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Synthesis of Fluorinated Chirons: Stereoselective Oxirane Formation by Reaction of Diazomethane on 1-Fluoro-3-arylsulfinyl-2-propanone and Ring Opening by Selected Nucleophiles

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Abstract: (*R*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanone (**1**) reacts with diazomethane affording (*S*)-2-(fluoromethyl)-2-{[(*R*)-(4-methylphenyl)sulfinyl]methyl}oxirane (**2**) as the main product. The influence of reaction conditions (solvent, temperature) on the chemo- and stereoselectivity has been studied. Several elaborations of **2**, including reactions on the chiral auxiliary and opening of the oxirane ring by carbon, nitrogen, oxygen, phosphorus and halogen nucleophiles, are described. Full structural elucidation of the products is provided.

INTRODUCTION

Enantioselective preparation of oxiranes constitutes a challenging and important synthetic problem, since these compounds are obviously highly valuable chiral synthons.[1] Numerous approaches have been explored in order to achieve the synthesis of oxiranes in optically pure form. Sharpless method, oxidation catalysed by metal complexes and porphyrins, and microbiologically mediated stereospecific oxidation which allow direct stereoselective epoxidation of various olefins, and microbiologically mediated enantioselective hydrolysis of starting racemic epoxy esters have been used widely.[2]

In the course of our study on the synthesis of versatile intermediates for biologically active organofluorine compounds via functionalization of readily available fluorochemicals,[3] we have been exploring a different approach for the preparation of chiral and optically pure selectively fluorosubstituted oxiranes.

It is well known that diazomethane reacts with the carbonyl group of aldehydes and ketones giving in most cases mixtures of products in which the corresponding homologous derivatives generally predominate, and with easily enolizable ketones it gives rise mainly to the corresponding methyl enol ethers. The oxiranes in most of the reported cases are only minor products. It has been already observed that the introduction of electron-withdrawing substituents on the carbonyl group favours the formation of the oxiranes and increases their yields.[4]

The introduction of a chiral auxiliary, the *p*-tolylsulfinyl group, next to fluorinated carbonyls allows the transfer of a methylene from diazomethane to carbonyl with high chemoselectivity and under efficient stereocontrol by the chiral sulfur atom. The substrates we have been using are 1-arylsulfinyl-3-halogen substituted-2-propanones. They possess two electron-withdrawing groups placed on both α-carbons, the sulfinyl chiral auxiliary group on one side and the halogen on the other side of the carbonyl. Both the substituents exert their activation on the central carbon-oxygen double bond, while each one tend to increase the acidity of a single methylene. As a consequence one can expect that the formation of oxiranes (through the transfer of the methylene to the electron-poor C=O bond) would be favoured over the formation of the corresponding methyl enol ethers. Moreover it has been observed that polar solvents, compatible with the use of diazomethane, like alcohols would largely increase the reaction rate. The particular attributes of the carbonyl epoxidation reaction, in addition to the importance of forming a new carbon-carbon bond under high stereocontrol,[5] result from the fact that the newly introduced carbon substituent is functionalised.

In an effort to further extend the earlier studies, we have searched for the best reaction conditions in the synthesis of the fluoro oxirane **2** from (*R*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanone (**1**) and in a number of reactions that could be selectively performed on the oxirane ring in order to obtain a large variety of open-chain compounds endowed with new functional groups. In the present paper we give a full account of our results.

A preliminary communication on the subject, and a paper dealing mainly with the reactions run on the carbon bearing the sulfinyl group of fluorinated oxiranes to obtain a number of sulfur-free fluorinated compounds, have been already published.[6]

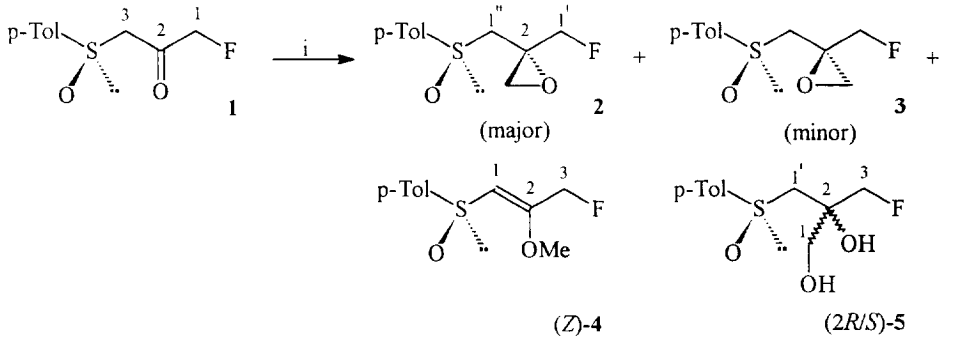
RESULTS AND DISCUSSION

Compound **1** is dissolved in different solvents: ethyl ether, benzene, methanol and an excess of ethereal solution of diazomethane is added. The results are summarised in Table 1, and the usually observed products of the reaction, whose ratio is strongly dependent on experimental conditions, *i.e.* solvent and temperature, are depicted in Scheme 1. In ethyl ether, at 0°C (entry 1), the ratio of the diastereoisomeric oxiranes **2** and **3** is high (d.e. = 88%), but the enolether **4** is formed in 16% yield. Similar results, but with lower diastereoselection (d.e. = 74%), are obtained in benzene at room temperature (entry 2). In methanol at 0°C (entry 3) a very high chemoselectivity is accompanied by a lower diastereoselectivity (d.e. = 60%) and by the formation, through opening of the preformed oxirane ring, of diols **5**. Decreasing the reaction temperature inhibits this side-reaction (10% at 0°C, 6% at -15°C and 2% at -78°C), but also decreases d.e. (60% at 0°C, 34% at -15°C and 24% at -78°C). In order to try to minimise diols formation, that can be negligible when reacting small amounts of **2** with a large excess of reagent, but can be a problem for large-scale preparations with stoichiometric amounts of diazomethane, TEA is added (entry 6). Actually, no diols **5** are detected, though both chemoselectivity (enolether **4** yield = 34%) and diastereoselectivity (d.e. = 15%) decrease.

In conclusion it can be stressed that by an appropriate selection of experimental conditions (entry 1) good yields of oxirane (2*S*,R_S)-**2** with high d.e. can be reached; furthermore the same oxirane is easily obtained in optically pure form after flash chromatography and fractional crystallisation.

The high diastereoselection in favour of (2*S*,R_S)-**2** may be related to the presence, in α to the carbonyl group of **1**, of a strong electron-withdrawing group such as fluorine. Similar results were indeed obtained when

the corresponding bromo- and chloro-derivatives were used, whereas corresponding methyl and hydroxymethyl carbonyl derivatives reacted with very low or no stereoselection.[7] Therefore the fluorine group should strongly favour a ground-state conformation of ketone **1** in which diazomethane can approach the carbonyl group from one side much better than from the other one, probably hindered by the p-tolyl group.[8]



i) CH_2N_2 (solvent, temperature: see Table 1)

Scheme 1

Table 1. Chemo- and Diastereoselectivity of CH_2N_2 Reaction on **1**

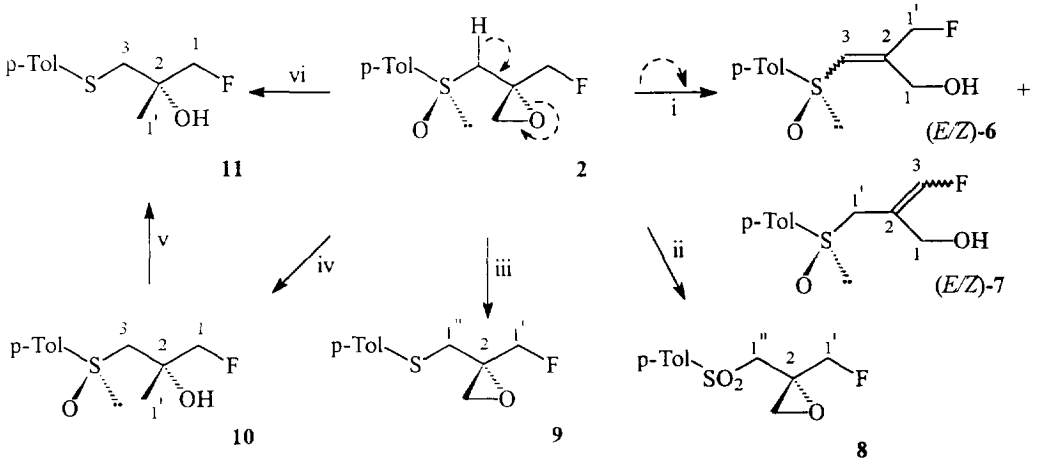
Entry	Solvent	Temperature (°C)	Global Yield (%)	Oxiranes 2 : 3 Ratio	Oxiranes 2 + 3 (+ 5) Yield (%)	Enolether 4 Yield (%)
1	ethyl ether	0	90	94 : 6	74	16
2	benzene	25	67	87 : 13	56	11
3	methanol	0	92	80 : 20	92	-
4	methanol	- 15	95	67 : 33	95	-
5	methanol	- 78	90	62 : 38	90	-
6	methanol + triethylamine	0	70	57 : 43	36	34

General Considerations on the Reactivity of 2

For any elaboration to be performed on oxirane **2** it is important to take into account the basicity *versus* nucleophilicity of the reactive species in the reaction medium used.[9]

When basicity overcomes nucleophilicity, a deprotonation at carbon 1" occurs and an irreversible opening of the oxirane ring, with contemporary loss of the stereogenic centre at carbon 2, takes place through a push-pull mechanism,[10] as described in Scheme 2, giving mainly hydroxymethyl olefins (*E*)-, (*Z*)-**6** and (*E*)-, (*Z*)-**7**. Specifically, when oxirane **2** was submitted at low temperature to the action of one equivalent of butyllithium, LDA, or lithium salt of phenylacetylene in anhydrous THF, or simply aqueous potassium hydroxide at room temperature, the only isolated products resulted to be the α,β-unsaturated sulfinyl derivatives (**6**), in mixture with their fluorovinyl isomers **7** (see Experimental).

On the contrary, the action of $LiAlH_4$ in anhydrous THF at low temperature lead, selectively, to the formation of the methyl carbinol **10**, due to the nucleophilic attack of the hydride species on the less substituted carbon of the oxirane ring.



i) LDA, THF, -78°C; or KOH, H_2O, r.t.; ii) MCPBA, CH_2Cl_2, r.t.; iii) $(CF_3CO)_2O$, NaI, acetone; iv) $LiAlH_4$, THF, -70°C; v) $(CF_3CO)_2O$, NaI, acetone; vi) $LiAlH_4$ (1 mol excess), THF, -70°C

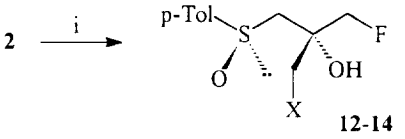
Scheme 2

Selective Reductions and Oxidations

The main reactions performed involving the sulfinyl chiral auxiliary group are the following: a) selective oxidation with *m*-CPBA to give the corresponding sulfonyl derivative **8** in 52% yield; b) selective reductions. Generally we make use of the Oae procedure[11] to obtain the corresponding thio ether **9** in 86% yield. The compound **9** may be fruitfully used in some transformations of the oxirane ring because of the different sensitivity to basic conditions of the protons α to sulfur (see onward). Selective reductive conditions for ring opening of the oxirane to give fluoromethyl methyl [(4-methylphenyl)sulfinyl]methyl tertiary alcohol **10** by $LiAlH_4$ in anhydrous THF at low temperature can be achieved. An excess of the same reducing agent at room temperature affords thiomethyl tertiary alcohol **11** in 86% yield.

Synthesis of β-Halohydrins 12-14

Among the large number of methodologies reported for the preparation of vicinal halohydrins by ring opening of oxiranes we used dilithium tetrahalocuprates, reagents readily prepared *in situ* from lithium halides and copper(II) halides. They have been used on functionalized oxiranes to afford the corresponding vicinal chlorohydrins and bromohydrins in high regioisomeric purity and high yields under mild, near neutral conditions.



12-14

	X
12	Cl
13	Br
14	I

i) (X = Cl) $CuCl_2$, LiCl, THF, 0°C; (X = Br) $CuBr_2$, LiBr, THF, 0°C; (X = I) CuI, LiI, THF, 0°C

Scheme 3

Chlorohydrin[12] **12** and bromohydrin[13] **13** were obtained in, respectively, 86% and 94% isolated yields by nucleophilic attack on the less substituted carbon (Scheme 3).

The same methodology was extended in order to obtain the corresponding iodohydrin **14**. A 90% conversion was observed, however iodohydrin **14** spontaneously converted back in part to the starting oxirane **2** during work-up and column chromatographic purification. Anyway an about 50% isolated yield of pure crystalline product could be achieved. All three halohydrins are converted back to oxirane **2** in nearly quantitative yield by triethylamine.

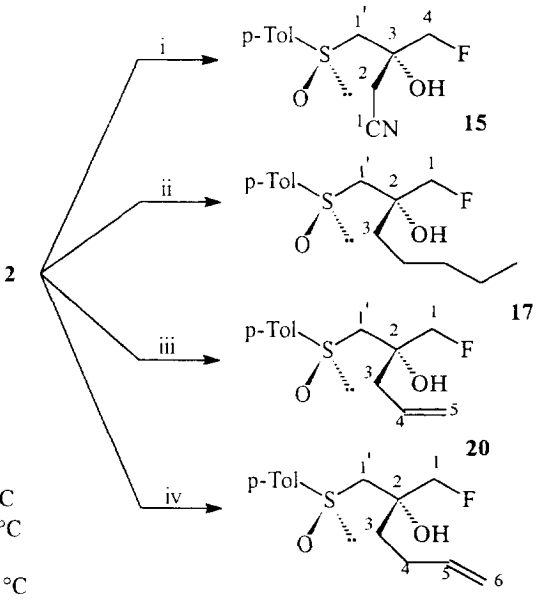
Carbon-carbon σ-Bond Forming Reactions

Nucleophilic ring opening of oxiranes with organometallic reagents has found widespread application in the formation of carbon-carbon σ bonds. Among the most common reagents employed are organo-magnesium, lithium, copper, zinc, aluminium, and boron compounds.[1b,1d,14] In some cases the basicity of some of these reagents or the use of strong Lewis acids as catalysts can promote undesired side reactions, in our case ring opening through abstraction of C-1" proton to give the allylic alcohol **6**. The reactivity of nucleophiles and catalysts must therefore be properly tuned.

One-carbon homologation can be achieved by "normal" ring opening by cyanide ion. The use of NaCN in acetonitrile under $LiClO_4$ catalysis[15] gave good yield (98%) of the corresponding hydroxynitrile **15** as the sole reaction product (Scheme 4). Selected reagents and conditions reported in the literature,[16] like Et_2AlCN, Me_3SiCN or acetone cyanohydrin under $Ti(OPr^i)_4$ catalysis were unnecessary. Attempts to open the oxirane ring of **2** using trimethylsilyl cyanide under zinc iodide catalysis, afforded only the O-trimethylsilyl-protected derivative **16** of the iodide-promoted nucleophilic ring opening (see experimental) that could be easily reconverted to the starting oxirane **2**.

The formation of carbon-carbon σ bonds with alkyl, vinyl or allyl reagents was more problematic. Butylmagnesium chloride or bromide gave poor yield in alkylated tertiary alcohol **17** because of the presence in solution of nucleophilic chloride or bromide ions that interfere in ring opening of oxirane affording the corresponding chlorohydrin **12** or bromohydrin **13** as major product.[17] Butyl cuprate[18] on oxirane **2** gave **17** in 40% yield, along with unreacted starting material that was recovered in 10% yield. Attack by the cupric anion on C-3 and on fluorine-bearing carbon C-1' of the α,β-unsaturated derivatives **6**, that easily formed in basic medium, gave rise respectively, through fluorine elimination, to the by-products (*R/S*)-2-{1'-[(*R*)-(4-methylphenyl)sulfinyl]pentyl}-2-propen-1-ols (**18**) and (*Z*)-[(*R*)-(4-methylphenyl)sulfinyl]-2-pentyl-2-propen-1-ol (**19**) (see Experimental). Vinyl and allyl magnesium bromides gave better yields of the corresponding allyl **20** and 3-butenyl **21** tertiary carbinols (34 % and 67% yield, respectively), bromohydrin **13** being minor product. The use of one equivalent of $TiCl_4$ catalyst resulted in chloride-promoted opening to form chlorohydrin **12** in

high yields. In an attempt to minimise chloride opening, the less reactive Lewis acid $Ti(OPr^i)_4$ was used, but it was ineffective: no reaction occurred between -70°C to room temperature.



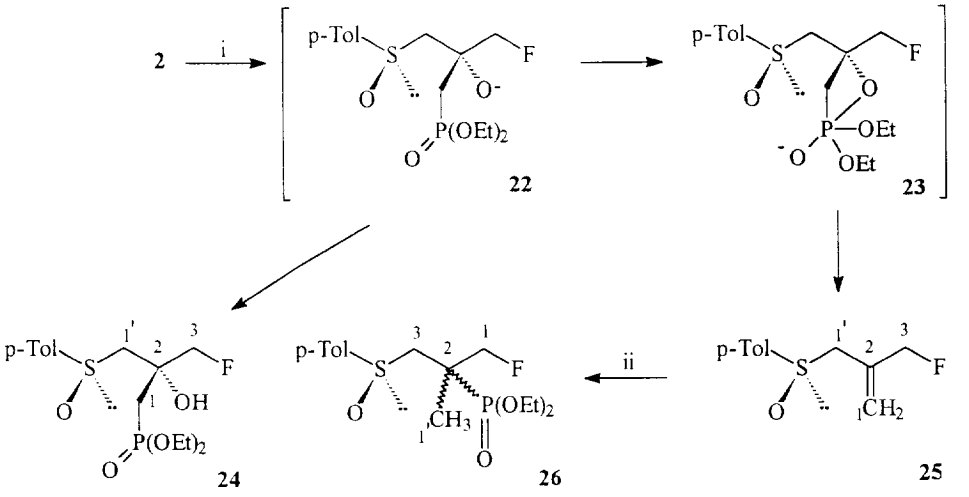
i: NaCN, CH_3CN, $LiClO_4$, 60 °C
ii: CuI, THF, butyllithium, - 20 °C
iii: CH_2=$CHMgCl$, THF, 5 °C
iv: CH_2=$CHCH_2MgCl$, THF, 5 °C

Scheme 4

Phosphorus Derivatives

Interest in phosphonate chemistry and biology is attributed to the fact that carbon-phosphorus bond in phosphonates, unlike phosphates, is not susceptible to the hydrolytic action of phosphatases, imparting stability and longer life under physiological conditions to phosphonate isosteres of biologically important phosphates. Very few examples are known in the literature concerning phosphorus of phosphorus-containing nucleophiles used in ring-opening reactions of oxiranes.[19]

The first step of the reaction is the generation of the lithium derivative of diethylphosphite by butyllithium in anhydrous THF or potassium *tert*-butoxide in DMF. The intermediate **22** formed through addition of the phosphite anion to the terminal carbon of oxirane **2** (Scheme 5). Protonation of **22** would allow isolation of phosphonate **24**, while cyclization to a four-membered oxaphosphethane ring **23** provides, upon quenching, the olefin **25** and the corresponding diethylphosphate ion, because of the formation of the strong P=O bond. In every case, both using buthyllithium or potassium *tert*-butoxide, the largely prevailing product of reaction was the methylene derivative **25**.[20] Depending on reaction conditions, different mixtures of 1-phosphonate **24**, olefin **25**, and 2-phosphonate **26** were isolated (see Experimental). The last product can be hypothesised deriving from **25** by further addition of diethyl phosphite ion to the double bond, as demonstrated reacting **25** in the same experimental conditions as **2** for longer time. To obtain high yields in 1-phosphonate derivative, the reaction had to be carried out on the corresponding thio derivative **9** (see onward).



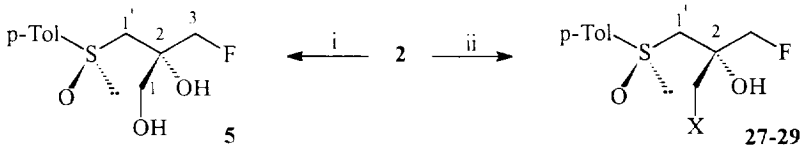
i: $(EtO)_2OPH$, LDA, THF, -60°C, or $(EtO)_2OPH$, *tert*-BuOK, DMF, 0°C
ii: $(EtO)_2OPH$, *tert*-BuOK, DMF, 0°C

Scheme 5

Oxygen- and Nitrogen-centred Nucleophiles[21]

In oxygen nucleophiles like hydroxy and alkoxy ions, basicity overcomes nucleophilicity so that ring opening of oxirane **2** by α-proton abstraction prevails to form hydroxymethyl olefins **6/7** as the sole reaction products. In order to obtain dihydroxy derivative **5** (Scheme 6) one should operate under acid-catalysed conditions. Treatment of **2** in THF/water mixture with perchloric acid at room temperature afforded $(2S,R_S)$-**5** in 95% yield.

On the contrary, nitrogen-centred nucleophiles like azide ion and primary and secondary amines like benzyl and dibenzylamine are strong nucleophiles and weak bases. Upon reaction with oxirane **2** in THF at r.t. they afforded the corresponding azide **27**, benzyl- **28** and dibenzylamino **29** derivatives, in 74%, 95% and 97% yield respectively, as the sole reaction products.



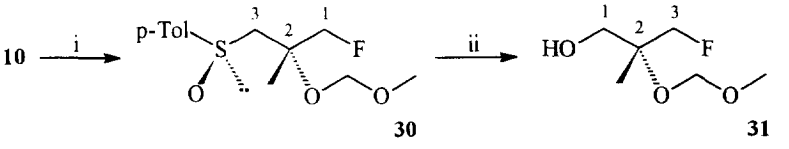
i) $THF/H_2O/HClO_4$, r.t.
ii) NaN_3, NH_4Cl, EtOH, r.t. (X = N_3); $PhCH_2NH_2$, THF, r.t. (X = NHBn); $(PhCH_2)_2NH$, THF, r.t.[X = $NH(Bn)_2$]

	X
27	N_3
28	NHBn
29	$N(Bn)_2$

Scheme 6

Pummerer Rearrangement[22] *Performed on 10*

One example of chemical transformation of the sulfoxide group to give a sulfur-free product was investigated (Scheme 7). Specifically, the sulfinyl alcohol **10**, deriving from **2** through $LiAlH_4$-promoted opening of the oxirane ring, was submitted, first of all, to protection of the hydroxy group. Formaldehyde dimethylacetale was used as solvent and the reaction was catalysed by P_2O_5. Rigorously anhydrous experimental conditions have to be used in order to avoid a certain amount (10%, see Experimental) of the C-2 epimer, (2*R*,*R*$_S$)-**30**, due to elimination/addition of water from the protonated tertiary alcohol. The intermediate methoxymethyl ether **30** was then submitted to Pummerer rearrangement, following the usual procedure, to give the derivative **31** in 70% global yield from **10**.

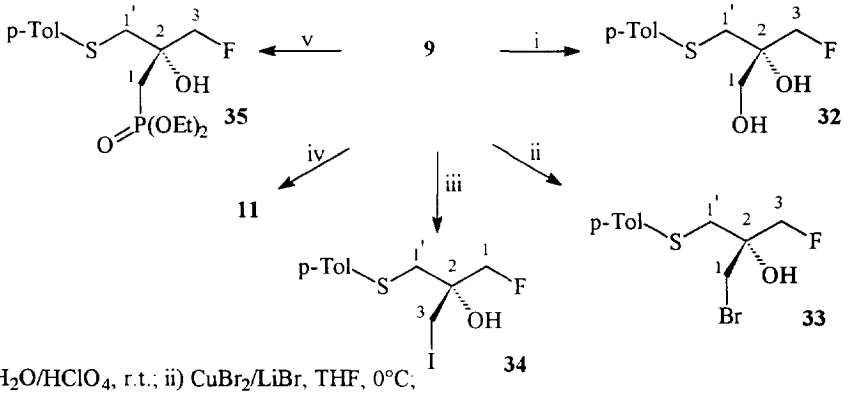


i) $H_2C(OCH_3)_2$, P_2O_5; ii) *sym*-collidine, CH_3CN, $(CF_3CO)_2O$, $HgCl_2$, $NaBH_4$

Scheme 7

Nucleophilic Ring Opening of the Thio Derivative 9

To the thio derivative **9**, obtained from **2** through reductive Oae procedure, some nucleophilic ring opening reactions were tested, in order to compare the reactivity of the oxirane moiety in the two substrates (Scheme 8).



i) $THF/H_2O/HClO_4$, r.t.; ii) $CuBr_2/LiBr$, THF, 0°C;
iii) NaI, THF, r.t.; iv) $LiAlH_4$, THF, -70°C;
v) $(CH_3)_3COK$, DMF, Et_2OPOH, 0°C

Scheme 8

Generally, the reactivity of **9** was similar to that found for **2**. In the obtainment of diol **32** and of bromohydrin **33**, the p-tolylthio group seemed to slow down the reaction if compared with sulfoxide moiety (see Experimental). On the other hand, the iodohydrin **34** could be obtained with simple adding of sodium iodide,

instead of the cupric species used for the obtainment of the corresponding sulfinyl derivative **14**, in similar reaction time and in comparable yields.

However, in the case of nucleophilic opening with a phosphorus-centred nucleophile, a clean difference in the chemical behaviour was observed. The reaction between **9** and phosphite ion lead to the phosphonate **35** in 76% yield, along with a 2:1 mixture of diethyl (*E*)- and (*Z*)-2-(fluoromethyl)-3-[(4-methylphenyl)thio]-2-propene phosphonate (**36**) (10% yield). Any further rearrangement, as observed for the corresponding sulfinylic alkylphosphonate **24** to give the methylenic derivative **25**, had never been detected.

Structural Assignments

The structure of compounds **1-21** and **24-36** was determined by elemental analyses and ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR studies, the results of which are collected in Tables 2 and 3 and in the experimental section, while the absolute configuration of the newly created C-2 chiral centre of compound **2** was assigned by X-ray analysis.[23]

The presence of oxirane moieties in compounds **3**, **8** and **9**, as well as in **2**, was evidenced by the values ranging between 4.1 and 4.3 Hz exhibited by the 3-methylene protons.

In the compounds **4**, **6**, **7**, **18-21**, **25** and **36** the presence of olefinic protons was revealed by the signals resonating between 4.97 and 6.70 ppm. In compounds **18a,b** and **25** they are part of *gem*-disubstituted double bonds since they were correlated with methylene olefinic carbons resonating at 120.17, 117.31 and 121.01 ppm, while in compounds **7** they exhibited characteristic geminal couplings of 81.8 and 82.5 Hz with the F atoms.[24] The determination of the stereochemistry of the double bonds followed from NOE experiments (see Experimental).

Table 2. ^{1}H and ^{19}F NMR Data of Compounds **2**, **3**, **8** and **9** in $CDCl_3$.

	2	**3**	**8**	**9**		**2**	**3**	**8**	**9**
3a	3.20	2.94	2.91	2.71	$J_{3a,3b}$	4.1	4.3	4.1	4.3
3b	2.93	2.90	2.86	2.63	$J_{1'a,1'b}$	10.5	10.7	10.6	10.3
1'a	4.58	4.92	4.90	4.76	$J_{1''a,1''b}$	14.0	13.6	14.3	14.3
1'b	4.32	4.46	4.34	4.40	$J_{3a,F}$	4.7	4.6	5.0	4.9
1''a	3.45	3.33	3.87	3.36	$J_{3b,F}$	1.0	1.0	1.2	1.0
1''b	2.87	2.78	3.01	2.96	$J_{1'a,F}$	47.3	47.6	47.3	47.3
	7.55	7.55	7.80	7.32	$J_{1'b,F}$	47.0	46.9	46.5	47.0
***p*-Tol**	7.36	7.35	7.40	7.10	$J_{1''a,F}$	<0.5	0.6	<0.5	<0.5
	2.43	2.42	2.47	2.32	$J_{1''b,F}$	1.3	1.3	1.2	1.7
F	-228.97	-228.74	-229.85	-230.03					

The presence in compounds **10**, **11**, **30** and **31** of methyl groups or in compounds **12-17**, **20**, **21**, **24**, **27-29**, and **32-35** of methylene protons having geminal couplings ranging between 9.1 and 16.7 Hz in place of the 3-methylene protons of the parent compounds **2** and **9** provided evidence of the opening of the oxirane rings.

Table 3. ^{1}H and ^{19}F NMR Data[a] for Compounds **5**, **10-14**, **16**, **17**, **20**, **21**, **24-35** in $CDCl_3$

	5	(R_S,S_C)-**10**	**11**	**12**	**13**	**14**	**16**	**17**	**20**	**21**	(R_S,R_C)-**24**
1a	3.71	4.28	4.26	3.78	3.65	4.84	4.67	4.78	4.77	4.80	2.53
1b	3.71	4.26	4.24	3.68	3.57	4.62	4.51	4.48	4.50	4.49	2.29
3a	4.60	3.07	3.21	4.76	4.81	3.46	3.71	1.62	2.42	1.72	4.56
3b	4.41	2.83	3.07	4.63	4.64	3.42	3.71	1.62	2.42	1.72	4.56
1'a	3.13	1.62	1.27	3.14	3.15	3.14	3.18	2.99	2.98	3.00	3.22
1'b	2.90			2.96	2.98	2.98	2.92	2.85	2.84	2.87	3.03
OR-2	4.30	4.34	2.50	4.73	4.70	4.82		4.48	4.52	4.57	2.40
	7.57	7.54	7.32	7.57	7.58	7.57	7.56	7.56	7.56	7.56	7.56
p-Tol	7.37	7.36	7.09	7.37	7.37	7.38	7.34	7.37	7.37	7.37	7.33
	2.43	2.43	2.31	2.43	2.44	2.42	2.42	2.43	2.43	2.43	2.42
F	-229.44	-227.29	-227.38	-226.94	-226.31	-223.83	-225.20	-233.81	-224.37	-223.66	-223.57
$J_{1a,1b}$	b	9.4	9.2	11.5	10.9	9.8	9.9	9.6	9.6	9.6	15.8
$J_{3a,3b}$	9.5	13.5	13.7	9.8	9.7	10.9	b	b	b	b	b
$J_{1'a,1'b}$	13.7			13.6	13.6	13.6	13.8	13.5	13.5	13.4	13.7
$J_{1a,F}$	b	47.0	47.2	1.7	1.8	46.8	47.1	47.5	47.1	47.1	1.9
$J_{1b,F}$	b	47.5	47.3	1.7	1.7	46.7	46.9	46.9	46.4	46.6	1.5
$J_{3a,F}$	47.1	1.0	1.5	46.7	46.6	1.8	1.7	b	b	b	46.8
$J_{3b,F}$	46.9	1.7	1.5	46.7	46.6	1.6	1.7	b	b	b	46.8
$J_{1'a,F}$	1.5	2.3	2.2	2.0	1.9	1.7	<0.5	1.3	1.5	1.6	1.6
$J_{1'b,F}$	1.5			1.9	2.0	2.3	2.3	2.3	2.2	2.2	1.9

Table 3 (continued)

	(R_S,R/S_C) **26a**	(R_S,S/R_C) **26b**	**27**	**28**	**29**	($R_S R_C$)- **30a**	($R_S S_C$)- **30b**	**31**	**32**	**33**	**34**	**35**
1a	4.88	4.80	4.77	2.92	2.90	4.69	4.50	3.62	3.64	3.58	4.44	2.32
1b	4.83	4.69	4.55	2.78	2.72	4.64	4.34	3.58	3.61	3.54	4.44	2.17
3a	3.09	3.13	3.41	4.56	4.51	3.08	3.05	4.42	4.38	4.45	3.44	4.41
3b	3.04	2.92	3.41	4.42	4.34	2.98	2.99	4.37	4.33	4.43	3.40	4.41
1'a	1.48	1.58	3.09	3.11	3.05	1.48	1.60	1.26	3.20	3.30	3.31	3.29
1'b			2.86	2.87	2.44				3.15	3.24	3.27	3.24
OR-2			4.88	2.00	4.50				3.05	2.70	2.65	2.00
	7.54	7.55	7.57	7.54	7.46	7.54	7.56		7.32	7.35	7.36	7.32
p-Tol	7.33	7.33	7.37	7.34	7.33	7.33	7.34		7.10	7.12	7.12	7.10
	2.41	2.41	2.44	2.41	2.44	2.42	2.41		2.31	2.32	2.33	2.31
F	-223.42	-222.36	-225.90	-226.38	-224.16	-225.82	-225.88		-231.84	-230.30	-228.67	-226.26
$J_{1a,1b}$	9.9	9.4	9.7	12.4	14.3	9.7	9.7	12.4	11.5	10.6	b	15.5
$J_{3a,3b}$	14.0	13.9	b	9.5	9.5	13.8	13.8	9.3	9.3	9.7	10.6	9.3[c]
$J_{1'a,1'b}$			13.6	13.7	13.8				13.9	14.0	14.1	13.6
$J_{1a,F}$	47.0	47.0	46.7	2.0	2.3	47.3	47.4	1.5	<1	1.7	46.7	1.6
$J_{1b,F}$	47.2	47.0	46.8	1.5	1.3	47.0	47.0	2.7	<1	1.8	46.7	1.4
$J_{3a,F}$	1.0	<0.5	1.7	47.1	47.5	1.3	1.5	47.1	46.8	46.8	1.7	46.9
$J_{3b,F}$	1.3	1.8	1.7	47.0	46.9	2.3	1.0	47.4	46.8	46.8	1.7	46.9
$J_{1'a,F}$	2.0	1.8	b	1.3	1.7	2.3	2.5	2.0	1.7	1.6	1.7	1.8
$J_{1'b,F}$			2.2	1.7	1.9				1.7	1.6	1.7	1.9

Table 3 (continued)

[a] In compound **5** the OH-1 proton resonates at 3.49 ppm; in compound **16** the 2-OSi^{t}Bu protons resonate at 0.22 ppm; in compound **17** the 3-$(CH_2)_3CH_3$ protons resonate at 1.6-1.1 and 0.87 ppm; in compound **20** the 3-$CH{=}CH_2$ protons resonate at 5.90 and 5.18 and 5.13 ppm; in compound **21** the 3-$CH_2CH{=}CH_2$ protons resonate at 2.23 and 2.16, 5.80, and 5.03 and 4.97 ppm; in compounds **24** the OEt protons resonate at 4.25-4.05 and 1.33 ppm; in compounds **26a,b** the OEt protons resonate at 4.25-4.05, and respectively at 1.33 and 1.31 and 1.36 and 1.35 ppm, moreover P-2 showed J = 12.2, 20.0, 8.1, 11.2, and 16.6 Hz in **26a** and J = 11.8, 21.0, 12.1, 9.6, and 16.5 Hz in **26b** with H_2-1, -3, and H_3-1', respectively; in compound **28** the 1-$NHCH_2Ph$ protons resonate at 2.00, 3.84 and 3.82, and 7.4-7.1 ppm; in compound **29** the 1-$N(CH_2Ph)_2$ protons resonate at 3.80 and 3.64, and 7.4-7.1 ppm; in compounds **30** the 2-OCH_2OMe protons resonate at 4.86 and 4.83 and 3.43, and 4.95 and 4.80 and 3.43 ppm, respectively; in compound **31** the OH-1 and 2-OCH_2OCH_3 protons resonate at 2.87, 4.81 and 4.77, and 3.43 ppm; in compound **32** the OH-1 proton resonates at 2.40 ppm; in compound **35** the OEt protons resonate at 4.12 and 1.34 ppm. [b]Not determined. [c]Observed in benzene-d_6.

Finally, the assignment of the structure of compounds **26a,b**, obtained by addition of phosphite ion on the double bond of compound **25**, may be summarised by the following spectral differences: ^1H; the absence of any olefinic resonances in the spectra of compounds **26a,b** with the concomitant introduction of methyl and ethyl signals. ^{31}P; the presence in compounds **26a,b** of signals at 28.3 ppm, showing the bond P,H couplings ranging between 8.1 and 21.0 Hz with the protons of the C-2 substituents.[24]

EXPERIMENTAL

General Details

Mps are uncorrected and were obtained on a capillary apparatus. $[\alpha]_D$ values were obtained on a JASCO DIP-181 polarimeter. TLC was run on silica gel 60 F_{254} Merck; flash column chromatographies were performed with silica gel 60 (60-200 μm, Merck). ^1H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on a Bruker CPX-300 or a Bruker AC 250L spectrometer in $CDCl_3$. C_6F_6 was used as internal standard (δ_F -162.90) for ^{19}F. H_3PO_4 (δ_p 0.00 was used as external standard for ^{31}P. Mass spectra were registered on a Hitachi-Perkin-Elmer ZAB 2F instrument. THF was freshly distilled from $LiAlH_4$, dichloromethane was distilled from P_2O_5, and DMF was stored over molecular sieves (4Å and 13Å). In other cases commercially available reagent-grade solvents were employed without purification.

Reaction of Diazomethane with (R)- or (S)-1-Fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanone (1): Synthesis of 2-(Fluoromethyl)-2-{[(4-methylphenyl)sulfinyl]methyl}oxiranes (2S,R$_S$)-2 and (2R,R$_S$)-3 or of Their Enantiomers (2R,S$_S$)-2 and (2S,S$_S$)-3. General Procedure.

To a solution of ketone **1** (1.0 mmol) in the chosen solvent (5 ml), a solution of diazomethane (*c.a.* 0.5 *M*) in ethyl ether was added portionwise at different temperatures up to complete using up of the starting ketone. Excess CH_2N_2 was removed by bubbling a nitrogen stream and the solvent was evaporated under reduced pressure. Isolation of pure products was accomplished by flash chromatographic separation and fractional crystallisation.

a) in ethyl ether, at 0°C, after 4 hours, a 15.7:1.0:3.6 mixture of (2*S*,R_S)/(2*R*,R_S)-**3**/(*Z*)-**4** (90% global yield) was obtained. After flash chromatography in 7:3 chloroform/ethyl acetate, (*Z*)-**4** could be obtained in optically pure form: R_F 0.30; $[\alpha]_D^{20}$ - 298.0 (*c* 1.0, $CHCl_3$); m.p. 77-79 °C (*i*-propyl ether), whilst (2*S*,R_S)-**2** and (2*R*,R_S)-**3** (R_F 0.35) were obtained as a mixture. Fractional crystallisation (*i*-propyl ether) allowed the obtainment of both oxiranes in optically pure form: (2*S*,R_S)-**2**, $[\alpha]_D^{20}$ + 263.0° (*c* 1.2, $CHCl_3$); m.p. 76-78 °C and (2*R*,R_S)-**2**, $[\alpha]_D^{20}$ + 242.5 (*c* 0.5, $CHCl_3$); m.p. 73-75 °C. ^1H and ^{19}F NMR data are reported on Table 2.

b) in benzene, at r.t., after 6 hours, a 6.7:1.0:1.5 mixture of (2*S*,R_S)-**2**/(2*R*,R_S)-**3**/(*Z*)-**4** (67% global yield) was obtained.

c) in methanol, at 0°C, after 5 minutes, a 4.0:1.0 mixture of (2*S*,R_S)-**2**/(2*R*,R_S)-**3** (92% global yield) was obtained. If reaction was left further, an approximately 4.0:1.0 diastereoisomeric mixture of (2*S*,R_S)-**5**/(2*R*,R_S)-**5** (up to 10% of the global mixture), due to the oxirane ring opening by moisture, was isolated.

d) in methanol, at - 15°C, after 10 minutes, a 2.0:1.0 mixture of (2*S*,R_S)-**2**/(2*R*,R_S)-**3** (95% global yield) was obtained. 1,2-Diols **5** were recovered after longer reaction time up to 6% yield.

e) in methanol, at - 78°C, after 20 minutes, a 1.6:1.0 mixture of (2*S*,R_S)-**2**/(2*R*,R_S)-**3** (90% global yield) was obtained. 1,2-Diols **5** were recovered after longer reaction time up to 2% yield.

f) in methanol, at 0°C, adding some drops of triethylamine, after 20 minutes, a 1.7:1.2:1.0 mixture of (2*S*,R_S)-**2**/(2*R*,R_S)-**3**/(*Z*)-**4** (70% global yield) was obtained, whilst no diols **5** were detected.

(2*S*,R_S)-**2**: ^{13}C NMR ($CDCl_3$) δ: 142.27 (s), 140.27 (s), 130.22 (d), and 123.97 (d) (ArC); 85.08 (dt, $J_{C,H}$ = 153 and $J_{C,F}$ = 174.5 Hz, C-1'); 58.62 (dt, $J_{C,H}$ = 140 and $J_{C,F}$ = 2 Hz, C-1"); 54.78 (d, $J_{C,F}$ = 22 Hz, C-2); 49.10 (dt, $J_{C,H}$ = 178 and $J_{C,F}$ = 6.5 Hz, C-3); and 21.45 (q, Me). Found C, 57.82; H, 5.73; $C_{11}H_{13}FO_2S$ requires: C, 57.88; H, 5.74.

(2*R*,R_S)-**3**: ^{13}C NMR ($CDCl_3$) δ: 142.17 (s), 140.27 (s), 130.22 (d), and 123.87 (d) (ArC); 84.15 (dt, $J_{C,F}$ = 174.5 Hz, C-1'); 60.35 (dt, $J_{C,F}$ = 2 Hz, C-1"); 54.61 (d, $J_{C,F}$ = 22.5 Hz, C-2); 49.82 (dt, $J_{C,F}$ = 7 Hz, C-3); and 21.45 (q, Me). Found C, 57.85; H, 5.70; $C_{11}H_{13}FO_2S$ requires: C, 57.88; H, 5.74.

(*Z*)-**4**: ^1H NMR ($CDCl_3$) δ: 7.55 and 7.32 (4 H, m, ArH), 5.67 (1 H, dt, *J* = 1.8 and 0.8 Hz, H-1), 4.91 (1 H, ddd, *J* = 46.7, 12.5 and 0.8 Hz, H-3a), 4.82 (1 H, ddd, *J* = 46.5, 12.5 and 0.8 Hz, H-3b), 4.05 (3 H, br s, OMe-2), and 2.40 (3 H, br s, ArMe). ^{19}F NMR ($CDCl_3$) δ: -220.30 (1 F, br dd, *J* = 46.7 and 46.5 Hz, F-3). Irradiation of H-1 in a NOE experiment enhanced H_2-3 (2.5%). Found C, 57.84; H, 5.75; $C_{11}H_{13}FO_2S$ requires: C, 57.88; H, 5.74.

Synthesis of (S)-3-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-1,2-propandiol (5)

To a solution of oxirane **2** (200 mg, 0.877 mmol) in a 1:1 THF/H_2O mixture (2 ml), 200 µl of perchloric acid were added at room temperature. After 24 hours, the solvents were evaporated and the residue was purified by flash chromatography (1:4 hexane/ethyl acetate) to give **5** in 95% yield: $[\alpha]_D^{20}$ +203.2 (*c* 1.1, $CHCl_3$). Found C, 53.79; H, 6.05; $C_{11}H_{14}FO_3S$ requires: C, 53.65; H, 6.09. EI/MS (70 eV) M^+ 246.

Base-promoted Opening of 2: Synthesis of (E)- and (Z)-2-(Fluoromethyl)-3-[(R)-(4-methylphenyl)sulfinyl]-2-propen-1-ols [(E)-6 and (Z)-6] and of (E)- and (Z)-3-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propen-1-ols [(E)- and (Z)-7].

Method A. To a solution of oxirane **2** (1.0 mmol) in anhydrous THF (5 ml) at- 78°C stirred under nitrogen, a 2.5 *M* solution in hexane of butyllithium (1.0 mmol) was added dropwise. After 10 min. the reaction

mixture was added with saturated aqueous solution of ammonium chloride, the organic layers were extracted with ethyl acetate (3 x 5 ml), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. Flash chromatographic purification in 1:1 hexane/ethyl acetate afforded a complex mixture of olefins (75% global yield) in equimolar ratio. The single products were not separated, but characterised through their ^1H and ^{19}F NMR spectra.

Method B. To a solution of oxirane **2** (1.0 mmol) in THF (5 ml) stirred at r.t., a solution of KOH (1.0 mmol) in water (5 ml) was added dropwise. After 5 min. the starting compound disappeared, THF was evaporated and pH was adjusted to 7 by adding aqueous hydrochloric acid. The following work-up was as usual and the four olefinic products were obtained.

(*E*)-**6**: ^1H NMR ($CDCl_3$) δ: 7.56 and 7.34 (4 H, m, ArH), 6.30 (1 H, br s, H-3), 5.04 (1 H, br ddd, J = 46.4, 14.0 and 1.7 Hz, H-1'a), 5.00 (1 H, br ddd, J = 46.5, 14.0 and 1.7 Hz, H-1'b), 4.70 (1 H, br dd, J = 13.9 and 2.2 Hz, H-1a), 4.35 (1 H, br d, J = 13.9 Hz, H-1b), 3.78 (1 H, br signal, OH-1), and 2.42 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -223.57 (1 F, br dd, J = 46.5 and 46.4 Hz, F-1'). Irradiation of H-3 in a NOE experiment enhanced H_2-1' (1%).

(*Z*)-**6**: ^1H NMR ($CDCl_3$) δ: 7.48 and 7.31 (4 H, m, ArH), 6.54 (1 H, br s, H-3), 5.41 (1 H, br ddd, J = 46.9, 11.7 and 1.2 Hz, H-1'a), 5.29 (1 H, br dd, J = 46.6 and 11.7 Hz, H-1'b), 4.30 (2 H, br s, H_2-1), 3.40 (1 H, br signal, OH-1), and 2.40 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -218.44 (1 F, br dd, J = 46.9 and 46.6 Hz, F-1'). Irradiation of H-3 in a NOE experiment enhanced H_2-1 (1%). (*E*)/(*Z*)-**6** mixture: found C, 57.89; H, 5.70; $C_{11}H_{13}FO_2S$ requires: C 57.91; H, 5.73.

(*E*)-**7**: ^1H NMR ($CDCl_3$) δ: 7.52 and 7.33 (4 H, m, ArH), 6.70 (1 H, br d, J = 82.5 Hz, H-3), 4.55 (1 H, br signal, OH-1), 3.97 (2 H, br d, J = 4.3 Hz, H_2-1'), 3.78 (1 H, br dd, J = 13.5 and 2.3 Hz, H-1a), 3.71 (1 H, br dd, J = 13.5 and 1.9 Hz, H-1b), and 2.41 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -123.84 (1 F, br d, J = 82.5 Hz, F-3). Irradiation of H_2-1' in a NOE experiment enhances H-3 (2%).

(*Z*)-**7**: ^1H NMR ($CDCl_3$) δ: 7.45 and 7.36 (4 H, m, ArH), 6.02 (1 H, br d, J = 81.8 Hz, H-3), 4.39 (1 H, br signal, OH-1), 4.38 (1 H, br d, J = 13.0 Hz, H-1'a), 4.11 (1 H, br dd, J = 13.0 and 3.5 Hz, H-1'b), 3.78 (1 H, br dd, J = 13.0 and 4.0 Hz, H-1a), 3.26 (1 H, br d, J = 13.0 Hz, H-1b), and 2.43 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -120.99 (1 F, br d, J = 81.8 Hz, F-3).

*Synthesis of (S)-2-(Fluoromethyl)-2-{[(4-methylphenyl)sulfonyl]methyl}oxirane (**8**)*

To a solution of **2** (114 mg, 0.5 mmol) in dichloromethane (2 ml) distilled from P_2O_5 was added *m*-CPBA (331 mg, 1.5 mmol) at room temperature under stirring. After complete using up of **2**, the mixture was diluted with dichloromethane (8 ml), washed with an aqueous solution of sodium hydrogen carbonate up to pH = 7. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by flash chromatography (65:35 hexane/ethyl acetate) to give **8** in 52% yield: $[\alpha]_D^{20}$ -12.50; $[\alpha]_{365}^{20}$ -34.03 (*c* 0.9, $CHCl_3$). Found C, 54.11; H, 5.34; $C_{11}H_{13}FO_3S$ requires: C, 54.09; H, 5.36.

*Synthesis of (S)-2-(Fluoromethyl)-2-{[(4-methylphenyl)thio]methyl}oxirane (**9**)*

To a stirred slurry of sodium iodide (880 mg, 5.86 mmol) and sulfinyl derivative **2** (445 mg, 1.95 mmol) in acetone (10 ml) under nitrogen atmosphere, a solution of trifluoroacetic anhydride (1.36 ml, 9.76 mmol) in the same solvent (5 ml) was added at -20°C. The reaction was quenched with saturated aqueous solution of

sodium sulfite and the organic layer was extracted with ethyl ether (3x5 ml), dried over anhydrous sodium sulfate, and concentrated to give a residue which, upon flash chromatographic purification (4:1 hexane/ethyl ether) afforded **9** (86% yield): $[\alpha]_D^{20}$ + 15.4° , $[\alpha]_{365}^{20}$ +54.5° (*c* 1.2, $CHCl_3$). Found C, 62.34; H, 6.10; $C_{11}H_{13}FOS$ requires: C, 62.26; H, 6.13.

As by-product, the iodomethyl derivative **34** was obtained in about 10% yield; its ^1H and ^{19}F NMR spectra were superimposable to those of the product obtained by the appropriate reaction (see onward).

Synthesis of (S)-1-Fluoro-2-methyl-3-[(R)-(4-methylphenyl)sulfinyl]-2-propanol (10)

Lithium aluminium hydride (100 mg, 2.65 mmol) was suspended under argon in anhydrous THF (30 ml). The slurry was cooled at -70°C and a solution of **2** (500 mg, 2.19 mmol) was added dropwise. After 10 min, a saturated aqueous solution of ammonium chloride (3 ml) and aqueous hydrochloric acid were added up to pH 3, the resulting mixture was extracted with ethyl acetate (3x10 ml), the combined organic layers were dried over anhydrous sodium sulfate and concentrated to give a residue which, upon flash chromatography (1:1 hexane/ethyl acetate) afforded **10** in 87.4% yield: $[\alpha]_D^{20}$ +270.9 (*c* 1.1, $CHCl_3$); m.p. 97-98°C (1:1 ethyl ether/*i*-propyl ether). Found C, 57.35; H, 6.17; $C_{11}H_{15}FO_2S$ requires: C, 57.38; H, 6.12.

Synthesis of (S)-1-Fluoro-2-methyl-3-[(4-methylphenyl)thio]-2-propanol (11)

Route A. The same procedure described for the obtainment of **10** starting from **2** was applied to the thio derivative **9** (300 mg, 1.41 mmol) using 1.69 mmol of $LiAlH_4$. After 1 hour, the usual work-up was followed and flash chromatography (9:1 hexane/ethyl ether) afforded **11** in 86% yield.

Route B. Starting from **2** (500 mg, 2.19 mmol), using a 2:1 excess of $LiAlH_4$ (166 mg, 4.38 mmol), **11** was obtained in 43% yield.

Route C. From **10**, following the same procedure described for the obtainment of **9** from **2**, the tertiary thio alcohol **11** was obtained in 96% yield.

Synthesis of (S)-1-Chloro-3-fluoro-2-{[(4-methylphenyl)sulfinyl]methyl}-2-propanol (12)

Cupric chloride (94.3 mg, 0.701 mmol) and lithium chloride (59.4 mg, 1.40 mmol) were dissolved in 1.0 ml of anhydrous THF at 0°C. Oxirane **2** (100 mg, 0.438 mmol) in THF (1.0 ml) was added dropwise at room temperature and the red solution was kept under stirring for 6 hours. 10 ml Of phosphate buffer (pH 7.4) were added and the organic layers were extracted with ethyl ether (3x10 ml), dried over anhydrous sodium sulfate and concentrated under vacuum. Flash chromatographic purification (1:1 hexane/ethyl acetate) afforded **12** in 86.3% yield: $[\alpha]_D^{20}$ +250 (*c* 0.96, $CHCl_3$); m.p. 91.5-93.5°C (*i*-propyl ether). Found C, 50.09; H, 5.33; Cl, 13.50; $C_{11}H_{14}ClFO_2S$ requires: C, 49.91; H, 5.33; Cl, 13.45. EI/MS (70 eV) M^+ 265

Synthesis of (S)-1-Bromo-3-fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propanol (13)

Following the same procedure described for **12**, using $CuBr_2$ (156 mg, 0.700 mmol) and LiBr (121 mg, 1.100 mmol) on oxirane **2**, the pure bromo derivative **13** was obtained in 30 min after flash chromatography (3:2 hexane/ethyl acetate) in 94% yield: $[\alpha]_D^{20}$ +219.3 (*c* 0.95, $CHCl_3$), m.p. 87-89°C (*i*-propyl ether). Found C, 42.78; H, 4.53; Br, 25.79; $C_{11}H_{14}BrFO_2S$ requires: C, 42.73; H, 4.56; Br, 25.84.

Synthesis of (S)-1-Fluoro-3-iodo-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propanol (14)

The same procedure described for **12** was employed with **2** using CuI (133 mg, 0.701 mmol) and LiI (98.7 mg, 1.400 mmol). After 24 hours, the solvent was evaporated and the crude submitted to flash chromatography (3:2 hexane/ethyl acetate) to give **14** in 48% yield: $[\alpha]_D^{20}$ +241.7 (*c* 1.3, $CHCl_3$), m.p. 92-93 °C). Found C, 36.98; H, 3.88; I, 35.73; $C_{11}H_{14}IFO_2S$ requires: C, 37.08; H, 3.93; I, 35.67.

Synthesis of (S)-4-Fluoro-3-hydroxy-3-{[(R)-(4-methylphenyl)sulfinyl]methyl}butanenitrile (15)

Sodium cyanide (64 mg, 1.315 mmol) was dissolved at 60°C in acetonitrile (2 ml), neat **2** (200 mg, 0.877 mmol) and lithium perchlorate (140 mg, 1.315 mmol) were added at the same temperature. After 45 min., 10 ml of water were added and the organic layers were extracted with ethyl ether (3x10 ml), dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. Flash chromatographic purification (3:2 chloroform/ethyl acetate) afforded **15** in 98% yield: $[\alpha]_D^{20}$ +267.0 (*c* 1.3, $CHCl_3$), m.p. 104-105°C; ^{1}H NMR ($CDCl_3$) δ: 7.57 and 7.39 (4 H, m, ArH), 5.27 (1 H, br signal, OH-3), 4.86 (1 H, dd, J = 46.7 and 9.9 Hz, H-4a), 4.54 (1 H, ddd, J = 46.7, 9.9 and 1.2 Hz, H-4b), 3.14 (1 H, ddd, J = 13.5, 1.8 and 1.2 Hz, H-1'a), 2.97 (1 H, dd, J = 13.5 and 2.1 Hz, H-1'b), 2.82 (1 H, dd, J = 16.7 and 1.5 Hz, H-2a), 2.74 (1 H, dd, J = 16.7 and 1.2 Hz, H-2b), and 2.44 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -223.72 (1 F, br t, J = 46.7 Hz, F-4). Found C, 56.51; H, 5.53; N, 5.46; $C_{12}H_{14}FNO_2S$ requires: C, 56.46; H, 5.52; N, 5.48. EI/MS (70 eV) M^+ 255.

A 1:2:0.25 molar ratio of oxirane **2**/trimethylsilyl cyanide/zinc iodide was suspended in CH_2Cl_2 (3 ml) and stirred at r.t. for 5 hours. After flash chromatography in 8:2 hexane/ethyl acetate, the only reaction product was O-trimethylsilyl-1-fluoro-3-iodo-2-{[(4-methylphenyl)sulfinyl]methyl}-2-propanol (**16**): 45% yield; R_F 0.35; $[\alpha]_D^{20}$ + 130.8 (*c* 1.0, $CHCl_3$); m.p. 133-134 °C (*i*-propyl ether); found C, 39.20; H, 5.12; I, 29.74; $C_{14}H_{22}FIO_2SSi$ requires: C, 39.25; H, 5.14; I, 29.67 (^{1}H and ^{19}F NMR spectra are reported in Table 3), along with unreacted starting oxirane **2** (50% recovered yield). The trimethylsilyl derivative **16** (200 mg, 0.45 mmol) was dissolved in methanol (3 ml) and stirred at r.t. with KF (250 mg, 4.3 mmol), giving rise to a 1:10 (95% global yield) mixture of iodine derivative **14** and recovered oxirane **2**.

Synthesis of (S)-1-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-heptanol (17)

To a suspension of copper(I) iodide (70 mg, 0.37 mmol) in anhydrous THF (2 ml) at -20°C under nitrogen, a 2.5 *M* solution of buthyllithium in hexane (0.3 ml) was added dropwise under stirring. After 15 min. at the same temperature, the reaction mixture was cooled at -68°C and a solution of **2** (50 mg, 0.22 mmol) in the same solvent (4.7 ml) was added dropwise. The temperature was allowed to reach slowly 0°C and after 30 min., the reaction was quenched with a saturated solution of ammonium chloride, the organic layer was extracted with ethyl acetate (3x10 ml) and dried over anhydrous sodium sulfate. The residue was purified by flash chromatography (2:1 hexane/ethyl acetate) to give the desired product **17** in 40% yield: R_F 0.35, $[\alpha]_D^{20}$ +206.7 (*c* 0.5, $CHCl_3$). Found C, 63.03; H, 8.02; $C_{15}H_{23}FO_2S$ requires: C, 62.94; H, 8.04. ^{13}C NMR ($CDCl_3$) δ : 142.24 (s), 140.27 (s), 130.27 (d), and 123.92 (d) (ArC); 85.72 (dt, $J_{C,F}$ = 178 Hz, C-1); 73.51 (d, $J_{C,F}$ = 18.5 Hz, C-2); 61.31 (t, C-1'); 38.38 (t), 32.08 (t), 22.50 (t), and 21.97 (t) (C-3, -4, -5, and -6); 21.46 (q, ArMe); and 13.97 (q, C-7). As by-products, the following compounds were detected: a not separable 55:45 mixture of C-1' diastereoisomers 2-{1'-[(*R*)-(4-methylphenyl)sulfinyl]pentyl}-2-propen-1-ols (**18**) (10% yield) and (*Z*)-3-[(*R*)-(4-methylphenyl)sulfinyl]-2-pentyl-2-propen-1-ol (**19**) (31% yield).

18a (Major diastereoisomer): ^{1}H NMR ($CDCl_3$) δ: 7.46 and 7.30 (4 H, m, ArH), 5.32 and 4.68 (2 H, br s, H_2-3), 3.96 and 3.73 (2 H, br d, J = 13.0 Hz, H_2-1), 3.49 (1 H, dd, J = 10.8 and 4.4 Hz, H-1'), 3.19 (1 H, br

signal, OH-1), 2.41 (3 H, br s, ArMe), 2.0-1.2 (6 H, m, H_2-2', -3', and -4'), and 0.87 (3 H, t, J = 6.5 Hz, H_3-5'). ^{13}C NMR ($CDCl_3$) δ: 141.97 (s), 140.74 (s), 129.62 (d) and 125.83 (d) (ArC); 138.09 (s, C-2); 120.17 (t, C-3); 70.75 (d, C-1'); 63.70 (d, C-1); 29.31 (t), 28.00 (t), and 22.29 (t) (C-2', -3', and -4'); 21.47 (q, ArMe); and 13.79 (q, C-5').

18b (Minor diastereoisomer): ^1H NMR ($CDCl_3$) δ: 7.46 and 7.29 (4 H, m, ArH), 5.22 and 4.66 (2 H, br s, H_2-3), 4.22 (1 H, br signal, OH-1), 3.89 and 3.85 (2 H, br d, J = 13.0 Hz, H_2-1), 3.32 (1 H, dd, J = 9.0 and 6.8 Hz, H-1'), 2.41 (3 H, br s, ArMe), 2.0-1.2 (6 H, m, H_2-2', -3', and -4'), and 0.88 (3 H, t, J = 6.5 Hz, H_3-5'). ^{13}C NMR ($CDCl_3$) δ: 141.82 (s), 141.77 (s), 129.36 (d) and 125.21 (d) (ArC); 137.31 (s, C-2); 117.31 (t, C-3); 66.29 (d, C-1'); 66.04 (t, C-1); 28.94 (t), 27.35 (t), and 22.47 (t) (C-2', -3', and -4'); 21.47 (q, ArMe); and 13.79 (q, C-5').

19: ^1H NMR ($CDCl_3$) δ: 7.52 and 7.31 (4 H, m, ArH), 6.02 (1 H, br s, H-3), 4.63 and 4.38 (2 H, br d, J = 13.5 Hz, H_2-1), 3.05 (1 H, br signal, OH-1), 2.40 (3 H, br s, ArMe), 2.24 (2 H, m, H_2-1'), 1.45 (2 H, m, H_2-2'), 1.32 (2 H, m, H_2-3'), 1.25 (2 H, m, H_2-4'), and 0.85 (3 H, t, J = 6.5 Hz, H_3-5'). ^{13}C NMR ($CDCl_3$) δ: 154.18 (s, C-2); 141.32 (s), 140.90 (s), 130.07 (d), and 124.54 (d) (ArC); 132.36 (d, C-3); 61.52 (t, C-1); 35.14 (t), 31.41 (t), 26.99 (t), and 22.38 (t) (C-1', -2', -3', and -4'); 21.41 (q, ArMe); and 13.94 (q, C-5'). Irradiation of H-3 in a NOE experiment enhanced H_2-1' (2.5%) and H_2-2' (2%).

Synthesis of (S)-1-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-4-penten-2-ol (20)

To a solution of vinylmagnesium chloride (1.55 ml, 2.625 mmol) in anhydrous THF (2.5 ml) at 5°C under argon, a solution of **2** (500 mg, 2.190 mmol) in the same solvent (5 ml) was added dropwise in 5 min. After 10 min., a saturated solution of ammonium chloride was dropped, the organic layers were extracted with ethyl acetate (3x10 ml), dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by flash chromatography (3:2 cyclohexane/ethyl acetate) to give **20** in 34% yield: $[\alpha]_D^{20}$ +176.7 (*c* 0.4, $CHCl_3$). Found C, 60.91; H, 6.66; $C_{13}H_{17}FO_2S$ requires: C, 60.94; H, 6.64.

The compound **12** deriving from oxirane opening by chloride ion was isolated in 50% yield.

Synthesis of (S)-1-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-5-hexen-2-ol (21)

Following the same procedure described above, starting from **2** (500 mg, 2.190 mmol) and allylmagnesium chloride (1.30 ml, 2.60 mmol), **21** was obtained in 67% yield: $[\alpha]_D^{20}$ +229.9 (*c* 1.16, $CHCl_3$); m.p. 75-76°C (*i*-propyl ether). Found C, 62.24; H, 7.12; $C_{14}H_{19}FO_2S$ requires: C, 62.20; H, 7.08.

*Reaction of Thio Oxirane **9** with Diethyl Phosphite Ion: Synthesis of Diethyl (R)-3-Fluoro-2-hydroxy-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}propanephosphonate (24), 3-Fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl} propene (25) and Diethyl 1-Fluoro-2-methyl-3-[(R)-(4-methylphenyl)sulfinyl]propane-2-phosphonate (26)*

Method A. To a solution of diethyl phosphite (81 μl, 0.63 mmol) in anhydrous THF (0.5 ml) stirred under nitrogen at -60°C, a 2.5 *M* solution (hexane) of buthyllithium (0.168 ml, 0.42 mmol) was added dropwise. To the clear solution, thio oxirane **9** (45 mg, 0.21 mmol) dissolved in the same solvent (0.3 ml) was added dropwise, and the reaction mixture was kindly wormed up to r.t. in 40 min. The reaction was quenched with saturated aqueous solution of ammonium chloride, the organic layers were extracted with ethyl acetate (3x1 ml) and dried over anhydrous sodium sulfate. Flash chromatographic separation in 6:4 hexane/ethyl acetate allowed

the obtainment of the methylene derivative **25**, whilst (*2R,S,R_S*)-**26** required a more polar eluent (3:7 hexane/ethyl acetate).

Olefin **25**: 55% yield; R_F 0.55 in 3:7 hexane/ethyl acetate; $[\alpha]_D^{20}$ + 210.5 (*c* 1.0, $CHCl_3$); Found C, 62.33; H, 6.08; $C_{11}H_{13}FOS$ requires: C, 62.26; H, 6.13; ^1H NMR ($CDCl_3$) δ: 7.50 and 7.33 (4 H, m, ArH), 5.38 and 5.11 (2 H, m, H_2-1), 4.79 (1 H, br dd, J = 46.7 and 11.7 Hz, H-3a), 4.68 (1 H, br dd, J = 46.7 and 11.7 Hz, H-3b), 3.56 (1 H, br d, J = 13.0 Hz, H-1'a), 3.52 (1 H, br d, J = 13.0 Hz, H-1'b), and 2.42 (3 H, br s, Me). ^{19}F NMR ($CDCl_3$) δ: -216.73 (1 F, br t, J = 46.7 Hz, F-3). ^{13}C NMR ($CDCl_3$) δ: 141.88 (s), 139.98 (s), 129.89 (d), and 124.24 (d) (ArC); 134.16 (d, $J_{C,F}$ = 16.5 Hz, C-2); 121.01 (dt, $J_{C,F}$ = 10 Hz, C-1); 84.67 (dt, $J_{C,F}$ = 168.5 Hz, C-3), 60.37 (t, C-1'); and 21.45 (q, Me).

2-Methyl phosphonate **26:** 10% yield; R_F 0.35 in 3:7 hexane/ethyl acetate as a not separable 65:35 mixture of the two C-2 diastereoisomers (from ^1H and ^{19}F NMR spectra analyses, see Table 3); Found C, 51.33; H, 6.88; $C_{16}H_{24}FO_4PS$ requires: C, 51.43; H, 6.86; ^{31}P NMR ($CDCl_3$) δ: 28.3 (1 P, m, P-2). The signals of the single diastereoisomers could not be distinguished.

Method B. To a suspension of potassium *tert*-butoxide (246 mg, 2.19 mmol) in anhydrous DMF (2 ml) stirred under nitrogen at 0 °C, a solution of diethyl phosphite (310 µl, 2.41 mmol) in DMF (100 µl) was added dropwise. After 30 min. at the same temperature, a solution of oxirane **2** (250 mg, 1.1 mmol) in DMF (2.7 ml) was added dropwise in two minutes. After five min., the reaction mixture was added with an acidic aqueous saturated solution of ammonium chloride (20 ml, pH = 3), extracted with ethyl ether (3 x 10 ml), the combined organic layers were washed with water (2 x 5 ml) and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (6:4 hexane/ethyl acetate) to give: the olefin **25** in 51% yield; R_F 0.35. A new elution in 3 : 7 hexane/ethyl acetate gave: diethyl phosphonate **24** in 3% yield: R_F 0.35; $[\alpha]_D^{20}$ + 149.8 (c 0.8, $CHCl_3$), found C, 49.23; H, 6.50; $C_{16}H_{24}FO_2PS$ requires: C, 49.18; H, 6.56; ^{31}P NMR ($CDCl_3$) δ: 27.58 (1 P, m, P-1) (^1H and ^{19}F NMR are in Table 3); and 2-methyl phosphonate **26** in 7% yield: R_F 0.30.

*Reaction of Olefin **25** with Diethyl Phosphite Ion.*

To a suspension of potassium *tert*-butoxide (40 mg, 0.36 mmol) in anhydrous (400 µl) stirred under nitrogen at 0 °C, a solution of diethyl phosphite (51 µl, 0.39 mmol) in DMF (20 µl) was added at the same temperature. After 30 min., a solution of olefin **25** (38 mg, 0.18 mmol) in DMF (450 µl) was added and the temperature was allowed to reach r.t. while the stirring was continued for 24 hours. The reaction mixture was worked up as usual, the crude purified by flash chromatography in 3:7 hexane/ethyl acetate to give 2-methyl phosphonate **26** in 75% yield as a one to one epimeric mixture. The same experiment was carried out on 1-phosphonate **24**, but only undecomposed and unreacted starting material was recovered.

Synthesis of (S)-3-Azido-1-fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propanol (27)

To a solution of oxirane **2** (700 mg, 3.07 mmol) in anhydrous ethanol (10 ml), neat sodium azide (240 mg, 3.68 mmol) and ammonium chloride (170 mg, 3.07 mmol) were added at room temperature. After 1 hour, the solvent was evaporated under vacuum and the residue was purified by flash chromatography (3:2 hexane/ethyl acetate) to give **27** in 79% yield: $[\alpha]_D^{20}$ +345 (*c* 0.9, $CHCl_3$). Found C, 48.78; H, 5.12; N, 15.51; $C_{11}H_{14}FN_3O_2S$ requires: C, 48.71; H, 5.17; N, 15.50.

Synthesis of (S)-1-(Benzylamino)-3-fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propanol (28)

To a solution of **2** (500 mg, 2.190 mmol) in THF (2 ml) neat benzylamine (495 mg, 4.385 mmol) at room temperature was added. After 26 hours, THF was evaporated off and the residue was purified by flash chromatography (3:2 hexane/ethyl acetate) to give **28** in 95% yield: $[\alpha]_D^{20}$ +164.46 (*c* 1.2, $CHCl_3$), m.p. 70-72 °C (*i*-propyl ether). Found C, 64.52; H, 6.63; N, 4.16; $C_{18}H_{22}FNO_2S$ requires: C, 64.46; H, 6.61; N, 4.17.

Synthesis of 1-(Dibenzylamino)- 3-fluoro-2-{[(R)-(4-methylphenyl)sulfinyl]methyl}-2-propanol (29)

Following the same procedure described above, using dibenzylamine (8.4 ml), in 7 days, **29** was obtained (97% yield): : $[\alpha]_D^{20}$ +93.94 (*c* 0.95, $CHCl_3$), m.p. 105-107 °C (*i*-propyl ether). Found C, 70.55; H, 6.64; N, 3.26; $C_{25}H_{28}FNO_2S$ requires: C, 70.56; H, 6.63; N, 3.29.

Synthesis of (S)-1-Fluoro-2-[(methoxymethyl)oxy]-2-methyl-3-[(R)-(4-methylphenyl)sulfinyl]propane (30)

To a solution of **10** (120 mg, 0.52 mmol) in formaldehyde dimethylacetal (10 ml) was added P_2O_5 (ca. 50 mg) and the slurry was vigorously stirred under nitrogen at room temperature for 24 hours. Then the reaction mixture was poured into a water/chloroform mixture cooled at 0°C. The pH was adjusted to ca. 7 with solid $NaHCO_3$ and the organic layers were extracted with ethyl acetate (3x10 ml). Flash chromatographic purification (4:1 chloroform/ethyl acetate) afforded **30** in 95.5% yield: R_F 0.30; $[\alpha]_D^{20}$ +121.5 (*c* 1.2, $CHCl_3$). Found C, 56.87; H, 6.95; $C_{19}H_{19}FO_3S$ requires: C, 56.93; H, 6.93. (2*R*,*R*$_S$)-**30** (10% yield) was also detected and isolated {[R_F 0.35; $[\alpha]_D^{20}$ +119.7 (*c* 1.2, $CHCl_3$)} if not perfectly anhydrous conditions were adopted during the reaction. ^1H And ^{19}F NMR of both diastereoisomers are reported in Table 3.

Synthesis of (R)-3-Fluoro-2-[(methoxymethyl)oxy]-2-methyl-1-propanol (31)

To a solution of **30** (130 mg, 0.474 mmol) and *sym*-collidine (0.28 ml, 2.08 mmol) in acetonitrile (2 ml) at -20°C stirred under argon, neat trifluoroacetic anhydride (0.27 ml, 1.90 mmol) was added dropwise. The temperature was raised up to 0°C, then solid potassium carbonate was added up to ca. pH 7, and a suspension of mercury(II) chloride (386 mg, 1.42 mmol) in acetonitrile (5 ml) was added dropwise. Mercury(II) sulfide was filtered off, the clear yellow solution was added of solid sodium borohydride (27 mg, 0.711 mmol) and metallic mercury precipitated immediately. After removal of the black powder, the solvent was evaporated under vacuum and the residue submitted to flash chromatography (9:1 chloroform/ethyl acetate) to give **31** as a colourless oil in 73.6% yield: $[\alpha]_D^{20}$ +7.7 (*c* 1.2, $CHCl_3$). Found C, 47.35; H, 8.57; $C_6H_{13}FO_3$ requires: C, 47.37; H, 8.55.

Synthesis of (S)-3-Fluoro-2-{[(4-methylphenyl)thio]methyl}-1,2-propandiol (32)

Route A. Starting from **5** (700 mg, 2.84 mmol), following the same reductive procedure described for **8** the thio 1,2-diol **32** was obtained in 96.5% yield: $[\alpha]_D^{20}$ -2.0 (*c* 1.2, $CHCl_3$). Found C, 57.27; H, 6.50; $C_{11}H_{15}FO_2S$ requires: C, 57.39; H, 6.52.

Route B. The same procedure described for the obtainment of **5** was applied to the thio derivative **9**. After 48 hours, the thio 1,2-diol **32** was obtained in 95% yield.

Synthesis of (S)-1-Bromo-3-fluoro-2-{[(4-methylphenyl)thio]methyl}-2-propanol (33)

Route A. Copper(II) bromide (680 mg, 3.04 mmol) and lithium bromide (530 mg, 6.08 mmol) were dissolved in anhydrous THF (2 ml) cooled at 0°C. The thio derivative **9** was dissolved in the same solvent (1 ml) and dropped at the same temperature. After 1 night at room temperature, a buffered solution (10 ml, pH 7.4)

was dropped, the mixture was diluted with water and the organic layers were extracted with ethyl acetate (3x5 ml), dried over anhydrous sodium sulfate and concentrated under vacuum to give a crude. Flash chromatographic purification (9:1 hexane/ethyl acetate) gave **33** in 79% yield: $[\alpha]_D^{20}$ +10.2 (*c* 1.1, $CHCl_3$). Found C, 45.18; H, 4.83; Br, 27.08; $C_{11}H_{14}BrFOS$ requires: C, 45.21; H, 4.79; Br, 27.05.

Route B. Starting from **13** (200 mg, 0.65 mmol), following the same procedure described for the obtainment of **9**, the bromo-thio derivative **33** was obtained in 60.6% yield, among with a 36.3% of the thio oxirane derivative **9**, deriving from nucleophilic bromine displacement during alkaline work-up.

Synthesis of (S)-1-Fluoro-3-iodo-2-{[(4-methylphenyl)thio]methyl}-2-propanol (34)

To a solution of thio derivative **9** (400 mg, 1.9 mmol) in THF (10 ml) was added solid sodium iodide (780 mg, 5.7 mmol) at room temperature. Stirring was continued for 24 hours and the solvent was evaporated to dryness. After flash chromatography (9:1 hexane/ethyl ether), **34** was obtained in 56% yield: $[\alpha]_D^{20}$ +16.6 (*c* 1.0, $CHCl_3$). Found C, 38.78; H, 4.10; I, 37.30; $C_{11}H_{14}FIOS$ requires: C, 38.82; H, 4.12; I, 37.35.

Synthesis of (R)-3-Fluoro-2-hydroxy-2-{[(4-methylphenyl)thio]methyl}propanephosphonate (35).

To a suspension of potassium *tert*-butoxide (95 mg, 0.84 mmol) in anhydrous DMF (0.9 ml) stirred under nitrogen at 0 °C, neat diethyl phosphite (126 µl, 0.98 mmol) was added. After 30 min., a solution of thio oxirane **9** (60 mg, 0.28 mmol) in THF (0.23 ml) was added at the same temperature. After 4 hours the starting compound had completely disappeared. The reaction mixture was quenched with sat. NH_4Cl, poured into an ice/water bath (10 ml), added with hydrochloric acid up to pH 3, the organic phases were extracted with ethyl ether (3x5 ml), dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. A flash chromatographic separation in 6:4 cyclohexane/ethyl acetate gave **35** in 76% yield: R_F 0.35; $[\alpha]_D^{20}$ -19.0 (*c* 0.5, $CHCl_3$). Found C, 51.38; H, 6.87; $C_{16}H_{24}FO_4PS$ requires: C, 51.43; H, 6.86; ^1H and ^{19}F NMR of both diastereoisomers are reported in Table 3; ^{13}C NMR ($CDCl_3$) δ: 136.85 (s), 132.70 (s), and 129.83 (d) (ArC); 85.82 (ddt, $J_{C,F}$ = 177.5 and $J_{C,P}$ = 8.5 Hz, C-3); 72.37 (dd, $J_{C,F}$ = 19 and $J_{C,P}$ = 4.5 Hz, C-2); 42.80 (ddt, $J_{C,F}$ = 11.5 and $J_{C,P}$ = 2.5 Hz, C-1'); 30.80 (ddt, $J_{C,F}$ = 2.5 and $J_{C,P}$ = 138 Hz, C-1); and 21.00 (q, ArMe). The carbons of the OEt groups give rise to signals at 62.26, 62.17, 16.37, and 16.26 ppm. ^{31}P NMR ($CDCl_3$) δ: 28.69 (1 P, m, P-1). As by-product, a 2:1 unresolvable mixture of diethyl (*E*)- and (*Z*)-2-(fluoromethyl)-3-[(4-methylphenyl)thio]-2-propene phosphonate **36** was detected (10% yield): R_F 0.25.

36 (Major isomer): ^1H NMR ($CDCl_3$) δ: 7.30 and 7.12 (4 H, m, ArH), 6.41 (1 H, m, H-3), 5.17 (2 H, br dd, J = 47.0 and 2.7 Hz, H_2-1'), 4.3-4.0 (4 H, m, OCH_2), 2.82 (2 H, br d, J = 21.6 Hz, H_2-1), 2.34 (3 H, br s, ArMe), and 1.35 (6 H, t, J = 6.9 Hz, Me). ^{19}F NMR ($CDCl_3$) δ: -217.42 (1 F, br dt, J = 8.5 and 47.0 Hz, F-1'). ^{31}P NMR ($CDCl_3$) δ: 26.1 (1 P, br signal, P-1).

36 (Minor isomer): ^1H NMR ($CDCl_3$) δ: 7.30 and 7.12 (4 H, m, ArH), 6.53 (1 H, m, H-3), 4.97 (2 H, br ddd, J = 47.2, 2.9 and 1.3 Hz, H_2-1'), 4.3-4.0 (4 H, m, OCH_2), 2.94 (2 H, br d, J = 22.0 Hz, H_2-1), 2.34 (3 H, br s, ArMe), and 1.35 (6 H, t, J = 6.9 Hz, Me). ^{19}F NMR ($CDCl_3$) δ: -212.60 (1 F, br dt, J = 9.0 and 47.2 Hz, F-1'). ^{31}P NMR ($CDCl_3$) δ: 26.0 (1 P, br signal, P-1).

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