Synthesis of the Two Enantiomers of 1-Chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ol by Microbial Reduction of the Parent Propanone and Transformation into 3,3-Difluorotetrahydrofuran Derivatives

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Both *R* and *S* enantiomers of 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ol were obtained with high enantioselection by microbial reduction of 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)-propan-2-one. The enantiomerically pure *R*-alcohol was obtained and transformed into 3,3-difluoro-4-methyl-2-[(*p*-tolylsulphonyl)methyl]tetrahydrofurans through a two-step synthesis.

New routes to homochiral, selectively fluorinated organic compounds, which can be convenient precursors to a wide variety of complex fluorinated organic molecules used in medicine and biology, are of increasing importance.[1]

Asymmetric microbial transformation of prochiral fluorinated organic compounds is one of the strategies that are currently being pursued.[2]

The three-carbon chirons 3-(*p*-tolylsulphenyl)-, 3-(*p*-tolylsulphinyl)- and 3-(*p*-tolylsulphonyl)-substituted 1-fluoropropan-2-ols have been obtained in optically pure form both by chemical[3] and microbial[4] approaches. Furthermore they have been employed in the asymmetric synthesis of some fluoroanalogues of biologically interesting natural compounds such as the four epimers of 3-deoxy-3-fluoromuscarine,[5] 3-deoxy-3-fluororibose,[6] and four 3,4-dideoxy-3-fluorohexoses.[7]

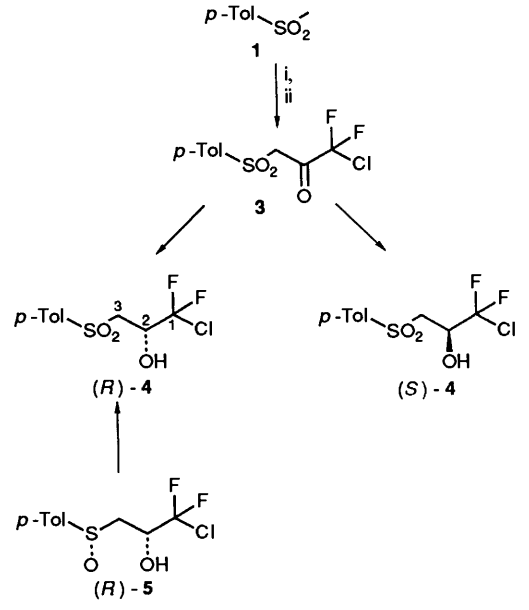
In order to increase further the number of simple fluorinated chirons, the microbial reduction of 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-one **3** was studied in detail, and both enantiomers of 1-chloro-1,1-difluoro-3-(*p*-tolylsylphonyl)propan-2-ol **4** were obtained with good enantioselection. The three-carbon fluorinated chiron (*R*)-**4** was usefully employed in the asymmetric synthesis of 3,3-difluorotetrahydrofuran derivatives **9** through a radical reaction forming a new carbon–carbon bond from the corresponding allyl ether.

Results and Discussion

The lithium derivative of methyl *p*-tolyl sulphone **1**, obtained with lithium diisopropylamide (LDA) (1.1 mol equiv.) in tetrahydrofuran (THF), was acylated *in situ* with ethyl chlorodifluoroacetate **2** to give, in 73% yield, 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-one **3**, which was submitted to microbial and chemical reduction (Scheme 1).

Microbial Reduction.—The 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-one **3** was subjected to the action of fermenting Baker's yeast and of growing cultures of several micro-organisms. The 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ols **4** were obtained in variable yield and enantiomeric purity. The enantiomeric compositions of the asymmetric alcohol produced by the microbial reductions were measured by gas chromatographic analysis of the diastereoisomeric esters prepared by reaction with (*S*)-2-phenylpropionyl chloride, and comparison with an authentic sample [prepared from the homochiral sulphinyl alcohol (2*R*,*S*$_S$)-**5**; see later].

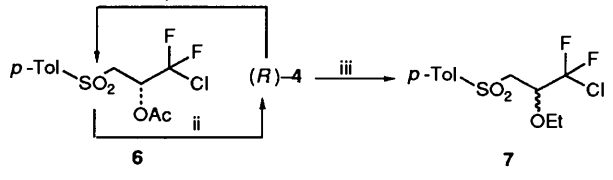
35 Micro-organisms were tested, but only those reported in Table 1 seem of interest for the fair percentage of recovered material and the observed enantioselection.



Scheme 1 *Reagents:* i, LDA; ii, $Cl_2FC–CO_2Et$

The majority of the micro-organisms gave high predominance of the (*R*)-alcohol, while only two *Cladosporium* spp., *capsici* and *herbarum*, and one strain of *Rhodotorula glutinis* (entries 7–9) gave the (*S*)-alcohol as the prevailing enantiomer. We prepared, in 68% yield and 78% enantiomeric excess (e.e.), (*R*)-1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ol (*R*)-**4** in gram quantity by means of fermenting Baker's yeast.

The enantiomerically pure alcohol (*R*)-**4** was obtained by crystallization of the corresponding acetate **6** and regeneration by means of a titanate-mediated transesterification[8] (Scheme 2).



Scheme 2 *Reagents and conditions:* i, Ac_2O, Py, room temperature; ii, $(Pr^iO)_4Ti$, Pr^iOH, reflux; iii, KOH in aq. EtOH or guanidine in aq. EtOH

Table 1 Composition (%) of the mixture obtained by microbial reduction of compound **3**

Entry	Micro-organism	Recovery	Relative proportions of compounds	
			Unchanged **3**	**4** (*S*:*R* ratio)
1	*Baker's yeast*	82	15	85 (11:89)
2	*Cladosporium suaveolens* CBS 157.58	80	30	70 (7:93)
3	*Candida lipolytica* CBS 20.74	80	74	26 (10:90)
4	*Ceratocystis ulmi* IPV[a]	80	75	25 (23:77)
5	*Rhizoctonia solani* IPV[a] A-19	80	67	33 (21:79)
6	*Beauveria sulfurescens* CBS 209.27	80	2	98 (12:88)
7	*Cladosporium capsici* CBS 148.38	80	43	57 (72:28)
8	*Cladosporium herbarum* CBS 132.29	80	20	80 (69:31)
9	*Rhodotorula glutinis* CBS–2371	50	10	90 (81:19)
10	*Saccharomyces cerevisiae* NCYC 739	50	48	52 (11:89)
11	*Bacillus polymyxa* ATCC 12321	65	28	72 (9:91)
12	*Zymomonas mobilis* ATCC 29191	60	15	85 (9:91)

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Attempts to regenerate the alcohol by potassium hydroxide or guanidine in aq. ethanol[9] were unsatisfactory, because they gave the ethyl ether of racemic 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ol, which probably arises *via* β-elimination followed by addition of ethanol.

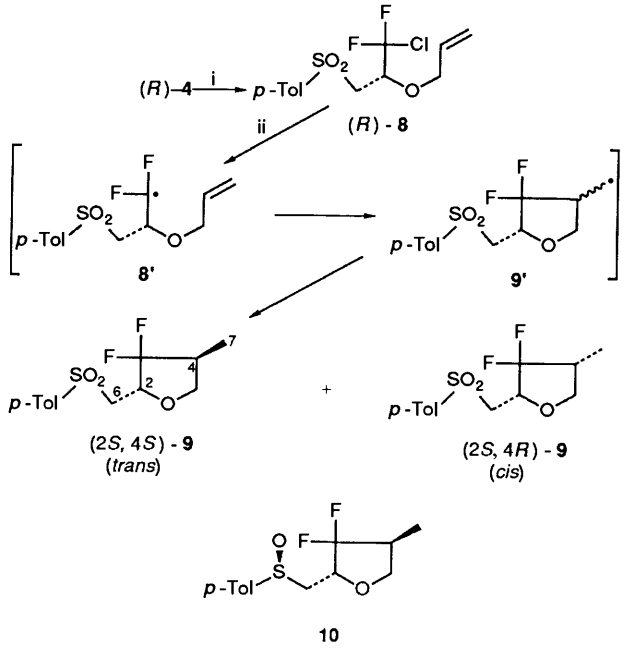
In order to have the appropriate samples to test the enantioselection of the microbial reductions, the alcohol **4** was obtained in the racemic form by lithium borohydride reduction of β-keto sulphone **3**, while the (*R*)-(+)-**4** enantiomer was prepared by mild oxidation, under phase-transfer conditions (potassium permanganate and catalytic tetrabutylammonium bromide in aq. methanol), of (2*R*,S_S)-(−)-1-chloro-1,1-difluoro-3-(*p*-tolylsulphinyl)propan-2-ol **5** (previously obtained in optically pure form).[10]

Chemical Transformations.—While the chirons previously reported have been utilized in asymmetric synthesis through chain elongations obtained by 'anion chemistry',[5–7] the chlorodifluoro chiron **4** is well suited for use in radical reactions.

The most representative applications of the radical reaction forming the carbon–carbon bonds are the *exo* cyclizations of hex-5-enyl radicals, or heteroatom-containing analogues, to five-membered cyclic compounds.[11]

Therefore, in order to show the synthetic utility of chirons **4**, that methodology was applied on a suitably functionalized derivative. The enantiomer (*R*)-**4** was treated with allyl bromide under phase-transfer conditions to give the corresponding allyl ether (*R*)-**8** in 84% yield. The difluoroalkyl radical **8′** was generated from the chlorocompound **8** by abstraction of the much more reactive chlorine atom, according to the tributyltin hydride method (see Scheme 3).

Radical **8′** was captured by the tethered olefin in a fast *exo-trig* cyclization giving the radical **9′**, which upon reductive trapping by tributyltin hydride gave a 95:5 mixture of the *trans* and *cis* 3,3-difluoro-4-methyl-2-[(*p*-tolylsulphonyl)methyl]-tetrahydrofurans (2*S*,4*S*)-**9** and (2*S*,4*R*)-**9** (51% yield). Evidence



Scheme 3 *Reagents and conditions:* i, allyl bromide, 5 mol dm^{-3} NaOH, ethyltrioctylammonium bromide, dichloromethane; ii, Bu_3SnH, benzene, 75 °C

for the proposed structure of the title compounds was provided by the ^1H, ^{13}C and ^{19}F NMR data reported in Table 2 for the *trans* isomer (2*S*,4*S*)-**9** and in the Experimental section for the remaining compounds, and by elemental analyses and mass spectral measurements.

The absolute configuration at C-2 of β-hydroxy sulphones and of tetrahydrofurans was derived from the chemical correlation described above, while the relative *trans* stereo-

Table 2 Selected ^1H, ^{13}C and ^{19}F NMR data for compound *trans*-**9** in $CDCl_3$

Atom[a]	δ	J	Hz	Carbon	δ	J(C,F)/Hz
2-H$^{\beta}$	4.30	2β,6a	3.1	C-2	75.92	35.5, 24.5
3-F^{a}	−108.81	2β,6b	8.7	C-3	128.48	258, 256
3-F^{b}	−116.37	2β,F^{a}	12.9	C-4	39.98	24.0, 21.5
4-H$^{\alpha}$	2.43	2β,F^{b}	11.5	C-5	72.84	6.0, 3.0
5-H$^{\beta}$	3.44	4α,5β	9.0	C-6	55.98	6.5, 2.5
5-H$^{\alpha}$	4.14	4α,5α	8.0	C-7	9.85	8.0, 2.0
6-H^{a}	3.39	4α,7	7.0	C-1′	136.66	
6-H^{b}	3.34	4α,F^{a}	20.2	C-2′,-6′	128.20	
7-H_3	1.07	4α,F^{b}	9.7	C-3′,-5′	129.85	
2′-,6′-H	7.82	5α,5β	9.0	C-4′	144.98	
		6a,6b	14.6			
3′-,5′-H	7.36	7,F^{b}	2.1	C-7′	21.66	
7′-H_3	2.45	F^{a},F^{b}	232.0			

[a] Primed locants refer to the *p*-tolyl group.

chemistry of the major diastereoisomer (2*S*,4*S*)-**9** was assigned on the basis of NOE difference experiments.

The *trans*-isomer (2*S*,4*S*)-**9** was also obtained by oxidization of the corresponding sulphinyl tetrahydrofuran with *m*-chloroperbenzoic acid (MCPBA).[12]

Experimental

IR spectra were taken on a Perkin-Elmer 177 spectrophotometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AC 250L spectrometer. Chemical shifts are in ppm downfield from tetramethylsilane as internal standard (δ_H and δ_C 0.00) for ^1H and ^{13}C nuclei, while C_6F_6 was used as internal standard (δ_F −162.90) for ^{19}F nuclei. *J*-Values are given in Hz. NOE difference spectra were obtained by subtracting, alternatively, right-off resonance-free induction decays (FIDs) from right-on resonance-induced FIDs. NOE-Values reported in the text have only qualitative significance. Mass spectra were obtained by a Finnigan-MAT ITMS instrument operating under electron-impact conditions. The samples were introduced by direct-inlet probe at a temperature of 140–150 °C. The He buffer gas pressure was of 1×10^{-4} mmHg. $[\alpha]_D$-Values were obtained on a Jasco DIP-181 polarimeter. M.p.s were obtained on a capillary apparatus and are uncorrected; 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 diisopropylamine was distilled from calcium hydride and stored over molecular sieves (4 and 13 Å). A 1.6 mol dm^{-3} solution of butyllithium in hexanes (Aldrich) was employed. In other cases commercially available reagent-grade solvents were employed without purification. GLC analyses were performed on a Dani 6800 gas chromatograph using a fused silica capillary OV-1701 column (25 m × 0.32 mm i.d., d_f 0.25 μm) and H_2 as carrier gas at a linear velocity of 54 cm s^{-1}.

Condensation of Methyl p-*Tolyl Sulphone* **1** *with Ethyl Chlorodifluoroacetate* **2**.—A solution of the sulphone **1** (3.00 g, 17.6 mmol) in dry THF (15 cm^3) was added dropwise to a stirred solution of LDA (19.4 mmol) [obtained from diisopropylamine (1.96 g, 19.4 mmol) and butyllithium (12.1 cm^3 of 1.6 mol dm^{-3} solution in hexanes, 19.4 mmol)] in the same solvent (25 cm^3) at −78 °C. After 5 min, a solution of ethyl chlorodifluoroacetate **2** (3.58 g, 24.7 mmol) in THF (5 cm^3) was added to the mixture at −78 °C, and the mixture was stirred for 15 min. The reaction was quenched by addition of saturated aq. ammonium chloride (200 cm^3). The pH was adjusted to 3 with dil. hydrochloric acid, and the mixture was extracted with ethyl acetate (3 × 200 cm^3). The combined organic phases were washed with brine (200 cm^3) and dried with sodium sulphate. Removal of the solvent under reduced pressure yielded a mixture (4.90 g) of product **3** and starting sulphone **1** (73% conversion). An analytical sample was obtained by crystallization (ethyl acetate–hexane), m.p. 70–72 °C; *m/z* 282 (M^+), 197 (M − CF_2Cl) and 155 (M − $CF_2ClCOCH_2$). The crude reaction mixture was submitted to microbial and chemical reduction as follows.

General Procedures for Microbial Reduction.—Each microorganism was grown for the given time (see below) at 30 °C in shaken Erlenmeyer flasks (300 cm^3) containing the given culture medium (50 cm^3). The carbonyl compound **3** (in standard procedure, 25 mg per flask), dissolved in dimethyl sulphoxide (DMSO) (0.5 cm^3), was added to the grown culture and incubation was continued for one further day.

Baker's yeast (25 g) was suspended in water (50 cm^3) containing sucrose (5 g) and the mixture was stirred at 30 °C. To the fermenting medium was added a solution of the ketone **3** (50 mg) in DMSO (0.5 cm^3) and the mixture was stirred for a further 15 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 dry extract (1 mg) was added to a clear solution of (*S*)-2-phenylpropionyl chloride (5 mg) in a mixture of pyridine (0.1 cm^3) and tetrachloromethane (0.1 cm^3) (the corresponding derivatives will be called PP derivatives); after being kept at room temperature overnight the samples were analysed by GLC.

Cladosporium suaveolens, *C. herbarum*, *C. capsici* and *Ceratocystis ulmi* were grown for 3 days at 150 rev min^{-1} on a medium containing glucose (20 g dm^{-3}), malt extract (10 g dm^{-3}) and peptone (5 g dm^{-3}) in deionized water, and adjusted to pH 7. *Beauveria sulfurescens*, *Bacillus polymyxa*, *Candida lipolytica*, *Rhizoctonia solani*, *Rhodotorula glutinis*, *Saccharomyces cerevisiae* and *Zymomonas mobilis* were grown for 3 days at 150 rev min^{-1} on a medium containing glucose (30 g dm^{-3}), malt extract (10 g dm^{-3}) and yeast extract (10 g dm^{-3}) in deionized water, and adjusted to pH 7. Growing cultures of *Absidia orchidis*, *Alternaria tenuis*, *Aspergillus niger*, *A. phoetidus*, *Aureobasidium* sp., *Botritys cinerea*, *Cladosporium peoniae*, *Escherichia coli*, *Fusarium oxysporum*, *Geotrichum candidum*, *Halobacterium halobium*, *Hansenula anomala*, *Kloeckera saturnus*, *Phanerochaete chrysosporium*, *Pichia etchellsii*, *Nocardia* sp., *Saccharomyces delbrueckii*, *Halobacterium salinarum*, *Sarcina lutea*, *Sporoboromyces roseus* and *Sporotrichum laxum* were also tested as reducing agents.

Gas-chromatographic Analysis.—The products from microbial transformation were analysed 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 200 °C (ketone t_R 14.6 min, alcohol t_R 20.2 min). The PP derivatives were analysed as follows: 1 min at 40 °C, then 20 °C min^{-1} to 220 °C, 2 min at 200 °C and finally 1 °C min^{-1} to 250 °C [PP derivatives: (*R*)-**4** t_R 28.4 min, (*S*)-**4** t_R 28.7 min].

Production of (R)-1-*Chloro*-1,1-*difluoro*-3-(p-*tolylsulphonyl*)-*propan*-2-*ol*, (R)-**4**.—A solution of 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-one **3** (1.0 g) in DMSO (10 cm^3) was added to a fermenting suspension of Baker's yeast (500 g) in water (1.0 dm^3) containing sucrose (100 g) and the mixture was stirred at 30 °C. After 20 h fermentation the yeast was separated by filtration through a Celite pad. The aq. phase and the filtration cake were extracted three times with diethyl ether. The combined organic phases were washed successively with saturated aq. sodium hydrogen carbonate and with brine, and were dried over sodium sulphate and the solvent was evaporated off. Flash chromatographic separation of the crude extract with hexane–ethyl acetate (65:35) yielded the alcohol (*R*)-**4** (0.68 g, 68%), 98% pure on GLC; e.e. 78%.

Enantiomerically Pure (R)-1-*Chloro*-1,1-*difluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol*, (R)-**4**.—The 78% enantiomerically pure alcohol (*R*)-**4** (100 mg) was dissolved in a mixture of pyridine (0.5 cm^3) and acetic anhydride (0.5 cm^3), and left overnight at room temperature. The reaction mixture was then diluted with diethyl ether (50 cm^3) and the ethereal solution was washed successively with water, aq. HCl (2% solution), water, saturated aq. $NaHCO_3$ and saturated aq. NaCl, dried over sodium sulphate and evaporated under reduced pressure. The solid acetyl derivative (*R*)-**6** was crystallized from hexane to constant [α] (twice) (90 mg, 80%), $[\alpha]_D^{20}$ +28.0° (*c* 1.0 in $CHCl_3$); m.p. 65 °C; $\delta_H(CDCl_3)$ 7.79 and 7.41 (4 H, m, ArH), 5.79 (1 H, dddd, *J* 7.8, 7.6, 7.3 and 4.3, 2-H), 3.54 (1 H, dd, *J* 14.8 and 7.6, 3-H^a), 3.51 (1 H, dd, *J* 14.8 and 4.3, 3-H^b), 2.48 (3 H, br s, Ar*Me*) and 2.01 (3 H, s, OAc); $\delta_F(CDCl_3)$ −64.6 (1 F, dd, *J* 168.0 and 7.8, 1-F^a) and −65.5 (1 F, dd, *J* 168.0 and 7.3, 1-F^b).

The enantiomerically pure acetyl derivative (*R*)-**6** (50 mg) was dissolved in propan-2-ol (5 cm^3), then treated with tetraisopropyl orthotitanate[8] (50 mg) and the mixture was refluxed overnight, cooled, treated with aq. HCl (5% solution; 1 cm^3) and extracted with diethyl ether (10 cm^3). The organic phase was washed with brine, dried over sodium sulphate and evaporated under reduced pressure. The recovered (*R*)-**4** (40 mg, 90%) was 99% pure on GLC; e.e. > 98%; $[\alpha]_D^{20}$ +12.0° (*c* 1.0 in $CHCl_3$), m.p. 61 °C.

When the acetate (*R*)-**6** was treated with potassium hydroxide in aq. ethanol or with guanidine in anhydrous ethanol, the ethyl ether of racemic 1-chloro-1,1-difluoro-3-(*p*-tolylsulphonyl)propan-2-ol, compound **7**, was obtained; ν_{max}/cm^{-1} 2980, 1600, 1315, 1150, 1030 and 960; $\delta_H(CDCl_3)$ 7.81 and 7.38 (4 H, m, ArH), 4.33 (1 H, dddd, *J* 8.5, 7.7, 5.8 and 2.5, 2-H), 3.85 (1 H, dq, *J* 8.7 and 7.0, OCH^aMe), 3.68 (1 H, dq, *J* 8.7 and 7.0, OCH^bMe), 3.49 (1 H, dd, *J* 14.6 and 8.5, 3-H^a), 3.42 (1 H, dd, *J* 14.6 and 2.5, 3-H^b), 2.45 (3 H, br s, Ar*Me*) and 1.05 (3 H, t, *J* 7.0, OCH_2Me); $\delta_F(CDCl_3)$ −63.1 (1 F, dd, *J* 167.8 and 7.7 Hz, 1-F^a) and −63.7 (1 F, dd, *J* 167.8 and 5.8 Hz, 1-F^b); *m/z* 314 and 312 (M^+).

Preparation of Racemic 1-*Chloro*-1,1-*difluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol* **4**.—A cooled solution (−40 °C) of lithium borohydride (0.74 g, 34 mmol) in a 9:1 (v/v) mixture (20 cm^3) of methanol and 32% aq. ammonia was added dropwise, under nitrogen, at −40 °C, into a solution, in the same solvent (6 cm^3), of the crude mixture obtained from the condensation of compounds **1** and **2** (see above) and containing the sulphonyl ketone **3** (4.9 g of mixture, 12.8 mmol of **3**). After the mixture had been stirred for 5 min, dil. HCl was added until pH 2 was reached, methanol was removed under reduced pressure, and the residue was extracted with ethyl acetate (3 × 100 cm^3). The combined organic phases were washed with brine (100 cm^3) and dried (Na_2SO_4). Evaporation to dryness and flash chromatography of the residue with hexane–ethyl acetate (7:3) afforded 1.76 g (48% yield) of pure racemic (±)-**4**, m.p. 86–88 °C (from Pr^i_2O).

Preparation of (R)-(+)-1-*Chloro*-1,1-*difluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol*, (R)-**4**, *by Oxidation of the Corresponding Sulphinyl Derivative* (2R,S_S)-**5**.—A solution of potassium permanganate (49 mg, 0.31 mmol) and tetrabutylammonium bromide (28 mg, 0.09 mmol) in water (5 cm^3) was added dropwise at room temperature into a solution of (2*R*,S_S)-1-chloro-1,1-difluoro-3-(*p*-tolylsulphinyl)propan-2-ol **5** (117 mg, 0.44 mmol)[10] in dichloromethane–acetic acid (95:5; 2.5 cm^3). Vigorous magnetic stirring was maintained for 4 h, then water (20 cm^3), saturated aq. sodium thiosulphate (5.0 cm^3), and dil. hydrochloric acid (1.0 cm^3) were added in that order. The aq. phase was extracted with dichloromethane (3 × 20 cm^3) and the combined 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 (7:3), afforded (R)-(+)-1-*chloro*-1,1-*difluoro*-3-(*p*-*tolylsulphonyl*)*propan*-2-*ol* (*R*)-**4** (101 mg, 80%) in pure form. An analytical sample was crystallized from Pr^i_2O–hexane, m.p. 61–62 °C (Found: C, 42.2; H, 4.0. $C_{10}H_{11}ClF_2O_3S$ requires C, 42.19; H, 3.89%); $[\alpha]_D^{20}$ +12.1° (*c* 0.7 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3410, 1580, 1240, 1130, 1090 and 1000; $\delta_H(CDCl_3)$ 7.83 and 7.41 (4 H, m, ArH), 4.58 (1 H, dddd, *J* 8.3, 7.3, 7.0 and 3.4 Hz, 2-H), 3.79 (1 H, br signal, 2-OH), 3.44 (1 H, dd, *J* 14.3 and 3.4, 3-H^a), 3.41 (1 H, dd, *J* 14.3 and 8.3, 3-H^b) and 2.48 (3 H, br s, Me); $\delta_F(CDCl_3)$ −65.2 (1 F, dd, *J* 167.8 and 7.0, 1-F^a) and −67.2 (1 F, dd, *J* 167.8 and 7.3, 1-Fb); *m/z* 284 (M^+), 199 (M − CF_2Cl) and 155 (M − $CF_2ClCHOHCH_2$).

Reaction of (R)-(+)-1-*Chloro*-1,1-*difluoro*-3-(p-*tolylsulphonyl*)*propan*-2-*ol*, (R)-**4**, *with Allyl Bromide*.—A solution of the alcohol (*R*)-**4** (0.50 g, 1.75 mmol), allyl bromide (0.76 cm^3, 8.7 mmol) and ethyltrioctylammonium bromide (40 mg, 0.09 mmol) in dichloromethane (2.5 cm^3) and 5 mol dm^{-3} aq. sodium hydroxide (3.5 cm^3) were vigorously stirred at room temperature. Within a few minutes a white solid had formed, which then slowly disappeared. After 12 h, when no more alcohol (*R*)-**4** was present, the biphasic system was treated with dichloromethane (5 cm^3) and a saturated aq. ammonium chloride (15 cm^3). The two layers were separated, the aq. phase was extracted with dichloromethane (2 × 15 cm^3) and the combined organic phases were dried with sodium sulphate. The solvent was evaporated off under reduced pressure and the crude product was purified by flash chromatography with hexane–ethyl acetate (8:2) to give pure compound (*R*)-**8** (0.48 g, 84%) as an oil; ν_{max}(Nujol)/cm^{-1} 2900, 1580, 1310, 1140 and 1020; $\delta_H(CDCl_3)$ 7.81 and 7.37 (4 H, m, ArH), 5.75 (1 H, dddd, *J* 17.2, 10.2, 6.0 and 5.9, 2′-H), 5.22 (1 H, dddd, *J* 17.2, 1.5, 1.5 and 1.5, 3′-H^a), 5.18 (1 H, dddd, *J* 10.2, 1.5, 1.2 and 1.2, 3′-H^b), 4.40 (1 H, dddd, *J* 8.3, 7.6, 5.6 and 2.5, 2-H), 4.29 (1 H, br dd, *J* 11.8 and 6.0, 1′-H^a), 4.18 (1 H, br dd, *J* 11.8 and 5.9, 1′-H^b), 3.51 (1 H, dd, *J* 14.6 and 8.3, 3-H^a), 3.46 (1 H, dd, *J* 14.6 and 2.5, 3-H^b) and 2.46 (3 H, br s, Me); *m/z* 324 (M^+) and 155 [M − $CF_2ClCH(OCH_2CH{=}CH_2)CH_2$].

Radical Cyclization of Compound (R)-**8**.—To a stirred solution of the allyl ether (*R*)-**8** (0.4 g, 1.12 mmol) and azoisobutyronitrile (AIBN) (6 mg, 0.035 mmol) in oxygen-free

benzene (2.5 cm^3) at 75 °C under nitrogen was very slowly added a solution of tributyltin hydride (0.33 cm^3, 1.25 mmol) in the same solvent (10 cm^3) (*ca.* 3 h). The reaction mixture was further stirred (*ca.* 4 h) at 75 °C, and after evaporation of the solvent the residue was vigorously stirred for 1 h with a saturated aq. solution of sodium fluoride (5 cm^3). The slurry was extracted with ethyl acetate (3 × 5 cm^3) and the combined organic phases were filtered and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by flash chromatography with hexane–ethyl acetate (8:2) to give 0.18 g of a 95:5 mixture of *trans*-**9** and *cis*-**9** (Found: C, 54.0; H, 5.5. $C_{13}H_{16}F_2O_3S$ requires C, 53.78; H, 5.55%); *m/z* 290 (M^+), 155 (M − 135) and 135 (M − $MeC_6H_4SO_2$). The selected ^1H, ^{13}C and ^{19}F NMR data for *trans*-**9** are reported in Table 2, while the ^1H and ^{19}F NMR data for *cis*-**9** are: $\delta_H(CDCl_3)$ 7.82 and 7.36 (4 H, m, ArH), 4.45 (1 H, br dddd, *J* 16.5, 8.5, 7.5 and 3.3, 2-H), 4.10 (1 H, ddd, *J* 9.0, 8.0 and 0.8, 5-H^{β}), 3.58 (1 H, ddd, *J* 9.0, 8.3 and 1.0, 5-H^{α}), 3.35 (2 H, m, 6-H_2), 2.50 (1 H, m, 4-H), 2.45 (3 H, m, Ar*Me*) and 1.07 (3 H, m, 7-H_3); $\delta_F(CDCl_3)$ −114.87 (1 F, ddd, *J* 230.5, 12.1 and 7.5, 3-F^a) and −124.78 (1 F, ddd, *J* 230.5, 17.5 and 16.5, 3-F^b).

Preparation of (2S,4S)-3,3-*Difluoro*-4-*methyl*-2-[(p-*tolylsulphonyl*)*methyl*]*tetrahydrofuran* **9** *by Oxidation of the Corresponding Sulphinyl Derivative* (2S,4S,S_S)-**10**.—A solution of compound **10** (400 mg, 1.46 mmol)[12] in dichloromethane (10 cm^3) was treated at room temperature with a solution of MCPBA (360 mg, 2.02 mmol) in the same solvent (10 cm^3). After 24 h the reaction mixture was treated with saturated aq. sodium thiosulphate (10 cm^3) and the organic phase was washed with saturated aq. sodium hydrogen carbonate (10 cm^3) and dried (Na_2SO_4). The solvent was evaporated off under reduced pressure and the residue was purified by flash chromatography with hexane–ethyl acetate (8:2) to afford (2*S*,4*S*)-3,3-difluoro-4-methyl-2-[(*p*-tolylsulphonyl)methyl]-tetrahydrofuran (*trans*-**9**) (266 mg, 63%).

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