Homochiral Fluoro-organic Compounds. Microbial Reduction of 1-Fluoro-3-(*p*-tolylsulphonyl)propan-2-one and of 1-Fluoro-3-(*p*-tolylsulphenyl)propan-2-one

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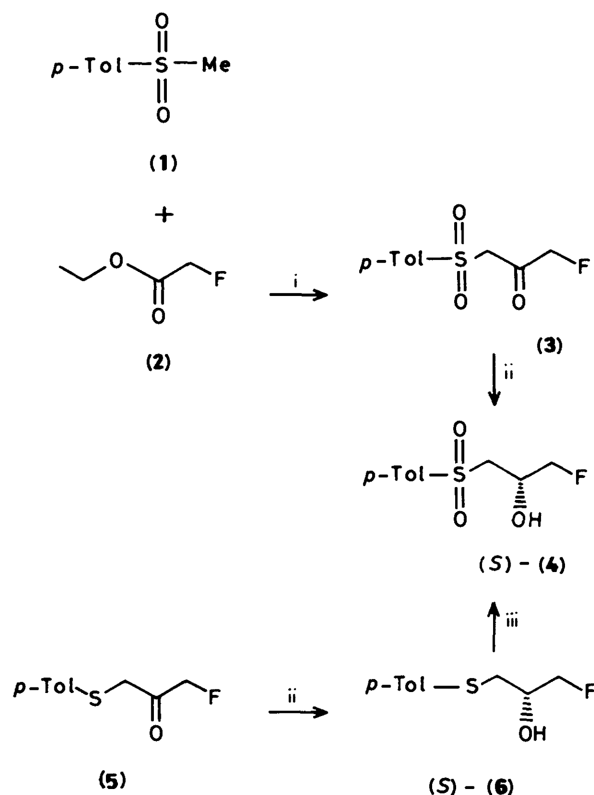
The reduction of 1-fluoro-3-(*p*-tolylsulphonyl)propan-2-one (**3**) and of the corresponding sulphenyl derivative (**5**) with Baker's yeast and with growing cultures of several micro-organisms has been studied. The production of (*S*)-1-fluoro-3-(*p*-tolylsulphonyl)propan-2-ol (**4**) and of (*S*)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol (**6**) in high enantiomeric purity has been achieved.

Asymmetric microbial reduction of carbonyl compounds[1] is a strategy for the preparation of optically pure secondary alcohols complementary to other methods involving the resolution of racemates[2] or the use of asymmetric reagents[3] and chiral templates.[4]

The development of new chirons and methodologies for the synthesis of homochiral fluoro-organic compounds was the objective of recent efforts in our laboratory,[5–9] and the (+)-(*R*)-1-fluoro-3-(*p*-tolylsulphinyl)propan-2-one and its corresponding alcohol (2*S*)-1-fluoro-3-[(*R*)-*p*-tolylsulphinyl]propan-2-ol were revealed to be very promising starting materials for that purpose. Simple elaborations and the final removal of the sulphinyl auxiliary group afforded several sulphur-free, oxygenated fluoro-organic componds in enantiomerically pure form, *viz.* α-fluoro ketones,[6] fluorohydrins,[7] fluoro epoxides, and β-fluoro-α-hydroxy aldehydes and acids.[8]

In order to expand further the availability of fluorinated chirons to be utilized in asymmetric synthesis of fluoro-organic compounds, the microbial reduction of 1-fluoro-3-(*p*-tolylsulphonyl)propan-2-one (**3**) and of 1-fluoro-3-(*p*-tolylsulphenyl)propan-2-one (**5**) was examined in detail: we expected to obtain the corresponding secondary alcohols (**4**) and (**6**), hopefully in both enantiomeric forms and in high optical purity.



Scheme 1. i, LDA–THF, −78 °C; ii, microbial reduction; iii, $KMnO_4$–Bu_4NBF_4–CH_2Cl_2–water

Results and Discussion

The fluoro-substituted sulphonylpropanone (3) was obtained in nearly quantitative yield by acylating the lithium derivative of methyl *p*-tolyl sulphone (**1**) (lithium di-isopropyl amide, LDA) [1.1 mol equiv. in tetrahydrofuran (THF)] with ethyl fluoroacetate (**2**) (Scheme 1), whereas the fluoro-substituted sulphenylpropanone (**5**) was obtained in 82% yield through deoxygenation [sodium iodide–trifluoroacetic anhydride (TFAA) in cooled acetone] of the corresponding fluoro sulphoxide as already described.[5a]

Reduction of 1-(1,3-dithian-2-yl)propan-2-one with Baker's yeast, *Aspergillus niger*, and *Geotrichum candidum* has already allowed some of us to obtain both antipodes of the corresponding alcohol in excellent enantiomeric purity.[10] The two sulphur-substituted fluoro ketones (**3**) and (**5**) were thus submitted to these reducing systems, and the action of *Aureobasidium sp.*, *Fusarium sp.*, *Kloeckera saturnus*, and *Rhizoctonia solani* was also examined. The results are summarized in the Table.

The (*S*)-1-fluoro-3-(*p*-tolylsulphonyl)propan-2-ol (**4**) was obtained with excellent enantiomeric purity (e.e. >97%) when the reduction of the fluoro substituted sulphonylpropanone (**3**) was accomplished with Baker's yeast and *Rhizoctonia solani*. The solid sulphonyl fluorohydrin (*S*)-(**4**) of more than 99.5% e.e. {$[\alpha]_D^{20}$ +11.8° (*c* 1.0 in $CHCl_3$), m.p. 54—55 °C} was isolated in 65% yield through crystallization (from di-isopropyl ether) of the crude alcohol prepared in gram quantity by reduction with fermenting Baker's yeast. All the other reducing species gave mixtures of enantiomers with predominance (89—11% e.e.) of the (*S*) enantiomer.

The results of the reduction of the corresponding fluoro-substituted sulphenylpropanone (**5**), although not exceptional, are still interesting; in fact, *Aspergillus niger* and *Rhizoctonia solani* both produce (*S*)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol (**6**) of good enantiomeric purity (e.e. 93%).

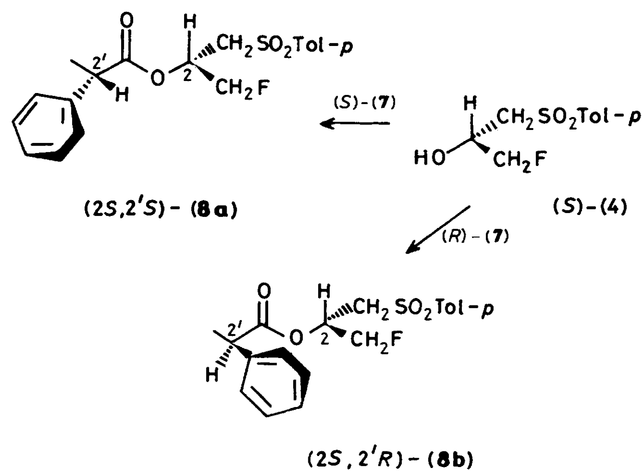
Gram quantities of the liquid sulphenyl fluorohydrin (**6**) were prepared in 90% yield using *Aspergillus niger*.

The reduction with Baker's yeast and with other growing micro-organisms gave lower enantiomeric excesses of the (*S*) enantiomer except for the *Auereobasidium sp.* which produces a slight excess of the (*R*) enantiomer.

Table. Absolute configuration and enantiomeric excess (%) of the prevailing antipode of the alcohols (4) and (6) obtained by microbial reductions of ketones (3) and (5)

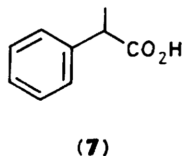
	Reagent	
	Sulphonyl fluoro-propanone (3)	Sulphenyl fluoro-propanone (5)
Baker's yeast	*S* (>97)	*S* (87)
Aspergillus niger IPV 238	*S* (89)	*S* (93)
Kloeckera saturnus CBS 5761	*S* (39)	*S* (57)
Aureobasidium sp. IPV A-130	*S* (11)	*R* (23)
Streptomyces sp. IPV 2645[a]	*S* (55)	(00)
Geotrichum candidum CBS 233.76[a]	*S* (51)	*S* (15)
Fusarium sp.	*S* (83)	*S* (80)
Rhizoctonia solani IPV A-19	*S* (>97)	*S* (93)

[a] See ref. 10.



Scheme 2.

The alcohols isolated from the bioconversions have gas-chromatography R_t values, and i.r. and n.m.r. spectra, identical with those of authentic samples which were obtained in the following manner: the alcohol (**4**) through oxidation (potassium permanganate under phase-transfer conditions)* of the sulphinyl residue of (+)-(2*S*)-1-fluoro-3-[(*R*)-*p*-tolylsulphinyl]-propan-2-ol,[7] and the alcohol (**6**) through deoxygenation (sodium iodide–TFAA) of the sulphinyl group of this last product.



(**7**)

The absolute configurations of the sulphonyl and sulphenyl alcohols (**4**) and (**6**) were thus established. The configuration of (**4**) was also determined by comparing the proton chemical shifts of the esters (**8a**) and (**8b**) obtained with (+)- and (−)-2-phenylpropionic acid, PP acid, (**7**) respectively. The chemical-shift differences between externally diastereotopic groups in the two esters ($\Delta\delta = [\delta_{(S)\text{-ester}} - \delta_{(R)\text{-ester}}]$, $\Delta\delta_{CH_2F} = 0.19$, and $\Delta\delta_{CH_2S} = -0.06$) were attributed to the shielding effect that the phenyl ring of the esterifying acid exerts on the facing protons of the secondary alcohol, see Scheme 2, and are in accord with the trend observed for a large number of PP esters of secondary alcohols.[9]

The enantiomeric composition of the alcohols obtained in all the experiments was determined by esterification with (*S*)-2-phenylpropionyl chloride and/or with (+)-methoxy(trifluoromethyl)phenylacetyl chloride (3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride), and comparing such derivatives with authentic samples by means of gas chromatographic analysis (see Experimental section).

While several successful microbial reductions of α-chloro ketones and α-sulphur-substituted ketones have been reported,[11] only few fluoro compounds of known absolute configuration have been obtained in acceptable enantiomeric excess by that method. Some trifluoromethyl ketones[12] and a few α-monofluoro ketones[13] have been reduced by Baker's yeast to the corresponding secondary alcohols, while some other chiral trifluoro-[14] or monofluoro-organic compounds[15] have been obtained by enzymatic hydrolysis. The production of the *S* fluoro sulphonyl and fluoro sulphenyl alcohols (**4**) and (**6**) by microbial reduction here reported may be of interest since these compounds can be used, instead of the corresponding sulphinyl analogue, in the synthesis of a large variety of differently functionalized fluoro-organic compounds by only slight modifications of the procedures already developed.[7,8,11]

* Under the same reaction conditions (+)-(**6**) was oxidized to (+)-(*S*)-(**4**) in high yield.

Experimental

I.r. spectra were taken on a Perkin-Elmer 177 spectrophotometer, and ^{1}H n.m.r. spectra on a Varian EM-390 or on a Bruker CPX-300 spectrometer with tetramethylsilane as internal standard and $CDCl_3$ as solvent unless otherwise stated. $[\alpha]_D^{20}$ 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 t.l.c. was performed on silica gel 60 F_{254} (Merck). For the condensation reaction of compound (**1**) an argon atmosphere was used; THF was freshly distilled from lithium aluminium hydride and di-isopropylamine was distilled from calcium hydride and stored over molecular sieves (4 Å 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. G.l.c. analyses were performed on a 25 m × 0.32 mm i.d. fused silica capillary column coated with OV-1701 (d_f 0.25 μm) using a Dani apparatus mod. 6500 and PTV injection system; carrier gas H_2, linear flow rate 54 cm s^{-1}.

Condensation of Methyl p-*Tolyl Sulphone* (**1**) *with Ethyl Fluoroacetate* (**2**).—A solution of the sulphone (**1**) (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 ethyl fluoroacetate (**2**) (1.45 ml, 15 mmol) in THF (5 ml) was added to the solution at −78 °C and the mixture was stirred for 15 min. The reaction was quenched by addition of saturated aqueous ammonium chloride (60 ml). The pH was adjusted to 7 with dil. 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 1-fluoro-3-(*p*-tolyl-

sulphonyl)propan-2-one (3) (2.21 g, 96%), m.p. 134—135 °C (from Pr^i_2O); $\nu_{max.}$(Nujol) 1 735, 1 460, 1 145, 1 080, and 1 010 cm^{-1}; $\delta_H(CDCl_3)$ 2.49 (s, 3 H, Me), 4.30 (d, $^4J_{H-F}$ 2.8 Hz, 2 H, CH_2S), 4.99 (d, $^2J_{H-F}$ 46 Hz, 2 H, CH_2F), and 7.40 and 7.78 (each d, 4 H, ArH) (Found: C, 52.3; H, 5.0. $C_{10}H_{11}FO_3S$ requires C, 52.16; H, 4.82%).

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, 50 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 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 g.l.c. 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) or of (+)-methoxy(trifluoromethyl)phenylacetyl chloride (5 mg) in a mixture of pyridine (0.1 ml) and tetrachloromethane (0.1 ml) (the corresponding derivatives will be called PP or MPTA derivatives); after being kept at room temperature overnight the samples were analysed by g.l.c. Each reduction was performed, in two flasks, at least twice.

A. niger (IPV 283) was grown for two days on Czapek-Dox medium at 150 rev min^{-1}. *G. candidum* (CBS 233.76) was grown for three 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. *Streptomyces sp.* (IPV 2645) was grown for 1 day, *Aureobasidium sp.* (IPV A-130) was grown for 2 days, and *Kloeckera saturnus* (CBS 5761), *Fusarium sp.*, and *Rhizoctonia solani* (IPV A-19) 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.

Gas-chromatographic Analysis.—1-*Fluoro*-3-(p-*tolylsulphenyl*)*propan*-2-*one* (**5**). The reduction products were analysed as follows: 1 min at 40 °C, then 20 °C min^{-1} to 135 °C, 2 min at 135 °C, and finally 1.5 °C min^{-1} to 180 °C (ketone R_t 16.6 min, alcohol R_t 18.8 min); the PP and MTPA derivatives were analysed as follows: 1 min at 40 °C, then 20 °C min^{-1} to 190 °C, 2 min at 190 °C, and finally 1.5 °C min^{-1} to 230 °C (PP derivatives R_t 29.3, 29.7 min; MPTA derivatives R_t 31.0, 31.4 min). The derivatives of (*S*)-1-fluoro-3-(*p*-tolylsulphenyl)-propan-2-ol (**6**) were eluted first.

1-*Fluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*one* (**3**). The analysis of the reduction products was performed as follows: 1 min at 40 °C, then 20 °C min^{-1} to 180 °C, 2 min at 180 °C, and finally 1 °C min^{-1} to 220 °C (ketone R_t 18.6 min, alcohol R_t 20.2 min); the analyses of the PP and MTPA derivatives were conducted as follows: 1 min at 40 °C, then 20 °C min^{-1} to 225 °C, 2 min at 225 °C, and finally 1 °C min^{-1} to 250 °C (PP derivatives R_t 33.0, 33.5 min; MTPA derivatives R_t 32.6, 33.2 min). The derivatives of (*S*)-1-fluoro-3-(*p*-tolylsulphonyl)propan-2-ol (**4**) were eluted first.

Production of (S)-1-*Fluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol* (**4**).—A solution of 1-fluoro-3-(*p*-tolylsulphonyl)propan-2-one (**3**) (2.0 g, 8.7 mmol) in DMSO (8 ml) was added to a fermenting suspension of Baker's yeast (500 g) in water (1.0 l) containing sucrose (100 g) and stirred at 30 °C. After 4 h fermentation the yeast was separated by filtration through a Celite pad. The aqueous phase and the filtration cake were extracted three times with ether. The ethereal extracts were washed successively with aqueous sodium hydrogen carbonate and with aqueous sodium chloride, were dried over sodium sulphate, and the ether was evaporated off. Flash chromatographic separation of the crude extract with hexane–ethyl acetate (50:40, v/v) yielded (*S*)-1-fluoro-3-(*p*-tolylsulphonyl)propan-2-ol (**4**) (1.7 g, 84%), 98% pure on g.c.; e.e. >97%. The solid product was crystallized from Pr^i_2O to obtain the pure alcohol (1.3 g), e.e >99.5%; $[\alpha]_D^{20}$ +11.8° (*c* 1.0 in chloroform).

Production of (S)-1-*Fluoro*-3-(p-*tolylsulphenyl*)*propan*-2-*ol* (**6**).—A solution of 1-fluoro-3-(*p*-tolylsulphenyl)propan-2-one (**5**) (1.0 g, 5.0 mmol) in DMSO (10 ml) was distributed into 40 Erlenmeyer flasks (300 ml) containing grown cultures of *Aspergillus niger*. The incubation was carried out for 1 day. The reduction product was isolated as described in the general procedure. Flash-chromatographic separation of the crude extract with hexane–ethyl acetate (70:30, v/v) yielded (*S*)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol (**6**) (0.90 g, 90%), 99% pure on g.l.c.; e.e. 93%; $[\alpha]_D^{20}$ +35.4° (*c* 1.0 in chloroform).

Oxidation of (+)-(2S)-1-*Fluoro*-3-[(R)-p-*tolylsulphinyl*]-*propan*-2-*ol*.—A solution of potassium permanganate (103 mg, 0.65 mmol) and of tetrabutylammonium tetrafluoroborate (60 mg, 0.18 mmol) in water (5.0 ml) was dropped into a stirred solution of (+)-(2*S*)-1-fluoro-3-[(*R*)-*p*-tolylsulphinyl]propan-2-ol[7] (200 mg, 0.92 mmol) in dichloromethane–acetic acid (95:5, v/v; 5.0 ml). Vigorous magnetic stirring was maintained for 2 h, then water (20 ml), saturated aqueous sodium sulphite (5.0 ml), and dil. hydrochloric acid (0.5 ml) were added in that order. The aqueous phase was extracted with dichloromethane (3 × 20 ml), and the collected organic phases were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give a residue which, upon flash chromatography on silica gel with hexane–ethyl acetate (1:1, v/v), afforded (S)-1-*fluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol* (**4**) (196 mg, 92%) in pure form. An analytical sample was crystallized from Pr^i_2O, m.p. 54—55 °C; $[\alpha]_D^{20}$ +12.3° (*c* 1 in chloroform); $\nu_{max.}$(KBr) 3 240 and 1 045 cm^{-1}; δ_H 2.51 (s, 3 H, Me), 3.36 (d, 2 H, CH_2S), 4.45 (dd, 2 H, CH_2F), 4.40 (m, 1 H, C*H*OH), and 7.43 and 7.87 (each d, 4 H, ArH). (Found: C, 60.0; H, 6.6. $C_{10}H_{13}FO_3S$ requires C, 59.92; H, 6.54%).

Similarly, (+)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol (**6**) (200 mg, 1.0 mmol) was oxidized with potassium permanganate (205 mg, 1.3 mmol) and tetrabutylammonium tetrafluoroborate (122 mg, 0.37 mmol) to give (+)-(*S*)-(**4**) (180 mg, 77%) in pure form.

Deoxygenation of (2S)-1-*Fluoro*-3-[(R)-p-*tolylsulphinyl*]-*propan*-2-*ol*.—TFAA (0.71 ml, 5.0 mmol) was added *via* a syringe into a stirred mixture of (2*S*)-1-fluoro-3-[(*R*)-*p*-tolylsulphinyl)propan-2-ol[7] (216 mg, 1.0 mmol) and sodium iodide (450 mg, 3.0 mmol) in acetone (20 ml) at −45 °C under argon. After the mixture had been stirred for 15 min at the same temperature, saturated aqueous sodium sulphite (30 ml) was added. The resultant light yellow mixture was treated with saturated aqueous sodium hydrogen carbonate until pH ~8 was reached. Acetone was evaporated off under reduced pressure and the residual aqueous mixture was extracted with ether (3 × 25 ml). The organic extracts were dried with anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residue was dissolved in THF (10 ml), and 1.0M sodium hydroxide (3.0 ml) was added to the stirring solution. After 30 min, the mixture was treated with dil.

hydrochloric acid (to pH 3), the organic products were extracted with ether (3 × 25 ml), and the combined extracts were dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure and flash chromatography with hexane–ethyl acetate (7:3, v/v) afforded the (+)-(*S*)-1-fluoro-3-(*p*-tolylsulphenyl)propan-2-ol (**6**) (188 mg, 94%) as a viscous oil, $[\alpha]_D^{20}$ +36.5° (*c* 1.0 in chloroform); $\nu_{max.}$(film) 3 400, 2 930, 1 495, 1 090, and 1 020 cm^{-1}; $\delta_H(CDCl_3)$ 2.38 (s, 3 H, Me), 3.03 (m, 2 H, CH_2S), 3.88 (m, 1 H, C*H*OH), 4.47 (dd, $^2J_{H-F}$ 47.2 Hz, 2 H, CH_2F), and 7.11 and 7.33 (each d, 4 H, ArH).

Synthesis of the Esters (**8a**) *and* (**8b**) *from* (+)-(S)-2-*Phenylpropionic acid* (**7**), *and its Enantiomer* (−)-(R)-(**7**), *and* (+)-(S)-(**4**).—4-Dimethylaminopyridine (2.5 mg, 0.02 mmol) was added to a dichloromethane solution (1.0 ml) of the sulphonyl alcohol (*S*)-(**4**) (46 mg, 0.2 mmol), (+)-(*S*)-2-phenylpropionic acid (**7**) (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 removal of the solvent furnished the ester (2*S*,2′*S*)-(**8a**) in nearly pure form. Flash chromatography with hexane–ethyl acetate (7:3, v/v) gave an analytically pure sample (69 mg, 94%), δ_H ($CDCl_3$) 1.44 (d, 3 H, 2′-Me), 2.48 (s, 3 H, Me), 3.37 (d, *J* 6 Hz, 2 H, CH_2S), 3.64 (q, 1 H, CHCO), 4.57 (dd, $J_{H,H}$ 4, $J_{H,F}$ 47 Hz, 2 H, CH_2F), and 5.36 (m, 1 H, C*H*OH).

Similarly, when the (*R*)-2-phenylpropionic acid was employed, the (2*S*,2′*R*)-ester (**8b**) was obtained, $\delta_H(CDCl_3)$ 1.44 (d, 3 H, 2′-Me), 2.50 (s, 3 H, Me), 3.43 (d, 2 H, CH_2S), 3.45 (q, 1 H, CHCO), 4.38 (dd, $J_{H,H}$ 3.5, $J_{H,F}$ 48 Hz, 2 H, CH_2F), and 5.40 (m, 1 H, C*H*OH).

Acknowledgements

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