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BIOTRANSFORMATIONS OF FLUORINATED SULPHENYL AND SULPHONYL COMPOUNDS

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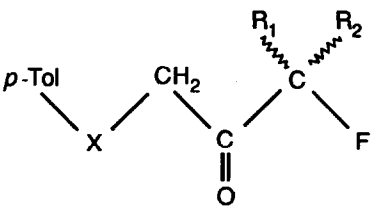
Abstract - optically active sulphenyl and sulphonyl fluorohydrins were obtained by reduction of ketones with baker's yeast or by enzymatic resolution of their racemic esters using *Candida cylindracea* lipase. Crystallization of partially optically active fluorohydrins gave enantiomerically pure forms. Enantioselectivity of the enzymatic reactions is affected by steric requirements of the substituents.

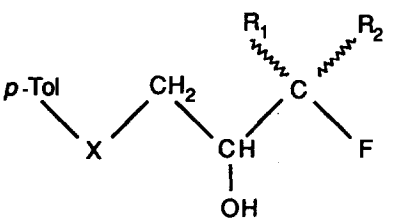
Introduction

Recently, α-fluoro α'-sulphenyl, sulphinyl and sulphonyl ketones **1-3** and related fluorohydrins **4-6** were revealed to be chiral fluorinated synthons. The removal of the auxiliary sulphur group afforded several oxygenated fluoro-organic compounds,[1,2] α-hydroxy-β-fluoro-alcohols, aldehydes, esters, epoxides and fluoro-sugars.[3]

These derivatives were obtained in enantiomerically and diastereomerically pure forms from optically pure α-fluoro-α'-sulphinyl ketones **2** derived from chiral sulphoxides and commercially-available α-fluoro-carboxylic acids.[4]



(1-3)



(4-6)

1,4 X=S **a)** R_1=H, R_2=H **d)** R_1=Ph, R_2=H

2,5 X=SO **b)** R_1=CH_3, R_2=H **e)** R_1=CH_3, R_2=Ph

3,6 $X=SO_2$ **c)** R_1=$CH_2CH=CH_2$, R_2=H

There are relatively few studies on the stereoselective transformation of monofluorinated materials.[5,6] During recent years, biochemical reactions performed by microorganisms or catalyzed by enzymes have been widely employed for the preparation of chiral compounds.[7]

With a view to developing methodologies that would assure enantio and diastereoselectivity in the synthesis of fluoro-organic compounds, we report here the results of biotransformation of fluorinated compounds **1,3** and **4,6**.

Asymmetric Induction with Baker's Yeast

Baker's yeast is the most widely used enzymatic system for the synthesis of chiral alcohols from ketones.[7] Several examples of successful microbial reduction of ketones have been reported, but only few monofluoro compounds have been reduced by baker's yeast to the corresponding hydroxy derivatives.[8]

We investigated yeast mediated reduction of racemic α-fluoro-α'-sulphenyl ketones **1b-e** and racemic α-fluoro-α'-sulphonyl ketones **3b-e** and the influence of the structural requirements of the substituents (R_1) at the fluorinated carbon atom on the enantioselectivity of these enzymatic reductions. In order to compare the results,[9] we also carried out the reduction of prochiral ketones **1a** and **3a** already reported in the literature.[8] The racemic ketones **1b-d** were synthesized through deoxygenation of the corresponding sulphinyl derivatives **2b-d**[2,3,4] following the procedure already described[2,10] for the synthesis of **1a,e**. The α-fluoro-α'-sulphonyl ketones **3d,e** were obtained through acylation of methyl 4-methylphenyl sulphone with the proper racemic 2-fluorocarboxylic ester, as described for the synthesis of **3a**.[8] Ketones **3b** and **3c** were synthesized, respectively, through oxidation of the corresponding sulphinyl analogue **2b**[4] and allylation of the sulphonyl propanone **3a**, following the general procedure already described.[4,10]

Compounds **1a-e** and **3a-e** were reduced with actively fermenting yeast according to the procedure described.[11] In a typical experiment, an ethanol or dimethylsuphoxide solution (1 ml) of the carbonyl compound (1.5mmol) was added to a suspension of fermenting baker's yeast (Fala Yeast, 5g) and glucose (2.7g) in water (45ml). When the g.l.c. or t.l.c. analysis showed >90% reduction of the ketone, the fermentation mixture was extracted with ethyl ether. The organic extracts evaporated gave the crude alcohols in good chemical yields (70-80%).

Under these conditions, the more sterically hindered ketones, 3-fluoro-3-phenyl-1-[(4-methylphenyl)sulphenyl]-2-butanone (**1e**) and 3-fluoro-3-phenyl-1-[(4-methylphenyl)sulphonyl] -2-butanone (**3e**), were not reduced.

Attempts were made to reduce the substrates **1a-e** and **3a-e** under different conditions but it was found that variations in the amount of sugar added[11] or in the concentration of reagent were not advantageous.[12]

The results of baker's yeast reduction are reported in Table I. Compounds **1a-d** and **3a-d** reduced readily to give the corresponding fluorohydrins, **4a-d** and **6a-d**, in medium to high enantiomeric excess (e.e. 10 - 85%). All solid fluorohydrins obtained in $\geq$ 60% enantiomeric excess gave the pure enantiomer in 50-60% yield by simple crystallization from ethyl ether/pentane.

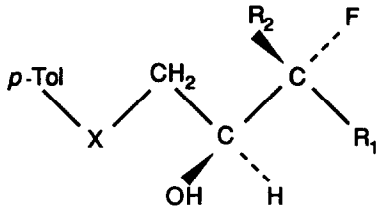
Compounds **4b-d** and **6b-d** were produced as a mixture of *syn* and *anti* diastereomers. Except for **6d**, they were resolved in diastereomerically pure form by column chromatography on silica gel. The optically active fluorohydrins **4a**, **6a** and both *syn* and *anti* sulphenyl products **4b-d** thus isolated showed identical physical and spectroscopical properties with those reported in the literature.[3,8,13]

Table I: Asymmetric reductions of ketones **1a-d** and **3a-d** by baker's yeast at 25°C to the fluorohydrins **4a-d** and **6a-d**.

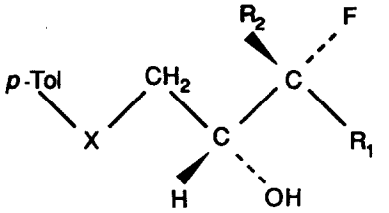
Product[a]	reaction time h. (days)	diast. ratio[b] *anti/syn*	$[\alpha]_D$[c]	e.e.[d]	abs. conf.[e]
4a	4	-	+30.8	>85	(S)
6a	4	-	+9.7	>80	(S)
4b	12	40/60	+14.4 *anti*	20	(2S,3S)
			+22.6 *syn*	50	(2S,3R)
6b	12	45/55	+8.9 *anti*	32	(2S,3S)
			+2.6 *syn*	21	(2S,3R)
4c	12	40/60	-19.2 *anti*	46	(2R,3R)
			-6.0 *syn*	30	(2R,3S)
6c	6	40/60	-4.1 *anti*	18	(2R,3R)
			-1.3 *syn*	8	(2R,3S)
4d	(6)	65/35	-52.5 *anti*	74	(2R,3R)
			-2.6 *syn*	76	(2R,3S)
6d	(6)	40/60	--- *anti*	≥80[f]	(2R,3R)[f]
			--- *syn*	≥80[f]	(2R,3S)[f]

a) The structures are confirmed by spectral data. For the new compounds **6b-d** microanalyses were in agreement with the calculated values; b) *anti/syn* ratio valued on the reaction mixture by ^{1}H-NMR spectroscopy or by gas-chromatography; c) optical activities of diastereomerically pure fluorohydrins measured in $CHCl_3$; d) enantiomeric excesses determined by ^{1}H-NMR analysis of the (R)-(-)-α-phenylpropionic esters and/or by ^{1}H-NMR spectra of fluorohydrins recorded in the presence of (+)-Eu(hfc)$_3$; e) absolute configuration of the exceeding enantiomer; f) e.e. and absolute configuration determined by ^{1}H-NMR analysis after conversion to the (S)-(+)-α-naphthylpropionic esters.

The *syn* and *anti* sulphonyl fluorohydrins **6b,c** were compared with authentic samples obtained through oxidation of the corresponding enantiomerically pure sulphinyl analogues **5b,c**.[2,3]



anti (erythro)



syn (threo)

The optical purity of each isomer isolated from enzymatic reactions was determined by comparison of the specific rotation with that of the pure enantiomer obtained as described before and/or by ^{1}H-NMR signal intensities after conversion of the hydroxy compound to its diastereomeric esters with optically pure (R)-(-)-α-phenylpropionic acid[13] and/or by ^{1}H-NMR spectra recorded in the presence of the chiral shift reagent, d-Eu(hfc)$_3$ [hfc=heptafluoropropyl-hydroxymethylene-(+)-camphorato].

In spite of repeated attempts, we were unable to separate the two diastereomeric fluorohydrins **6d**. Nevertheless, the enantiomeric excess and the absolute configuration of each fluorohydrin were assigned by ^{1}H-NMR spectroscopy after conversion of the crude reaction mixture to the diastereomeric esters with optically pure (S)-(+)-α-naphthylpropionic acid,[14] following the known procedure.[13] The ^{1}H-NMR spectrum of the esters was compared with the spectra of the esters of each *syn* and *anti* fluorohydrin **6d** obtained by oxidation of the corresponding diastereomerically pure and partially optically active *syn* and *anti* sulphinyl derivatives **5d**.[2]

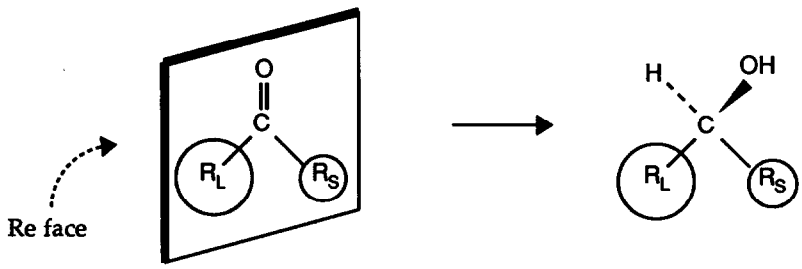
Further examination of the results of Table I shows that yeast reductions proceed with low diastereoselection, *syn* and *anti* fluorohydrins being obtained in nearly equivalent amounts. Moreover, enantioselectivity seems to be strongly affected by the substituents at the carbonyl group: the yeast reduction of unsubstituted ketones **1a** and **3a** occurs with high degree of enantioselection (e.e. ≥ 80%), whereas enantioselectivity drops significantly (e.e. 10-50%) for the reduction of compounds **1b,c** and **3b,c** containing a methyl or an allyl substituent at the fluorinated carbon atom (R_1= CH_3; CH_2-CH=CH_2). Reduction of the ketones **1d** and **3d** (R_1= Ph) occurred much more slowly, but in both cases the hydroxy compounds **4d** and **6d** were obtained with high enantiomeric excess (≥ 80%).

Moreover, the absolute stereochemistry of the reaction shows that yeast reductions afforded alcohols **4a,b** and **6a,b** (R_1= H; CH_3), whose predominant enantiomers have (S) configuration at the induced chiral center, and products **4c,d** and **6c,d** (R_1= CH_2-CH=CH_2; Ph), which have the opposite (R) configuration.

Prelog's rule is widely used to predict the stereochemical course of enzymatic reduction,[7] *i.e.* depending upon the relative size of the groups R_L (larger) and R_S (smaller), which is recognized by the oxidoreductase(s) in the yeast, reduction occurs from Re face.

The observed outcome of the yeast reductions of fluoro ketones **1a-d** and **3a-d** is in agreement with this rule if we assume that (in terms of steric hindrance) CH(F)C_6H_5 > CH(F)CH_2CH=CH_2 >

$CH_2XC_6H_4CH_3$ > $CH(F)CH_3$ > CH_2F, (X= S, SO_2). Furthermore, it seems that, when there is little difference between the relative sizes of the two substituents at the carbonyl group, *i.e.* $CH(F)CH_2CH{=}CH_2$ versus *p*-CH_3-C_6H_4-SO_2-CH_2, the enzyme reducing system does not readily discriminate between the two diastereofaces of ketones.



Alternatively, these results might be due to the action of more than one oxidoreductase contained in the yeast which produce alcohols of opposite configuration at different rates.[15]

Lipase-Catalyzed Resolution of Racemic Fluorohydrins 4a-c,e

For some compounds, and particularly when yeast reduction failed, we attempted resolution of the racemic fluorohydrins using hydrolytic enzymes as lipases.[16,17] It is well known[18] that lipases catalyze the enantioselective hydrolysis of a broad structural range of racemic esters.

Racemic hydroxy compounds **4a-c,e**, obtained by chemical reduction of ketones **1a-c,e** with sodium borohydride in methanol, were converted into the corresponding butyric esters. The latter were subjected to hydrolysis using *Candida cylindracea* lipase and porcine pancreatic lipase (PPL).

The reactions were carried out at 25 °C in a phosphate buffer at pH 7.5 and halted at 50% conversion. Of the hydrolases tested, only *Candida cylindracea* lipase exhibited satisfactory results. Both the unreacted esters and the *syn* and *anti* fluorohydrins were recovered in optically active forms by extraction from the aqueous phase and by separation on column chromatography, as indicated in the experimental section.

The enantiomeric excesses of the optically active hydrolyzed fluorohydrins were determined as described before. The enantiomeric excess of both *syn* and *anti* unreacted **4e** butyric esters (38%) was determined after alkaline hydrolysis to the corresponding alcohols. In Table II the results obtained by hydrolysis of the butyrates of compounds **4a-c,e** with *Candida cylindracea* lipase are summarized.

The hydrolytic enzyme afforded optically active alcohols **4a-c** and **4e** in low (5-20%) to moderate (60%) enantiomeric excesses, respectively. Nevertheless, both the hydrolyzed solid *syn* and *anti* fluorohydrins **4e** (e.e. 60%) were obtained in enantiomerically pure forms by crystallization from ethyl ether/ligroine (60% yield).

Table II: Enzymatic hydrolysis of the racemic esters of fluorohydrins **4a-c,e**.

Fluorohydrins[a]	% conversion	$[\alpha]_D$[b]	e.e.[c]	abs. conf.[d]
±4a	50	+3.1	8	(S)
±4b	50	+2.4 *anti*	5	(2S,3S)
		+7.3 *syn*	11	(2S,3R)
±4c	50	+2.1 *anti*	5	(2S,3S)
		+4.4 *syn*	25	(2S,3R)
±4e	50	+24.4 *anti*	57	(2S,3R)
		+11.7 *syn*	58	(2S,3S)

a) The butyric esters of racemic fluorohydrins were used as substrates; b) optical activities of diastereomerically pure fluorohydrins measured in $CHCl_3$; c) enantiomeric excesses determined by ^{1}H-NMR analysis of the (R)-(-)-α-phenylpropionic esters and/or by ^{1}H-NMR spectra of fluorohydrins recorded in the presence of (+)-Eu(hfc)$_3$; d) absolute configuration of the exceeding enantiomers of the hydrolized fluorohydrins **4a-c,e**.

It is worth noting that the highest optical purity was obtained for the more sterically hindered compound **4e** (the corresponding ketone **1e** was not reduced by baker's yeast).

Candida cylindracea lipase showed preferential activity on the derivatives having (S)-configuration at the carbinylic center, *i.e.* in all cases we obtained the enantiomerically enriched unreacted esters having (R) configuration at the carbinylic center and the predominant enantiomer of the hydrolyzed fluorohydrins (S)-configurated at the same carbon atom.

No attempt was made to optimize conditions; improvements may be possible by variation of the enzyme system and/or esters moiety.[19]

Given the broader substrate specificity of the lipases, when active, and the possibility of obtaining both the enantiomers, these systems represent a convenient method of synthesizing optically active fluorinated compounds.

Finally, we investigated the possibility of obtaining optically active fluorohydrins **4,6** through stereoselective transformation catalyzed by yeast or lipases and their steric requirements. This microbial approach offers an alternative easy synthetic route to chiral monofluorinated synthons.

Experimental

Optical rotations were measured on a Perkin-Elmer 241 polarimeter in $CHCl_3$ solutions. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian XL-200 spectrometer. Chemical shifts are reported in δ values from TMS as internal standard (s=singlet, d=doublet, dd=double doublet, dt=double triplet, dq=double quartet, t=triplet, q=quartet and m=multiplet). Elemental analyses (C, H, S) for novel derivatives, performed with a Carlo Erba Elemental Analiser model 1106, were within 0.4% of calculated values. G.l.c. analyses were performed on a Hewlett-Packard

5890-A gas-chromatograph (capillary column HP1 Methyl Silicone Gum 5m x 0.55mm x 2.65μm coated).

(*R*)-(-)-α-phenylpropionic acid, $[\alpha]_D$ -68 ($CHCl_3$), was purchased from Aldrich; (*S*)-(+)-α-naphthylpropionic acid, $[\alpha]_D$ +115 (absolute EtOH), was obtained as described in ref. 14. Fresh baker's yeast (*FALA*, Strasbourg) and commercially available glucose were used for the reactions. The porcine pancreatic lipase and lipase from *Candida cylindracea* were purchased from Sigma. Ketones **1a**,[10] **3a**[8] and **1e**[2] were synthesized as already described.

Sulphenyl ketones **1b-d** (yield ≥ 90%) were obtained through deoxygenation of the sulphinyl analogues[2,3,4] **2b-d**, as described for **1a,e**.[2,10]

3-Fluoro-1-[(4-methylphenyl)sulphenyl]-2-butanone **(1b)**: ^{1}H-NMR: 1.52 (dd, 3H, $C\underline{H}_3CF$), 2.37 (s, 3H, $C\underline{H}_3Ar$), 3.88 (d, 2H, $C\underline{H}_2S$), 5.10 (dq, 1H, $C\underline{H}F$), 7.1-7.4 (m, 4H, Ar$\underline{H}$).

3-Fluoro-1-[(4-methylphenyl)sulphenyl]-5-hexen-2-one **(1c)**: ^{1}H-NMR: 2.33 (s, 3H, $C\underline{H}_3Ar$), 2.58 (m, 2H, $C\underline{H}_2CF$), 3.80-3.83 (m, 2H, $C\underline{H}_2S$), 5.00 (m, 1H, $C\underline{H}F$), 5.15 (m, 2H, $CH=C\underline{H}_2$), 5.70 (m, 1H, $C\underline{H}=CH_2$), 7.1-7.4 (m, 4H, Ar$\underline{H}$).

3-Fluoro-1-[(4-methylphenyl)sulphenyl]-3-phenyl-propanone **(1d)**: ^{1}H-NMR: 2.33 (s, 3H, $C\underline{H}_3Ar$), 3.80 (d, 2H, $C\underline{H}_2S$), 5.98 (d, 1H, $C\underline{H}F$), 7.0-7.3 (m, 4H, Ar$\underline{H}$), 7.47 (m, 5H, Ar$\underline{H}$).

Sulphonyl ketones **3b-e** were obtained as follow:

3-Fluoro-1-[(4-methylphenyl)sulphonyl]-2-butanone **(3b)** was obtained (93% yield) by oxidation of the sulphinyl analogue **2b**[4] with *m*-chloroperoxybenzoic acid in $CHCl_3$ at 0°C. ^{1}H-NMR: 1.50 (dd, 3H, $C\underline{H}_3F$), 2.51 (s, 3H, $C\underline{H}_3Ar$), 4.39-4.42 (m, 2H, $C\underline{H}_2S$), 5.00 (dq, 1H, $C\underline{H}F$), 7.4-7.9 (m, 4H, Ar$\underline{H}$).

3-Fluoro-1-[(4-methylphenyl)sulphonyl]-5-hexen-2-one **(3c)**. Following the procedure already described,[10] dilithiation of **3a** with lithium diisopropylamide followed by reaction with allyl bromide (Aldrich) afforded **3c**: (yield 44%) ^{1}H-NMR: 2.47 (s, 3H, $C\underline{H}_3Ar$), 2.6 (m, 2H, $C\underline{H}_2CF$), 4.3 (d, 1H, $C\underline{H}_2S$), 4.5 (d, 1H, $C\underline{H}_2S$), 4.92 (m, 1H, $C\underline{H}F$), 5.17 (m, 2H, $CH=C\underline{H}_2$), 5.7 (m, 1H, $C\underline{H}=CH_2$), 7.4-7.8 (m, 4H, Ar$\underline{H}$). The oxidation of (3S, R_S)-**2c**, (e.e. > 95%), with *m*-chloroperoxybenzoic acid afforded the (S)-(-)-**3c**, $[\alpha]_D$ -62.0 (c 1.0).

3-Fluoro-3-phenyl-1-[(4-methylphenyl)sulphonyl]-propanone **(3d)**.

Following the procedure already described for **3a**,[8] acylation of the lithium derivative of the methyl 4-methylphenyl sulphone (Alpha Ventron) by methyl 2-fluoro-2-phenylacetate afforded **3d** in 93% yield. ^{1}H-NMR: 2.5 (s,3H, $C\underline{H}_3Ar$), 4.31 (d, 2H, $C\underline{H}_2S$), 6.0 (d, 1H, $C\underline{H}F$), 7.3-7.9 (m, 9H, Ar$\underline{H}$).

3-Fluoro-3-phenyl-1-[(4-methylphenyl)sulphonyl]-2-butanone **(3e)**.

Likewise,[8] acylation of the lithium derivative of the methyl 4-methylphenyl sulphone (Alpha Ventron) with methyl 2-fluoro-2-phenylpropionate gave **3e** in 95% yield. ^{1}H-NMR: 1.78 (d, 3H, $C\underline{H}_3$), 2.49 (s, 3H, $C\underline{H}_3Ar$), 4.26 (dd, 1H, $C\underline{H}_2S$), 4.60 (dd, 1H, $C\underline{H}_2S$), 7.3-7.8 (m, 9H, Ar$\underline{H}$).

General procedure for asymmetric reductions by yeast.

Fresh commercial baker's yeast (Fala, 5g) and glucose (2.7g) were suspended in tap water (45ml) and stirred at room temperature until the mixture began to bubble vigorously (30-60'); a solution of the ketone (1.5mmol) in ethanol or dimethylsulphoxide (1ml) was then added.

Occasionally, aliquots were withdrawn, extracted with ethyl ether and analyzed on g.l.c.. In the case of a slow rate of reduction, an equal amount of fermenting yeast was added after 48h. When more than 90% conversion was obtained, the suspension was saturated with NaCl, extracted with ethyl ether and, after drying, the solvent was evaporated. The diastereomeric *anti/syn* ratio of the crude fluorohydrins **4-6** was determined by g.l.c. or ^{1}H-NMR in C_6D_6. The two diastereomeric derivatives were separated (except **6d**) by column chromatography on silica gel (petroleum ether/ethyl ether as eluant) and characterized by ^{1}H-NMR spectroscopy; all compounds showed the expected spectroscopical properties.

1-Fluoro-3-[(4-methylphenyl)sulphenyl]-2-propanol **(4a)**:[8] yield 62%; (S)-(+)-**4a**, $[\alpha]_D$ +30.8 (c 1.0) e.e. > 85%.

3-Fluoro-1-[(4-methylphenyl)sulphenyl]-2-butanol **(4b)**:[13] yield 83%; (2S,3S)-(+)-**4b**, $[\alpha]_D$ +14.4 (c 1.0) e.e. 20%. (2S,3R)-(+)-**4b**, $[\alpha]_D$ +22.6 (c 1.0) e.e. 50%

3-Fluoro-1-[(4-methylphenyl)sulphenyl]-5-hexen-2-ol **(4c)**:[3] yield 71%; (2R,3R)-(-)-**4c**, $[\alpha]_D$ -19.2 (c 0.8) e.e. 46%, ^{1}H-NMR: 2.33 (s, 3H, C$\underline{H}_3$Ar), 2.47 (m, 2H, C$\underline{H}_2$-CH=CH$_2$), 2.9 (m, 1H, C$\underline{H}_2$S), 3.3 (m, 1H, C$\underline{H}_2$S), 3.7 (m, 1H, C$\underline{H}$OH), 4.45 (m, 1H, C$\underline{H}$F), 5.14 (m, 2H, CH=C$\underline{H}_2$), 5.82 (m, 1H, C$\underline{H}$=CH$_2$), 7.1-7.3 (m, 4H, Ar$\underline{H}$). (2R,3S)-(-)-**4c**, $[\alpha]_D$ -6.0 (c 0.8) e.e. 30%, ^{1}H-NMR: 2.33 (s, 3H, C$\underline{H}_3$Ar), 2.5 (m, 2H, C$\underline{H}_2$-CH=CH$_2$), 3.04 (m, 1H, C$\underline{H}_2$S), 3.1 (m, 1H, C$\underline{H}_2$S), 3.65 (m, 1H, C$\underline{H}$OH), 4.6 (m, 1H, C$\underline{H}$F), 5.14 (m, 2H, CH=C$\underline{H}_2$), 5.8 (m, 1H, CH$_2$=C$\underline{H}$), 7.1 - 7.29 (m, 4H, Ar$\underline{H}$)

3-Fluoro-3-phenyl-1-[(4-methylphenyl)sulphenyl]-2-propanol **(4d)**:[13] yield 60%; (2R,3R)-(-)-**4d**, $[\alpha]_D$ -52.5 (c 0.9) e.e. 74%. (2R,3S)-(-)-**4d**, $[\alpha]_D$ -2.6 (c 0.9) e.e. 76%.

1-Fluoro-3-[(4-methylphenyl)sulphonyl]-2-propanol **(6a)**:[8] yield 78%; (S)-(+)-**6a**, $[\alpha]_D$ +9.7 (c 1.0) e.e. > 80%.

3-Fluoro-1-[(4-methylphenyl)sulphonyl]-2-butanol **(6b)**: yield 77%; (2S,3S)-(+)-**6b**, $[\alpha]_D$ +8.9 (c 2.0) e.e. 32%, ^{1}H-NMR: 1.36 (dd, 3H, C$\underline{H}_3$), 2.5 (s, 3H, C$\underline{H}_3$Ar), 3.23 (m, 1H, C$\underline{H}_2$S), 3.4 (m, 1H, C$\underline{H}_2$S), 4.1 (m, 1H, C$\underline{H}$OH), 4.52 (m, 1H, C$\underline{H}$F), 7.3-7.8 (m, 4H, Ar$\underline{H}$). (2S,3R)-(+)-**6b**, $[\alpha]_D$ +2.6 (c 2.0) e.e. 21%, ^{1}H-NMR: 1.37 (dd, 3H, C$\underline{H}_3$), 2.5 (s, 3H, C$\underline{H}_3$Ar), 3.31 (m, 1H, C$\underline{H}_2$S), 3.41 (m, 1H, C$\underline{H}_2$S), 4.2 (m, 1H, C$\underline{H}$OH), 7.4-7.9 (m, 4H, Ar$\underline{H}$). Oxidation of 3-fluoro-1-[(R)-(4-methylphenyl)sulphinyl]-2-butanol (2S,3S)-(+)-**(5b)**[2] **e.e.** > 95% with potassium permanganate and tetrabutylammonium tetrafluoroborate, according to the procedure described for **6a**,[8] afforded (2S,3S)-(+)-**6b**, $[\alpha]_D$ +28.0 (c 1.05) in 81% yield. Similarly, (2S,3R,R$_S$)-(+)-**5b**[2] e.e. > 95% afforded (2S,3R)-(+)-**6b**, $[\alpha]_D$ +12.0 (c 1.0) in 80% yield.

3-Fluoro-1-[(4-methylphenyl)sulphonyl]-5-hexen-2-ol **(6c)**: yield 77%; (2R,3R)-(-)-**6c**, $[\alpha]_D$ -4.1 (c 3.1) e.e. 18%,^{1}H-NMR: 2.46 (s, 3H, C$\underline{H}_3$Ar), 2.47 (m, 2H, C$\underline{H}_2$-CH=CH$_2$), 3.27 (m, 1H, C$\underline{H}_2$S), 3.47 (m, 1H, C$\underline{H}_2$S), 4.14 (m, 1H, C$\underline{H}$OH), 4.4 (m, 1H, C$\underline{H}$F), 5.1 (m, 2H, CH=C$\underline{H}_2$), 5.8 (m, 1H, C$\underline{H}$=CH$_2$), 7.34-7.8 (m, 4H, Ar$\underline{H}$). (2R,3S)-(-)-**6c**, $[\alpha]_D$ -1.3 (c 3.0) e.e. 8%, ^{1}H-NMR: 2.46 (s, 3H, C$\underline{H}_3$Ar), 2.46 (m, 2H, C$\underline{H}_2$-CH=CH$_2$), 3.3 (m, 1H, C$\underline{H}_2$S), 3.41 (m, 1H, C$\underline{H}_2$S), 4.27 (m, 1H, C$\underline{H}$OH), 4.45 (m, 1H, C$\underline{H}$F), 5.15 (m, 2H, C$\underline{H}_2$=CH), 5.78 (m, 1H, C$\underline{H}$=CH$_2$), 7.4-7.8 (m, 4H, Ar$\underline{H}$). Optically pure *syn* and *anti* **6c** were obtained by oxidation of **5c**[3] (600mg, 2.34mmol) with *t*-butyl-hydroperoxide (315 mg, 3.51 mmol) sodium acetate (288mg, 3.51mmol) and vanadyl acetylacetonate (50mg) in benzene (70ml). After refluxing the reaction mixture for 1h, water (20 ml) and aqueous hydrochloric acid (10 ml) were added. The aqueous layer was extracted with chloroform, the collected organic

phases were dried with sodium sulphate, evaporated under reduced pressure and flash chromatographed (*n*-hexane/ethyl acetate 7:3). (2S,3S,R_S)-(+)-**5c**[3] e.e. > 95% gave the pure sulphonyl fluorohydrin (2S,3S)-(+)-**6c** in 71% yield, $[\alpha]_D$ +22.8 (c 1.7). (2S,3R,R_S)-(+)-**5c**[3] e.e. > 95% afforded the sulphonyl alcohol (2S,3R)-(+)-**6c** in 67% yield, $[\alpha]_D$ +17.2 (c 2.1).

Analysis of the mixture of diastereomeric fluorohydrins 3-fluoro-3-phenyl-1-[(4-methylphenyl)-sulphonyl]-2-propanol (**6d**).

The enantiomeric excess and absolute configuration of *syn* and *anti* fluorohydrins **6d**, obtained from yeast reduction as an unresolvable mixture (yield 71%), were determined as follows: compounds **6d** were converted[13] into the corresponding esters with optically pure (S)-(+)-α-naphthylpropionic acid.[14] The composition of the reaction mixture was determined by ^{1}H-NMR using as key signals those for the CH_3 substituent of the aromatic group, which appears as a singlet at different chemical shifts for each diastereomer. Assignment of the signals to each diastereomer was based on a comparison of its spectrum with those of the same compounds obtained by oxidation[8] of the corresponding sulphinyl derivatives **5d**[2] having known absolute configuration and optical purity. From the relative intensities, in the case of the *anti* fluorohydrin **6d**, we observe the ^{1}H-NMR naphthylpropionic ester signal of the major enantiomer (2R,3R) at δ 2.37 and that of the minor enantiomer (2S,3S) at δ 2.48. In the case of the *syn* fluorohydrin **6d**, the naphthylpropionic ester of the major enantiomer (2R,3S) shows the ^{1}H-NMR signal at δ 2.30 and that of the minor enantiomer (2S,3R) at δ 2.48. Since the ester frequencies of both diastereomeric minor enantiomers overlap, and as the ratio of the three signal intensities observed is *ca* 90 : 90 : 10, we deduce that enantiomeric excess must be at least ≥ 80%.

General procedure for lipase catalyzed hydrolysis of butyric esters.

Butyric esters were synthesized according to the standard procedure (butyric acid, dicyclohexylcarbodiimide, 4-dimethylamino pyridine, methylene chloride)[13] from the racemic fluorohydrins obtained by $NaBH_4$ reduction of ketones **4,6** in methanol solution.

Enzymatic resolution: the butyric esters (*syn* and *anti* mixture, 1mmol) were suspended in phosphate buffer (pH 7.5; 0.1M, 75 ml) in an Erlenmayer flask, equipped with magnetic stirrer. The crude lipase from *Candida cylindracea* (350 mg) was added without purification. When hydrolysis reached 50% conversion (g.l.c.) the slurry was extracted with diethyl ether; the organic phase was washed with water and dried over anhydrous magnesium sulphate. After removal of the solvent, column chromatography on silica gel (petroleum ether/ethyl ether as eluant) afforded the unreacted ester, and the separated optically active *syn* and *anti* fluorohydrins.

3-Fluoro-3-phenyl-1-[(4-methylphenyl)sulphenyl]-2-butanol (**4e**).[13] Conversion reached 50% after two days. The hydrolyzed fluorohydrins showed *anti* (2S,3R)-(+)-**4e**, $[\alpha]_D$ +24.4 (c 1.0) e.e. 57% and *syn* (2S,3S)-(+)-**4e**, $[\alpha]_D$ +11.7 (c 1.0) e.e. 58%. From the unreacted ester (*syn*/*anti* mixture) we obtained fluorohydrin (2R,3S)-(-)-**4e**, $[\alpha]_D$ -12.6 (c 1.0) e.e. 38% and fluorohydrin (2R,3R)-(-)-**4e**, $[\alpha]_D$ -8.2 (c 1.0) e.e. 38% by hydrolysis in KOH and methanol.

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References and Notes

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