Homochiral Fluoro-organic Compounds. Synthesis of the Two Enantiomers of (*Z*)-3-Fluoro-4-phenyl-1-(*p*-tolylsulphonyl)but-3-en-2-ol through Microbial Reduction

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The reduction of (*Z*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphonyl)but-3-en-2-one with growing cultures of *Geotrichum candidum* and *Phanerochaete chrysosporium* afforded (*S*)- and (*R*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphonyl)but-3-en-2-ol in enantiomerically pure form.

A widely used approach to the synthesis of enantiomerically pure drugs and natural products is based on the use of small and easily available compounds from a pool of chirality.[1] The increasing need for optically pure regio- and stereo-selectively fluorinated compounds in both academic and industrial laboratories has made their synthesis an important focus of current research.[2] Accordingly, there is a considerable interest in highly efficient routes to single enantiomers of fluorinated chirons since no fluoro compounds are available in the pool of chirality. Asymmetric microbial transformations of prochiral fluorine containing compounds is one of the strategies that are currently being pursued.[3] The (+)-ethyl 4,4,4-trifluoro-3-hydroxybutanoate[4] and the (−)-ethyl hydrogen 2-fluoro-2-methylmalonate[5] have been obtained through microbiological transformations. These four-carbon fluorinated chirons have been used in numerous asymmetric syntheses.

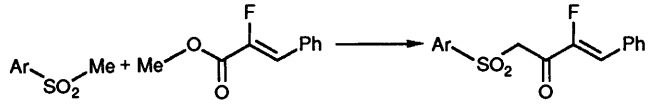
The production of (*S*)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol and (*S*)-1-fluoro-3-(*p*-tolylsulphonyl)propan-2-ol in high enantiomeric purity by reduction of the corresponding ketones with Baker's yeast or growing cultures of *Rhizoctonia solani* IPV A-19 and *Aspergillus niger* IPV 238 has recently been reported by us.[6] The synthetic usefulness of these three-carbon fluorinated chirons in which C-1, C-2, and C-3 are substituted with fluorine, oxygen, and sulphur respectively, has already been described.[7]

We thought it could be interesting to make available a *five-carbon* fluorinated chiron carrying two different functionalities on the terminal carbons. (*Z*)-3-Fluoro-4-phenyl-1-(*p*-tolylsulphonyl)but-3-en-2-one (**1**) was the substrate chosen since it is capable of giving a five-carbon fluorinated chiron by reduction to a saturated alcohol followed by oxidative cleavage of the phenyl ring by known procedures.[8] The microbial reduction of the α,β-unsaturated-α-fluoro ketone moiety of this compound is now described, together with an alternative asymmetric synthesis of all the products formed during the microbial manipulations and the assignment of their absolute and relative configurations.

Results and Discussion

The butenone (**1**) was obtained in nearly quantitative yield by acylating the lithium derivative of methyl *p*-tolyl sulphone (**5**) [lithium di-isopropylamide (LDA) (1.1 mol equiv.) in tetrahydrofuran (THF)] with methyl (*Z*)-2-fluoro-3-phenylpropenoate (**6**).

Microbial Transformations.—The transformation of the fluorinated α,β-unsaturated ketone (**1**) into the α-fluoro alcohol (**4**)



(**5**) (**6**) (**1**)

(Scheme 1) requires two combined enzyme-catalysed reactions: the reductions of the carbon–oxygen and the conjugated carbon–carbon double bonds. The search for a growing micro-organism capable of producing in one pot the two specific reactions required was initiated from a set of micro-organisms which had been successfully used either in the asymmetric reduction of sulphur- and fluoro-substituted ketones[6,10] or in the NADH-dependent reduction of α,β-unsaturated-α-substituted ketones to homochiral α-substituted ketones.[11] Because of the poor preliminary results obtained, the search was then extended to a much larger number of micro-organisms.

The results obtained with eight growing micro-organisms after product extraction and analysis of the crude product under standard conditions are reported in the Table; the other micro-organisms tested, which are reported in the Experimental section, gave less satisfactory results. All micro-organisms, except *Pichia etchellsii* (entry 6, Table) showed a much higher preference for reducing the carbonyl group instead of the carbon–carbon double bond. This is true also for micro-organisms (*e.g. Beauveria sulphurescens*) which have already been successfully used for selective reduction of α,β-unsaturated ketones to the corresponding saturated ones.

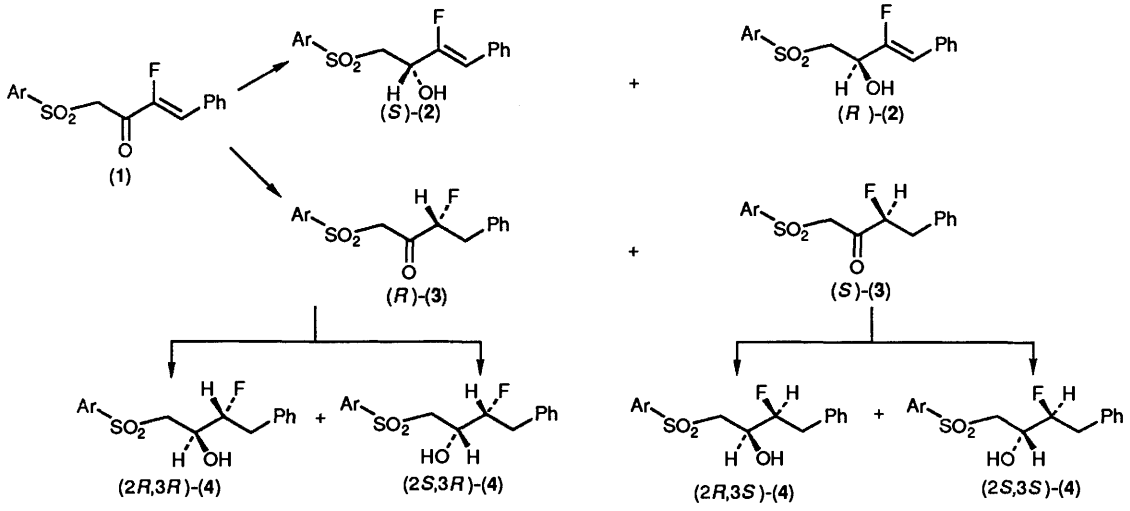
We found that the micro-organisms which were capable of simultaneously reducing the carbonyl and the double bond showed a quite low enantio- and diastereo-selectivity, and gave rise to different mixtures of all the four diastereoisomeric alcohols (entries 6 and 7, Table). The unfavourable results may be due to different enzymatic activities operating at the same time at comparable rates on the carbonyl and on the double bond of the substrate. However, a quite high enantioselection was observed when the substrate was treated with micro-organisms capable of reducing preferentially the ketone to give the α-fluorinated allylic alcohols (**2**) (entries 1–5, Table). Our attention was therefore focused on finding the micro-organism and the appropriate conditions for obtaining both the (*R*)- and (*S*)-enantiomers of the fluorobutenol (**2**).

Gram quantities of (+)-(*R*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphonyl)but-3-en-2-ol (**2**) were prepared by reducing (**1**) with growing *Phanerochaete chrysosporium* for 24 h, extracting the mixture with ether, flash chromatography of the crude product

Table. Composition of the product mixture obtained by microbial reduction of (1).

Entry	Micro-organism	% Recovery	% Yields of isolated compounds				
			Unreacted (1)	(2) (*R*:*S* ratio)	(3)	*anti*-(4)[a] (2*S*,3*S*:2*R*,3*R* ratio)	*syn*-(4)[a] (2*S*,3*R*:2*R*,3*S* ratio)
1	*Geotrichum candidum* CBS233.76	59	0	100 (1:99)	—	0	0
2	*Fusarium oxysporum* IPV[b]	70	5	88 (2:98)	—	3	4
3	*Ceratocystis ulmi* IPV[b]	63	9	81 (3:97)	—	4	6
4	*Phanerochaete chrisosporium* CBS 104.82	91	15	66 (98:2)	—	9	10
5	*Kloeckera saturnus* CBS 5761	86	0.5	76 (92:8)	—	3	21
6	*Pichia etchellsii* CBS 2011	70	3	14 (29:71)	20	30 (61:39)	32 (29:71)
7	*Sporotrichum aureum* CBS 441.70	65	28	10 (57:43)	—	24 (68:32)	38 (30:70)
8	*Beauveria sulfurescens* CBS 209.27	79	3	24	—	23	50

[a] S. Masamune, S. Asrof Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557. [b] IPV: Istituto Patologia Vegetale (Università di Milano, Italy).



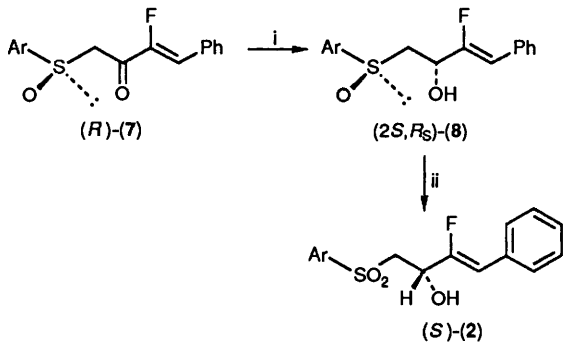
Scheme 1. Compounds obtained through microbial reduction of (1).

on silica gel [60% yields, 95% enantiomeric excess (e.e.)], and crystallizing the eluate from di-isopropyl ether to give the optically pure compound ($[\alpha]_{365}^{20}$ +27.8°).

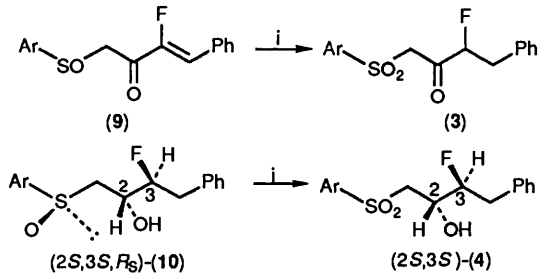
The corresponding (−)-(*S*)-compound (**2**) was obtained most efficiently by reducing the unsaturated ketone (**1**) with *Geotrichum candidum*. The crude product (98% e.e.) was obtained in 65% yield after chromatography on silica gel of the extract of the culture. Crystallization from di-isopropyl ether gave enantiomerically pure (*S*)-(**2**) ($[\alpha]_{365}^{20}$ −28.4°).

Determination of the Absolute and Relative Configurations.— The configurations of the products isolated from microbial transformations were assigned by using chemical correlations and ^{1}H NMR analysis of diastereoisomeric derivatives of the secondary hydroxy groups. The (*R*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)but-3-en-2-one (**7**) was reduced with di-isobutylaluminium hydride (DIBAH) in THF at low temperature to give a single diastereoisomer (**8**) of (R_s)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)but-3-en-2-ol. The selective oxidation of the sulphinyl residue with potassium permanganate under phase-transfer conditions afforded the corresponding sulphonyl alcohol (**2**) (Scheme 2) having physical and spectral data identical with those of the compound obtained from the reduction with *Geotrichum candidum*. This secondary alcohol was esterified with (*R*)- and (*S*)-2-phenylpropionic acid to afford the diastereoisomeric esters. The chemical shift differences between the externally diastereotopic groups in these two esters [$\Delta\delta = \delta(2'S) - \delta(2'R)$ of the CH_2S and =CH hydrogens] allowed us to assign the (*S*) absolute configuration to the alcoholic stereocentre. This stereochemical assignment was in agreement with the results obtained in the DIBAH reduction of several other α-fluoro-α'-sulphinyl ketones.[7a] 3-Fluoro-4-phenyl-1-(*p*-tolylsulphonyl)butan-2-one (**3**), (2*S*,3*S*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphonyl)butan-2-ol (**4**), and the corresponding (2*S*,3*R*)-(**4**) were obtained by selective oxidation, with potassium permanganate, of the sulphinyl residue of 3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)butan-2-one (**9**), (2*S*,-3*S*,R_s)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)butan-2-ol (**10**) and the corresponding (2*S*,3*R*, R_s)-(**10**), respectively (Scheme 3).[7a]

These products were used to determine the composition of the crude residue from the extract of the growing cultures by GLC comparison. The enantiomeric excesses of the saturated and unsaturated alcohols (**2**) and (**4**), respectively, were



Scheme 2. *Reagents:* Ar = *p*-MeC_6H_4 i, DIBAH–THF, −78 °C; ii, $KMnO_4$–Bu_4NBF_4–CH_2Cl_2–water.



Scheme 3. *Reagents:* Ar = *p*-MeC_6H_4 i, $KMnO_4$–Bu_4NBF_4–CH_2Cl_2–water.

established by GLC and/or HPLC analyses of the 2-phenylpropionic esters and comparison with authentic samples.

Experimental

IR spectra were taken on a Perkin-Elmer 177 spectrophotometer and ^1H NMR spectra on a Varian EM-390 or on a Bruker CPX-300 spectrometer with tetramethylsilane as internal standard and $CDCl_3$ as solvent.^{19}F NMR spectra were recorded on a Bruker WP 80 SY instrument (75.39 MHz): δ_F values are in ppm upfield from $CFCl_3$ and C_6F_6 was used as internal standard ($\delta_F = -162.9$ ppm). $[\alpha]_D$ values were obtained on a Jasco DIP-181 polarimeter. M.p.s are uncorrected and were obtained on a capillary apparatus; column chromatography was performed with silica gel 60 (63-200 μm) (Merck) and TLC was performed on silica gel 60 F_{254} (Merck). THF was freshly distilled from lithium aluminium hydride and di-isopropylamine was distilled from calcium hydride and stored over molecular sieves (4 and 13 Å). A 1.6M solution of butyl-lithium in hexanes (Aldrich) was employed. In other cases commercially available reagent-grade solvents were employed without purification. GLC analyses were performed on a C. Erba 4160 gas chromatograph using a glass capillary bonded OV-1 column (25 m × 0.32 mm i.d., d_f 0.4 μm). HPLC analyses were done on a Hibar LichroCART 250-4, packed with Lichrospher Si60 (5 μm) Merck, using a Jasco apparatus with a UV detector.

Condensation of Methyl p-*Tolyl Sulphone* (**5**) *with Methyl* (Z)-2-*Fluoro*-3-*phenylpropenoate* (**6**).—A solution of the sulphone (**5**) (1.70 g, 10 mmol) in dry THF (20 ml) was added dropwise to a stirred solution of LDA (10.5 mmol) in the same solvent (10 ml) at −78 °C. After 3 min a solution of the methyl ester (**6**) (1.89 g, 10.5 mmol) in THF (5 ml) was added to the solution at −78 °C and the mixture was stirred for 15 min. The reaction was quench. by addition of saturated aqueous ammonium chloride (60 ml). The pH was adjusted to 7 with dilute hydrochloric acid, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 70 ml). The combined organic phases were dried with sodium sulphate. Removal of the solvent under reduced pressure, and flash chromatography with hexane–ethyl acetate (6:4, v/v) gave pure (Z)-3-*fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*but*-3-*en*-2-*one* (**1**) (2.80 g, 88%), m.p. 115–116 °C (from ethyl acetate) (Found: C, 64.3; H, 5.0. $C_{17}H_{15}FO_3S$ requires C, 64.1; H, 4.75%); IR (KBr) ν_{max} 2 920, 1 670, 1 630, 1 320, and 1 150 cm^{-1}; δ_H (90 MHz): 2.48 (3 H, s, ArMe), 4.52 (2 H, d, CH_2S), 6.93 (1 H, d, =CH, $^3J_{H,F}$ 24 Hz), and 7.2–7.9 (9 H, m, ArH).

General Procedures for Microbial Reduction.—Each microorganism was grown for the given time (see below) at 30 °C in shaken Erlenmeyer flasks (300 ml) containing the given culture medium (50 ml). The carbonyl compound (in standard procedure, 25 mg per flask), dissolved in dimethyl sulphoxide (DMSO) (0.5 ml), was added to the grown culture and the incubation was continued for one further day.

Baker's yeast (25 g) was suspended in water (50 ml) containing sucrose (5 g) and the mixture was stirred at 30 °C. To the fermenting medium was added a solution of the ketone (50 mg) in DMSO (0.5 ml) and the mixture was stirred for a further 5 h. Each resulting mixture was extracted twice with diethyl ether, the combined extracts were dried over sodium sulphate, and the ether was evaporated off. The composition of the crude residue was determined by GLC analysis.

For the determination of the enantiomeric composition of the secondary alcohol produced, the dried extract (1 mg) was added to a clear solution of (*S*)-2-phenylpropionyl chloride (5 mg) in a mixture of pyridine (0.1 ml) and tetrachloromethane (0.1 ml) (the corresponding derivatives will be called PP derivatives); after being kept at room temperature overnight the samples were analysed by GLC when the enantiomeric composition of the unsaturated alcohol (**2**) was needed or by HPLC when the enantiomeric composition of the saturated alcohol (**4**) was necessary. Each reduction was performed, in two flasks, at least twice.

Geotrichum candidum (CBS 233.76) and *Pichia etchellsii* (CBS 20.11) were grown for 3 days at 150 rev. min^{-1} on a medium containing glucose (50 g l^{-1}), yeast extract (10 g l^{-1}), and peptone (10 g l^{-1}) in deionized water, and adjusted to pH 7. *Kloeckera saturnus* (CBS 57.61), *Fusarium oxysporum IPV* and *Beauveria sulfurescens* (CBS 209.27) were grown for 3 days at 150 rev. min^{-1} on a medium containing glucose (30 g l^{-1}), malt extract (10 g l^{-1}), and yeast extract (10 g l^{-1}) in deionized water, and adjusted to pH 7. *Ceratocystis ulmi* (IPV) was grown for 2 days, and *Phanerochaete chrysosporium* (CBS 104.82) and *Sporotrichum aureum* (CBS 441.70) were grown for 3 days at 150 rev. min^{-1}, on a medium containing glucose (20 g l^{-1}), malt extract (20 g l^{-1}) and peptone (5 g l^{-1}) in deionized water and adjusted to pH 7. Fermenting Baker's yeast and growing cultures of *Alternaria tenuis*, *Aspergillus niger*, *Botrytis cinerea*, *Cladosporium suaveolens*, *Hansenula anomala*, *Mortierella isabellina*, *Polyporus durus*, *Rhizoctonia solani*, *Sporotrichum azureum*, *Sporotrichum laxcum*, *Sporotrichum pruinosum*, *Streptomyces sp.* IPV 2645, and *Ustilago maydis* were also tested as reducing agents.

Gas-chromatographic Analysis.—The products from microbial transformation were analysed as follows: carrier gas H_2, linear velocity 70 cm s^{-1}, column temperature programmed from 205 to 250 °C at 2 °C min^{-1} [the saturated ketone (**3**), *anti*-alcohol (**4**), *syn*(alcohol (**4**), saturated ketone (**1**), and unsaturated alcohol (**2**) had respectively t_R 16.4, 17.5, 18.7, 20.1, and 20.8 min]. The PP derivatives of alcohol (**2**) were analysed as follows: carrier gas H_2, linear velocity 90 cm s^{-1}; colum temperature 250 °C (t_R 28.6 and 30.2 min). The PP derivative of (*R*)-(**2**) was eluted first.

HPLC Analysis.—The PP derivatives of microbial reduction

products were eluted with hexane–propan-2-ol (98:2, v/v) at a 0.6 ml min^{-1} flow rate in the following order: (*S*)-(**2**) (t_R 17.5 min); (*R*)-(**2**) (18.8); (2*S*,3*S*)-(**4**) (20.3); (2*R*,3*R*)-(**4**) (21.3); (2*S*,3*R*)-(**4**)(23.5); (2*R*,3*S*)-(**4**) (24.8).

Production of (S)-3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*but*-3-*en*-2-*ol* (**2**).—A solution of the ketone (**1**) (1.0 g, 3.1 mmol) in DMSO (30 ml) was distributed into 10 Erlenmeyer flasks (300 ml) containing grown cultures of *Geotrichum candidum*. The incubation was continued for 7 h. The reduction products were isolated as described in the general procedure. Flash chromatographic separation of the crude extract with hexane–ethyl acetate (60:40, v/v) yielded the (*S*)-alcohol (**2**) (0.65 g, 65%) pure on GLC; enantiomeric excess (e.e) 98%. An analytical sample after crystallization di-isopropyl ether) was > 99.9% enantiomerically pure; m.p. 106 °C; $[\alpha]_{435}^{20}$ −9.1°, $[\alpha]_{365}^{20}$ −28.4° (*c* 2.0 in $CHCl_3$).

Production of (R)-3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*but*-3-*en*-2-*ol* (**2**).—A solution of the ketone (**1**) (1.0 g, 3.1 mmol) in DMSO (20 ml) was distributed into 40 Erlenmeyer flasks (300 ml) containing grown cultures of *Phanerochaete chrysosporium*. The incubation was carried out for 24 h. The reaction product was isolated and purified as described in the preceding preparation. The (*R*)-alcohol (**2**) was obtained (0.60 g, 60%) pure on GLC; e.e. 95%. An analytical sample after crystalization (di-isopropyl ether) had an e.e. > 99.9%; m.p. 106 °C; $[\alpha]_{435}^{20}$ + 9.2°; $[\alpha]_{365}^{20}$ + 27.8° (c 2.0 in $CHCl_3$).

Synthesis of (2S,R_s)-3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphinyl*)-*but*-3-*en*-2-*ol* (**8**).—A solution of DIBAH (1.0M in hexane, Fluka; 12 ml) was dropped at −78 °C, under argon atmosphere *via* a syringe into a stirred solution of (*R*)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)but-3-en-2-one (**7**) (3.02 g, 10.0 mmol) in THF (100 ml). Stirring was continued for 15 min, saturated aqueous sodium carbonate (25 ml) was added, the mixture was stirred for 10 min at room temperature, and the pH was lowered to *ca.* 3 with 10M hydrochloric acid. The mixture was extracted with ethyl acetate (3 × 100 ml) and the combined organic layers were dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure and flash chromatography with hexane–ethyl acetate (1:1, v/v) gave the (2S,R_s)-*alcohol* (**8**) (2.86 g, 94%), m.p. 142–143 °C (from ethyl acetate); $[\alpha]_D^{20}$ + 186° (*c* 1.0 in $CHCl_3$) (Found: C, 67.3; H, 5.85. $C_{17}H_{17}FO_2S$ requires C, 67.1; H, 5.6); δ_H (300 MHz): 2.40 (3 H, s, ArMe), 3.06 (1 H, dd, CHS), 3.14 (1 H, dd, CHS), 4.87 (1 H, m, CHO), 5.97 (1 H, m, =CH, $^3J_{H,F}$ 38 Hz), and 7.2–7.7 (9 H, m, ArH).

Synthesis of 3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*butan*-2-*one* (**3**).—A solution of potassium permangate (92 mg, 0.52 mmol) and tetrabutylammonium tetrafluoroborate (55 mg, 0.17 mmol) in water (4.0 ml) was dropped into a stirred solution of 3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)butan-2-one (**9**) (250 mg, 0.82 mmol) in dichloromethane–acetic acid (95:5, v/v; 10 ml). Vigorous magnetic stirring was maintained for 2 h, then water (20 ml), saturated sodium sulphite (5.0 ml), and dilute hydrochloric acid (1.0 ml) were added in that order. The aqueous phase was extracted with dichloromethane (3 × 20 ml), and the combined organic phases were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give a residue which, upon flash chromatography with cyclohexane–ethyl acetate (8:2, v/v), afforded the butan-2-one (**3**) (220 mg, 84%); δ_H (90 MHz): 2.50 (3 H, s, ArMe), 2.99 (1 H, m, CHS), 3.30 (1 H, m, CHS), 4.09 (1 H, m, CHCF), 4.40 (1 H, m, CHCF), 5.10 (1 H, m, CHF), and 7.1–7.9 (9 H, m, ArH).

Synthesis of (2S,3S)-*and* (2S,3R)-3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*butan*-2-*ol* (**4**).—The oxidation of (2*S*,3*S*,R_s)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)butan-2-ol (**10**) (7 mg, 0.023 mmol) with potassium permanganate 2.53 mg, 0.016 mmol) and tetrabutylammonium tetrafluoroborate (1.5 mg, 0.004 mmol) afforded the (2*S*,3*S*)-fluorobutanol (**4**) (5.8 mg, 81%); IR (Nujol) ν_{max} 3 430, 1 290, and 1 135 cm^{-1}; δ_H (300 MHz): 2.48 (3 H, s, ArMe), 2.8–3.1 (m, 2 H, CH_2CF), 3.23 (1 H, dd, CHS), 3.42 (1 H, dt, CHS), 4.10 (1 H, m, CHO), 4.54 (1 H, m, CHF), and 7.1–7.4, 7.8 (9 H, m, ArH); δ_F (75 MHz): −190.7. The oxidation of the corresponding (2*S*,3*R*,R_s)-compound (**10**) (12 mg, 0.03 mmol) under the same conditions afforded the (2S,3R)-*fluorobutanol* (**4**) (9.1 mg, 75% yield) (Found: C, 63.5; H, 5.6. $C_{17}H_{19}FO_3S$ requires: C, 63.3; H, 5.9%); IR (Nujol) ν_{max} 3 400, 1 320, 1 150, and 750 cm^{-1}; δ_H (300 MHz): 2.46 (3 H, s, ArMe), 3.0–3.1 (2 H, m, CH_2CF), 3.27 (1 H, dd, CHS), 3.43 (1 H, dd, CHS), 4.23 (1 H, m, CHO, $^3J_{H,F}$ 22.5 Hz), 4.59 (1 H, m, CHF, $^2J_{H,F}$ 47 Hz), and 7.2–7.4, 7.8 (9 H, m, ArH); δ_F (75 MHz): −195.7.

Synthesis of (S)-3-*Fluoro*-4-*phenyl*-1-(p-*tolylsulphonyl*)*but*-3-*en*-2-*ol* (**2**).—The oxidation of (2*S*,R_s)-3-fluoro-4-phenyl-1-(*p*-tolylsulphinyl)but-3-en-2-ol (**8**) with potassium permanganate and tetrabutylammonium tetrafluoroborate as described above afforded the (S)-*butenol* (**2**) in 88% yield, m.p. 105–106 °C (from ethyl acetate); $[\alpha]_{365}^{20}$ −28.1° (*c* 1.6 in $CHCl_3$) (Found: C, 64.0; H, 5.6. $C_{17}H_{17}FO_3S$ requires: C, 63.7; H, 5.35%); δ_H (300 MHz): 2.43 (s, 3 H, ArMe), 3.48 (m, 2 H, CH_2S), 4.80 (m, 1 H, CHO), 5.91 (d, 1 H, =CH, $^3J_{H,F}$ 40 Hz), and 7.2–7.5 (m, 9 H, ArH).

Synthesis of Esters Between (S)-(**2**) *and* (R)- *or* (S)-2-*Phenylpropionic Acid*.—4-Dimethylaminopyridine (2.5 mg, 0.02 mmol) was added to a dichloromethane solution (1.0 ml) of the sulphonyl alcohol (*S*)-(**2**) (64 mg, 0.2 mmol), (−)-(*R*)-2-phenylpropionic acid (37 mg, 0.22 mmol), and dicyclohexylcarbodi-imide (50 mg, 0.24 mmol). After 4 h at room temperature the insoluble dicyclohexylurea product was removed by filtration and washed with hexane (3 × 1 ml), and the combined filtrates were washed successively with 1M hydrochloric acid (1 ml), saturated aqueous sodium hydrogen carbonate (1 ml), and brine (1 ml). The organic phase was dried over sodium sulphate, and solvent removal under reduced pressure furnished the (*R*)-2-phenylpropionate of (*S*)-(**2**) in nearly pure form. Flash chromatography with hexane–ethyl acetate (9:1, v/v) afforded an analytically pure sample (83 mg, 92%); δ_H (300 MHz): 1.45 (3 H, d, CH_3CH), 2.43 (3 H, s, ArMe), 3.44 (1 H, q, $CHCH_3$), 3.59 (2 H, m, CH_2S), 5.33 (1 H, d, =CH), 5.81 (1 H, m, CHO), and 7.1–7.4, 7.79 (14 H, m, ArH). Similarly, when the (*S*)-2-phenylpropionic acid and (*S*)-(**2**) were employed the isolated ester showed the spectrum: δ_H (300 MHz): 1.45 (3 H, d, CH_3CH), 2.36 (3 H, s, ArMe), 3.51 (1 H, dd, CHS), 3.60 (1 H, dd, CHS), 3.66 (1 H, q, $CHCH_3$), 5.70 (1 H, m, =CH), 5.76 (1 H, m, CHO), and 7.1–7.4, 7.68 (14 H, m, ArH).

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