate (**4b**)(nc)*

Into a solution of zinc borohydride (80 mmol) in diethyl ether (20 ml), ethyl 4-chloro-4,4-difluoro-3-oxobutanoate (4.0 g, 20 mmol) in diethyl ether (10 ml) was added dropwise at 0 °C. After 2 h stirring at room temperature, the reaction mixture was quenched with 1 N HCl, and the ethereal layer was then dried over magnesium sulfate. On removal of the solvent, distillation gave ethyl 4-chloro-4-,4-difluoro-3-hydroxybutanoate (**4b**) in a yield of 60%, b.p., 109 °C/65 Torr. ^{19}F NMR ($CDCl_3$) δ: −11.0 (d.d, J_{F-F} = 170 Hz, J_{F-Hvic} = 8 Hz); −14.1 (d.d) ppm. ^1H NMR ($CDCl_3$) δ: 1.28 (CH_3, t, J_{H-H} = 7.2 Hz); 2.52 (CHaHb, d.d, J_{Ha-Hb} = 16.8 Hz, $J_{Ha-Hvic}$ = 7.8 Hz); 2.75 (CHaHb, d.d, $J_{Hb-Hvic}$ = 4.8 Hz); 3.50 (OH); 4.13 (CH_2, q); 4.45 (CH, d.q) ppm. IR (cm^{-1}): 3450 (OH). Analysis: Calcd. for $C_6H_9F_2O_3$ (167.1): C, 35.67; H, 4.49%. Found: C, 35.94; H, 4.33%. High-resolution MS: Calcd. for $C_6H_9F_2O_3$: 167.1325. Found: 167.1317.

Preparation of acetate esters

Method A

A mixture of 1-phenyl-2,2-difluoroethanol (1.6 g, 10 mmol), acetyl chloride (12 mmol) and pyridine (1.6 ml) in dichloromethane (20 ml) was stirred at room temperature. After 6 h stirring, the mixture was quenched with 1 N HCl. Oily materials were extracted with dichloromethane, and the organic layer was then washed with 5% aq. $NaHCO_3$, water and brine. On removal of the solvent, the acetate was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as an eluent, and was obtained in 92% yield. ^{19}F NMR ($CDCl_3$) δ: 46.5 (CFa, d.d.d, J_{Fa-Fb} = 274 Hz, $J_{Fa-Hgem}$ = 50 Hz, $J_{Fa-Hvic}$ = 11 Hz); 50.9 (CFb, d.d.d, $J_{Fa-Hgem}$ = 51 Hz, $J_{Fa-Hvic}$ = 8 Hz). ^1H NMR ($CDCl_3$) δ:2.10 (CH_3, s); 5.83 (CHF_2, d.t, J_{H-Hvic} = 4.2 Hz); 5.83 (CH, d.t) ppm.

Method B

A mixture of 1-benzyl-2-chloro-2,2-difluoroethanol (1.2 g, 6 mmol), acetyl chloride (0.5 ml, 12 mmol) and pyridine (1.0 ml) in dichloromethane (20 ml) was stirred at room temperature. After 6 h stirring, the mixture was quenched with 1 N HCl and then worked-up as usual. The acetate ester was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as an eluent, and was obtained in 87% yield. ^{19}F NMR ($CDCl_3$)

δ: −13.5 (CFa, d.d, J_{Fa-Fb} = 173 Hz, $J_{Fa-Hvic}$ = 8 Hz); −16.5 (CFb, d.d, $J_{Fa-Hvic}$ = 8 Hz) ppm. ^{1}H NMR ($CDCl_3$) δ: 1.92 (CH_3, s); 2.90 (CHaHb, d.d, J_{Ha-Hb} = 14.4 Hz, $J_{Ha-Hvic}$ = 9.6 Hz); 3.19 (CHaHb, d.d, $J_{Hb-Hvic}$ = 3.6 Hz); 5.30–5.70 (CH, m); 7.10–7.30 (Ar–H) ppm.

Other acetate esters were prepared in the same manner.

Asymmetric hydrolysis

A suspension of lipase-MY (Meito Sangyo Co. Ltd., 5 g) in buffer solution (60 ml, pH 7.3) from 1/15 M aq. Na_2HPO_4 solution (46.1 ml) and 1/15 M aq. KH_2PO_4 solution (13.9 ml), was stirred for 15 min at 40–41 °C in a Culstir flask for suspension culture with double arms and jacket (100 ml, Sibata Scientific Technology Ltd.). Into the mixture, the acetate derivative of 1-chloro-1,1-difluoro-4-phenyl-2-butanol (20 mmol) was added, and then the whole mixture was stirred at 40–41 °C. After 11 h stirring, the mixture was acidified with 1 N HCl and the oily materials extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and the solvent 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/ethyl acetate (5:1) as eluent.

Synthesis of the (S)-enantiomer

(a) In the above asymmetric hydrolysis, the acetate derivative of 1-chloro-1,1-difluoro-4-phenyl-2-butanol (**2h**) was hydrolyzed for 15 h with lipase-MY, and then (*R*)-(+)-1-chloro-1,1-difluoro-4-phenyl-2-butanol (> 90% ee; hydrolysis ratio, 52%) and the corresponding (*S*)-acetate derivative were separated by column chromatography.

(b) A suspension of cellulase (*Trichloderma viride*, Amano Seiyaku Co. Ltd., 3 g) in buffer solution (60 ml, pH 7.3) was stirred for 15 min at 40–41 °C in the Culstir flask (200 ml). The recovered (*S*)-acetate derivative of 1-chloro-1,1-difluoro-4-phenyl-2-butanol (10 mmol) was added to the mixture and the whole mixture then stirred at 40–41 °C. After 10 h stirring, the mixture was acidified with 1 N HCl and the oily materials then extracted with ethyl acetate. The products were separated by column chromatography on silica gel using a mixture of n-hexane/ethyl acetate (5:1) as eluent.

(c) A mixture solution of the recovered (*S*)-acetate derivative of 1-chloro-1,1-difluoro-4-phenyl-2-butanol (10 mmol), and 2 mol l^{-1} aq. NaOH (5 ml) acetone (5 ml) was stirred at room temperature. After 2 d stirring, the mixture was acidified with 1 N HCl and the oily materials then extracted with ethyl acetate. The products were separated by column chromatography using the mixture of n-hexane/ethyl acetate (5:1) as eluent.

Determination of optical purity

A mixture solution of (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid chloride (MTPA-Cl) (1.1 mmol) and (*R*)-(+)-1-chloro-1,1-difluoro-4-phenyl-2-butanol (**2h**) (1 mmol) in pyridine (1 ml) was stirred at room temperature.

After 3 d stirring, the whole mixture was poured into water and the oily materials extracted with a 1 N HCl solution, 5% $NaHSO_4$, saturated $Na_2S_2O_3$ solution, and then brine. After removing the solvent, the diastereomeric ratio was determined by ^{19}F NMR signal intensities and/or GLC (carrier gas, He; flow, 20 ml min^{-1}; capillary column 30 m packed with Silicon GEXE-60 on Chromosorb W) at 200 °C.

Determination of absolute configuration

Synthesis of (R)-(+)-1,1-difluoro-2-nonanol (9) derived from ***4a***

(*a*) *Protection by dihydropyran* – A mixture of (+)-ethyl 4,4-difluoro-3-hydroxybutanoate (3.5 g, 20 mmol), $[\alpha]_D^{21}CHCl_3 + 19.81°$ (c 0.90), >90% ee, dihydropyran (1.4 g, 20 mmol) and *p*-toluenesulfonic acid (50 mg) in methylene chloride (40 ml) was stirred for 3.5 h at room temperature. On removal of the solvent, product **5** was separated by column chromatography on silica gel in 87% yield.

(b) Reduction on compound ***5*** *with lithium aluminum hydride* – Into the reaction vessel was placed lithium aluminum hydride (13 mmol), freshly dried diethyl ether (30 ml) added via a syringe under an atmosphere of argon, and then compound **5** (2.5 g, 10 mmol) in diethyl ether (5 ml) at 0 °C. After addition of the reagent, the reaction mixture was stirred for 5 h at room temperature, and the reaction mixture was then quenched with saturated NH_4Cl solution. Oily materials were extracted with diethyl ether, and the resulting ethereal extract was dried over anhydrous magnesium sulfate. On removal of the solvent, product **6** was separated by column chromatography on silica gel in 84% yield.

(c) Oxidation of compound ***6*** – Into the three-necked flask was placed dimethyl sulfoxide (1.2 g, 20 mmol), oxalyl chloride (1.38 g, 20 mmol) added via a syringe under an atmosphere of argon at −50 °C, and then compound **6** (2.1 g, 10 mmol) at the same temperature. After 15 min stirring, triethylamine (2 g) was added to the mixture at −50 °C and the latter was then allowed to warm up to room temperature. The mixture was poured into water, and the oily materials extracted with diethyl ether. On removal of the solvent, the resulting products were chromatographed on silica gel. A solution of the crude compound (2.1 g, 10 mmol) and *p*-toluenesulfonic acid (0.1 g) in methylene chloride (20 ml) was stirred for 1 h at room temperature, poured into water and then worked up as usual. On removal of the solvent, product **7** was separated by column chromatography on silica gel in 63% yield.

(d) Wittig-type reaction – Into a solution of n-butyllithium (12 mmol) and diethyl ether (30 ml) under an atmosphere of argon, penthyltriphenyl phosphonium bromide (4 g, 10 mmol) in diethyl ether (10 ml) was added via a syringe at 0 °C. After 30 min stirring, aldehyde **7** (3.0 g, 10 mmol) was added at 0 °C, the reaction mixture stirred for 2 h at room temperature,

and the mixture then quenched with sat. NH_4Cl solution. Oily materials were extracted with ethyl acetate. On removal of the solvent, the resulting product **8** was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as eluant and obtained in 85% yield.

(e) Hydrogenation of a carbon–carbon bond — A solution of compound **8** (1.8 g, 10 mmol) and Pd–C (0.3 g) in methanol (20 ml) under atmospheric hydrogen was stirred at room temperature. After 24 h stirring, the mixture was poured into water and the oily materials were extracted with diethyl ether. On removal of the solvent, the (*R*)-(+)-1,1-difluoro-2-nonanol (**9**) obtained was purified by column chromatography on silica gel: $[\alpha]_D^{21}CHCl_3 + 19.4°$ (c 0.78), >84% ee.

(R)-(+)-1,1-Difluoro-2-octanol derived from ***4a***

(a) Wittig-type reaction — Into a solution of n-butyllithium (12 mmol) in diethyl ether (30 ml) under an atmosphere of argon, butyltriphenyl phosphonium bromide 4 g, 10 mmol) in diethyl ether (10 ml) was added via a syringe at 0 °C. After 30 min stirring, aldehyde **7** (3.0 g, 10 mmol) was added at that temperature, the reaction mixture stirred for 3 h at room temperature and the mixture then quenched with sat. NH_4Cl solution. Oily materials were extracted with ethyl acetate. On removal of the solvent, the product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as eluant, and obtained in 87% yield.

(b) Hydrogenation of a carbon–carbon bond — A solution of the above crude compound and Pd–C (0.3 g) in methanol (20 ml) under atmospheric hydrogen was stirred at room temperature. After 24 h stirring, the mixture was poured into water, and the oily materials extracted with diethyl ether. On removal of the solvent, (*R*)-(+)-1,1-difluoro-2-octanol (**2d**) was purified by column chromatography on silica gel: $[\alpha]_D^{21}$ $CHCl_3 + 7.87°$ (c 1.04), >88% ee.

*(R)-(+)-1,1-Difluoro-2-decanol (**2j**) derived from (+)-1-chloro-1,1-difluoro-2-decanol*

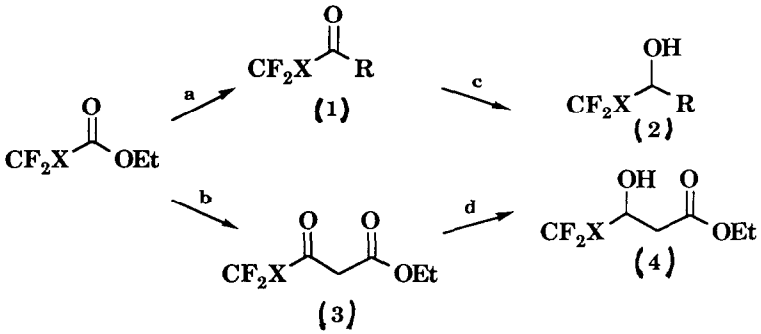
A solution of (+)-1-chloro-1,1-difluoro-2-decanol (0.09 g, 0.4 mmol), tributyl tinhydride (0.48 mmol) and azoisobutyronitrile (10 mg) in toluene (3 ml) under an atmosphere of argon was refluxed for 3 h. The mixture was quenched with carbon tetrachloride. On removal of the solvent, (*R*)-(+)-1,1-difluoro-2-decanol (**2j**) was isolated by column chromatography on silica gel.

The absolute configurations of other materials were confirmed in the same manner.

Results and discussion

We have found that racemic alcohols, readily prepared by the reduction of the corresponding ketones with $NaBH_4$, are versatile intermediates for

enzyme-catalyzed kinetic resolution. Ethyl difluoroacetate or methyl chlorodifluoroacetate was converted into the corresponding difluoromethyl or chlorodifluoromethyl ketones (**1**) (Table 1). Reduction of the ketones **1** with lithium aluminum hydride gave poor yields of the corresponding secondary alcohols because halogen was displaced preferentially. Sodium borohydride was the preferred reducing agent (Table 2). A difluoromethyl **4a** and a chlorodifluoromethyl-β-hydroxyester **4b** were prepared from the keto esters **3** as shown below.



X = H or Cl

(a) RMgX, Et_2O, −78 °C; (b) CH_3CO_2Et, Pr^i_2NLi, Et_2O; (c) $NaBH_4$, EtOH; (d) $Ph_2(Me)SiH$ or $Zn(BH_4)_2$, Et_2O

Enzyme-catalyzed kinetic resolution

The alcohols **2** and **4** were converted to their acetate esters using acetyl chloride. The relative reactivity of enantiomers, the extent of hydrolysis conversion, and the enantiomeric excess (ee) of substrate and product in the enzyme-catalyzed kinetic resolutions have been correlated by Sih and coworkers [23, 24].

A survey of the asymmetric hydrolysis of two acyl derivatives of compound **2a** with a variety of hydrolases is provided in Table 3. In the hydrolysis of the acetate derivative of 1-phenyl-2,2-difluoroethanol, lipase P gave a greater enantiomeric excess than lipase-MY. Increasing the steric bulk of the acyl moiety gave the optically pure material.

As shown in Scheme 1, when the hydrolysis was carried to less than 45% conversion, the alcohol was greatly enriched in either the *R* or the *S* enantiomer. The determination of the absolute configuration is discussed below. The results shown in Table 4 clearly demonstrate that asymmetric hydrolysis is useful for the preparation of the desired difluoromethylated chiral molecules, and that the asymmetric hydrolysis by lipase-MY proceeds smoothly to afford the (*R*)-enantiomer and by lipase P to afford the (*S*)-enantiomer except with 1-phenyl 2,2-difluoroethanol.

Similarly, the preparation of the chlorodifluoromethylated chiral molecules was achieved by asymmetric hydrolysis. The results are summarized in Table 4.

(*S*)-Enantiomers were obtained from the recovered acyl derivatives by hydrolysis using a cellulase and/or by a chemical method (2 mol l^{-1} aq.

TABLE 1

Physical properties of ketones **1**

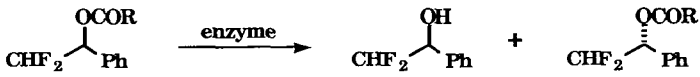
Ketone	Yield (%)	B.p. °C (Torr)	^{19}F NMR δ ppm (J Hz)	^{1}H NMR δ ppm (J Hz)
$PhC(O)CHF_2$ (**1a**)	83	63–66 (10)	41 (d, 44.8)	6.12 (t); 7.40–8.20 (Ar–H)
$PhCH_2C(O)CHF_2$ (**1b**)	77	82–83 (10)	46 (d, 50.0)	3.83 (s); 5.63 (t); 7.10–7.40 (Ar–H)
$PhCH_2CH_2C(O)CHF_2$ (**1c**)	84	100 (10)	47 (d, 50.0)	2.92 (4H, m); 5.55 (6); 7.00–7.40 (Ar–H)
$n\text{-}C_6H_{13}C(O)CHF_2$ (**1d**)	64	71–73 (35)	46 (d, 50.0)	0.70–1.80 (11H, m); 2.70 (2H, m); 5.80 (t)
$n\text{-}C_8H_{17}C(O)CHF_2$ (**1e**)	80	94–96 (22)	47 (d, 52.8)	0.80–1.80 (15H, m); 2.60 (2H, m); 5.60 (t)
$PhC(O)CF_2Cl$ (**1f**)	82	79–82 (9)	−17 (s)	7.30–8.20 (Ar–H)
$PhCH_2C(O)CF_2Cl$ (**1g**)	67	80 (10)	−10 (s)	3.96 (CH_2, s); 7.00–7.40 (Ar–H)
$PhCH_2CH_2C(O)CF_2Cl$ (**1h**)	82	80 (9)	−10 (s)	2.90–3.10 (4H, m); 7.00–7.40 (Ar–H)
$n\text{-}C_6H_{13}C(O)CF_2Cl$ (**1i**)	80	82–83 (37)	−9 (s)	1.10–2.00 (11H, m); 2.72 (2H, t, J=6.9)
$n\text{-}C_8H_{17}C(O)CF_2Cl$ (**1j**)	54	95 (17)	−9 (s)	1.10–2.10 (15H, m); 2.70 (2H, t, J=6.30

TABLE 2

Physical properties of carbinols **2**

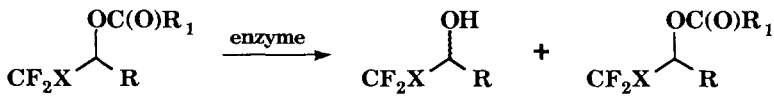
Ketone	Yield (%)	B.p. °C (Torr)	^{19}F NMR δ ppm (J Hz)	^{1}H NMR δ ppm (J Hz)
$PhCH(OH)CHF_2$ (**2a**)	83	93–94 (10)	47 (dd, $J_{F-Hgem}=53$, $J_{F-Hvic}=10$)	2.93 (OH); 4.65 (CH, dt, $J_{H-H}=4.80$; 5.66 (CHF, dt); 7.30 (Ar–H)
$PhCH_2CH(OH)CHF_2$ (**2b**)	78	100–102 (10)	50 (dd, $J_{F-Hgem}=56$, $J_{F-Hvic}=10$)	2.06 (OH); 2.68 (CH_aH_b, dd, $J_{Ha-Hb}=13.8$; $J_{H-H}=4.2$); 2.92 (CH_aH_b, $J_{H-H}=8.1$); 3.80 (CH, dtt); 5.52 (CHF, dt, $J_{H-CHOH}=10$); 7.30 (Ar–H)
$PhCH_2CH_2CH(OH)CHF_2$ (**2c**)	66	116–118 (11)	50 (dd, $J_{F-Hgem}=57$, $J_{F-Hvic}=10$)	1.60–2.20 (2H, m); 2.05 (OH); 2.50–3.10 (2H, m); 3.30–3.90 (CH, m); 5.50 (CHF, dt, $J_{H-H}=4.5$); 7.10–7.40 (Ar–H)
$n\text{-}C_6H_{13}CH(OH)CHF_2$ (**2d**)	91	106–108 (11)	47 (ddd, $J_{Fa-Fb}=265$, $J_{F-Hgem}=53$; $J_{F-Hvic}=10$); 52.2 (ddd, $J_{F-Hgem}=52.4$; $J_{F-H}=10.4$)	0.70–1.80 (13H, m); 2.40 (OH); 3.30–3.90 (CH, m); 5.80 (CHF, dt, $J_{H-H}=4.0$)
$n\text{-}C_8H_{17}CH(OH)CHF_2$ (**2e**)	85	99–100 (11)	48 (ddd, $J_{Fa-Fb}=268$, $J_{F-Hgem}=51$, $J_{F-Hvic}=10$); 52 (ddd, $J_{F-Hgem}=53$, $J_{F-Hvic}=11$)	0.70–1.00 (3H); 1.10–1.70 (14H, m); 2.07 (OH); 3.40–390 (CHOH), m); 5.50 (CHF, dt, $J_{H-CH}=4.5$)
$PhCH(OH)CF_2Cl$ (**2f**)	81	99–100 (11)	−13 (dd, $J_{F-F}=170$); −16 (dd, $J_{F-Hvic}=8$)	3.00 (OH); 4.90 (CHOH, dd); 7.20–7.50 (Ar–H)
$PhCH_2CH(OH)CF_2Cl$ (**2g**)	85	106 (9)	−12 (dd, $J_{F-F}=170$); −15 (dd, $J_{F-Hvic}=8$)	2.69 (CH_aH_b, dd, $J_{Ha-Hb}=15.0$, $J_{H-H}=9.8$); 3.00 (CH_aH_b, dd, $J_{H-H}=3.0$); 3.70–4.10 (CH, m); 7.00–7.30 (Ar–H)
$PhCH_2CH_2CH(OH)CF_2Cl$ (**2h**)	73	106 (8)	−12 (dd, $J_{F-F}=171$); −15 (dd, $J_{F-Hvic}=8$)	1.50–2.20 (2H, m); 2.20–2.50 (OH), 2.50–3.10 (2H, m); 3.60–4.00 (CH, m); 7.00–7.30 (Ar–H)
$n\text{-}C_6H_{13}CH(OH)CF_2Cl$ (**2i**)	90	98–99 (30)	−12 (dd, $J_{F-F}=169$); −15 (dd, $J_{F-Hvic}=8$)	0.80–2.00 (13H, m); 2.20–2.40 (OH); 3.60–4.10 (CHOH, m)
$n\text{-}C_8H_{17}CH(OH)CF_2Cl$ (**2j**)	89	87–89 (12)	−12 (dd, $J_{F-F}=170$); −15 (dd, $J_{F-Hvic}=8$)	0.80–2.10 (17H, m); 2.10 (OH); 3.70–4.10 (CHOH, m)

TABLE 3



R	Enzyme	Hydrolysis conversion (%)	Time (h)	Optical purity (% ee)	Absolute config.	E^a
CH_3	lipase-MY	83	2	30	*S*	2.2
CH_3	lipase PL679	52	10	91	*S*	104
CH_3	lipase P	50	1	>95	*S*	145
i-C_3H_7	lipase-MY	34	1	44	*S*	3.2
i-C_3H_7	lipase P	38	5.5	>95	*S*	370

[a]C. S. Chen, T. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc., 104* (1982) 7294.



Scheme 1.

NaOH/acetone system) (Table 5). The optical purity was sufficiently high to allow the use of these compounds as practical chiral intermediates in fluorine chemistry.

Determination of absolute configuration

We have investigated the absolute configurations of some of the optically active alcohols as shown in Schemes 2 and 3. (+)-Ethyl 4,4-difluoro-3-hydroxybutanoate (**4a**) ($[\alpha]_D^{21}$MeOH, +19.81° (c 0.90), >90% ee) was converted into the tetrahydropyran ether and then reacted with lithium aluminum hydride to give the corresponding alcohol **6**. Oxidation of the alcohol then gave the corresponding aldehyde **7**. A Wittig reaction with n-pentyltriphenyl phosphonium bromide and n-butyllithium in diethyl ether at room temperature gave the unsaturated carbinol **8**, and then catalytic reduction of the carbon–carbon double bond gave (+)-1,1-difluoro-2-nonanol (**9**) ($[\alpha]_D^{21}$MeOH, +19.4° (c 0.78), >84%% ee). The absolute stereochemistry of (*R*)-(+)-1,1-difluoro-2-nonanol (**9**) was confirmed by Taguchi and coworkers [25].

This result shows that (+)-ethyl 4,4-difluoro-3-hydroxy-butanoate (**4c**) is the (*R*)-(+)-enantiomer. Schemes 2 and 3 illustrate the use of compound **7** to prepare a variety of carbinols possessing the difluoromethyl group. Further, chlorodifluoromethylated carbinols were reduced to the corresponding difluoromethylated carbinols with tributyltin hydride as shown in Scheme 3. These results establish the absolute configuration of carbinols possessing difluoromethyl or chlorodifluoromethyl groups produced from asymmetric hydrolysis.

TABLE 4

Optical resolution with lipase

Substrate[a]	Lipase	Hydrolysis[b] conversion (%)	Time (h)	$[\alpha]_D^{21}$ $CHCl_3$ (°)	Optical[c] purity (% ee)	Absolute config.	E[d]
$PhCH(OH)CHF_2$ (**2a**)	lipase-MY	35	2	+3.89 (c 1.03)	30	*S*	2.16
	lipase P	50	1	+21.96 (c 1.16)	>95	*S*	104.1
	lipase P[e]	38	5.5	+22.07 (c 0.89)	>99	*S*	370.7
$PhCH_2CH(OH)CHF_2$ (**2b**)	lipase-MY	30	1	+23.44 (c 0.99)	56		4.45
	lipase P	52	1.5	−26.72 (c 0.93)	64		9.24
$PhCH_2CH_2CH(OH)CHF_2$ (**2c**)	lipase-MY	33	1.5	+17.14 (c 0.95)	47		3.45
	lipase P	55	2.5	−24.50 (c 1.55)	73		18.82
$n\text{-}C_6H_{13}CH(OH)CHF_2$ (**2d**)	lipase-MY	51	4	+6.60 (c 1.07)	33	*R*	2.71
	lipase P	54	1	−1.92 (c 1.03)	10	*S*	1.35
$n\text{-}C_8H_{17}CH(OH)CHF_2$ (**2e**)	lipase-MY	21	5.5	+2.04 (c 1.05)	28	*R*	1.91
$CHF_2CH(OH)CH_2CO_2Et$ (**4a**)	lipase-MY	39	0.4	+19.81 (c 0.90)	>90	*R*	
	lipase P	46	0.3	−7.16 (c 1.08)	32	*S*	2.49
$PhCH(OH)CF_2Cl$ (**2f**)	lipase-MY	25	7.5	−13.82 (c 1.01)	73	*R*	8.11
$PhCH_2CH(OH)CF_2Cl$ (**2g**)	lipase-MY	26	3.5	+44.96 (c 0.94)	64		5.65
$PhCH_2CH_2CH(OH)CF_2Cl$ (**2i**)	lipase-MY	44	5	+22.44 (c 1.06)	88		32.4
$n\text{-}C_8H_{17}CH(OH)CF_2Cl$ (**2j**)	lipase-MY	49	19	+20.45 (c 0.89)	85	*R*	31.0
$CF_2ClCH(OH)CH_2CO_2Et$ (**2b**)	lipase-MY	24	0.7	+18.59 (c 1.03)	64	*R*	5.54

[a]Each structure was determined by means of IR, NMR and mass spectral data. For the new compounds, the microanalyses were in satisfactory agreement with the calculated values (C, H, N; ±0.4).

[b]The hydrolysis conversion was determined by ^{19}F NMR signal intensity.

[c]The optical purity was determined by ^{19}F NMR after conversion of the compound to its diastereomeric ester by optically active MTPA.

[d]C. S. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc.*, *104* (1982) 7294.

[e]$PhCH(OCOC_3H_7)CHF_2$ was used.

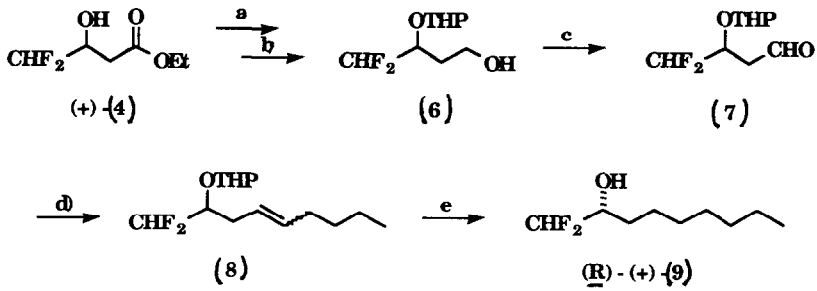
TABLE 5

Preparation of (*S*)-enantiomers[a]

Substrate	Yield (%)	Method[b]	Time (h)	$[\alpha]_D^{21}$ $CHCl_3$ (°)	Optical purity (% ee)
$CHF_2CH(OH)CH_2CO_2Et$ (**4a**)	87	B	1.5	−20.47 (c 1.16)	93
$PhCH_2CH(OH)CF_2Cl$ (**2g**)	96	A	3	−61.11 (c 1.34)	87
$PhCH_2CH_2CH(OH)CF_2Cl$ (**2h**)	89	B	6.5	−37.58 (c 1.09)	>95
$n\text{-}C_6H_{13}CH(OH)CF_2Cl$ (**2i**)	86	B	4	−24.56 (c 1.37)	>95
$n\text{-}C_8H_{17}CH(OH)CF_2Cl$ (**2j**)	89	B	5	−22.62 (c 0.73)	94
$CF_2ClCH(OH)CH_2CO_2Et$ (**4b**)	94	B	2	−25.87 (c 1.34)	>90

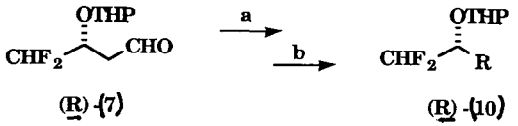
[a](*S*)-Acetate recovered from hydrolysis with lipase-MY (hydrolysis conversion 55–60%) was used.

[b]Method A; aqueous NaOH/acetone; method B; collulase.

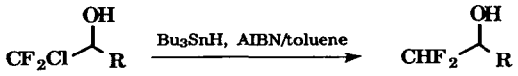


(a) Dihydropyran, H^+; (b) $LiAlH_4$, Et_2O; (c) Swern oxidation; (d) Ph_3P, $C_5H_{11}Br$, Bu^nLi, Et_2O; (e) H_2, Pd–C, CH_3OH

Scheme 2.



(a) Ph_3P, $C_nH_{2n+1}Br$, Bu^nLi, Et_2O; (b) H_2, Pd–C, CH_3OH



Scheme 3.

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