Pergamon

Tetrahedron 54 (1998) 11825–11840

TETRAHEDRON

Synthesis and Reactivity of Enantiomerically Pure 2-Fluoromethyl-2-(1'-*p*-Tolylsulfinyl)alkyl Oxiranes

Alberto Arnone, Pierfrancesco Bravo,* Massimo Frigerio and Fiorenza Viani

C.N.R. - Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Vadim A. Soloshonok*

National Industrial Research Institute of Nagoya, Hirate-cho 1-1, Kita-ku, Nagoya City, Aichi Prefecture 462, Japan

Received 11 June 1998; accepted 21 July 1998

Abstract: This paper presents an efficient procedure for preparing enantio- and diastereomerically pure 2-fluoromethyl-2-(1'-*p*-tolylsulfinyl)alkyl oxiranes, designed as versatile chirons to be transformed to a series of synthetically useful and biologically relevant compounds. In particular, (2*S*)-2-fluoromethyl-2-(1'-*p*-tolylsulfinyl)alkyl oxiranes, prepared by the reaction between (R_S)-α-alkyl-β-keto-γ-fluoro sulfoxides and diazomethane, can be efficiently obtained in diastereomerically pure state *via* formation, purification and re-cyclization of the corresponding bromohydrins. Synthetic value of these oxiranes was demonstrated by their transformation to various sulfur-free synthetically and biologically interesting compounds *via* the reductive desulfurization, *Pummerer*, ring-opening and *syn*-elimination reactions. The presence of the methyl in α-position to the sulfoxide group in the starting compounds was found to interfere with a normal course of the *Pummerer* rearrangement giving rise to the corresponding vinyl sulfides in low chemical yield. By contrast the thermal *syn*-elimination reaction of the *p*-tolyl sulfoxide group provided an efficient entry to the sulfur-free vinyl derivatives.

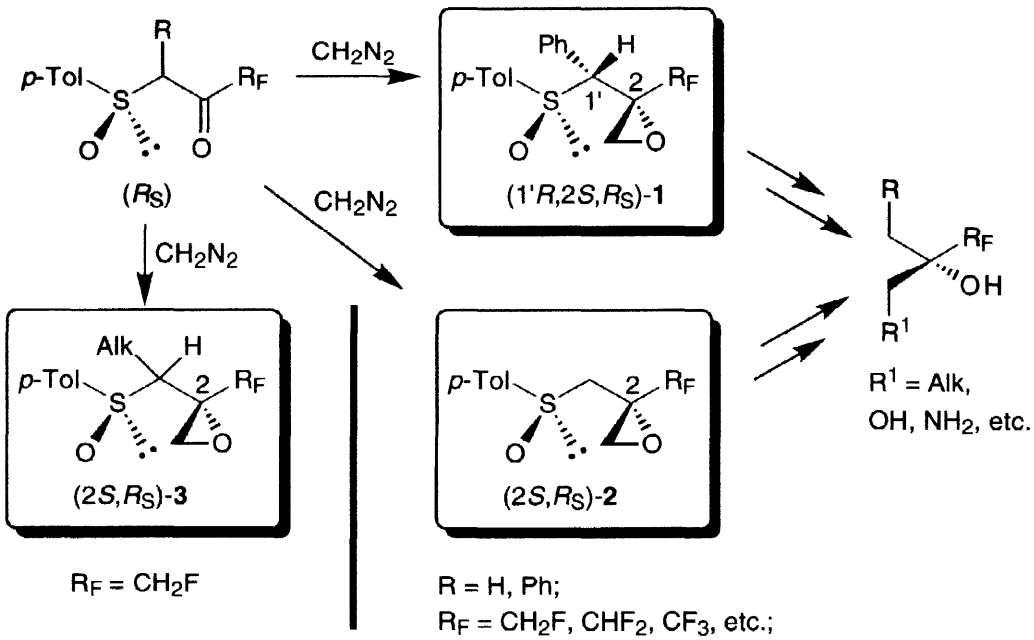
INTRODUCTION

With the growing importance of enantiomerically pure fluorine containing compounds in the pharmaceutical, agrochemical and functional materials (liquid crystals) industries,[1] the asymmetric synthesis of fluoro-organic compounds has received much attention recently.[2] Driven initially by the necessity of preparing biologically relevant compounds in an enantiomerically pure form, this field of research has gained a tremendous impetus with a discovery of the unique stereocontrolling properties of fluorine substituents.[3]

From the methodological point of view the chiral building block approach has been proven to be synthetically powerful, flexible and versatile route to the rational design of selectively fluorinated novel functional materials and compounds with pre-supposed biological activity.[2b] As a part of on going study into the viability of chiral sulfoxide chemistry for the asymmetric synthesis of polyfunctional, selectively fluorinated, and biologically relevant compounds through the corresponding chirons[4] we discovered the highly diastereoselective methylene transfer reaction from diazomethane to the carbonyl of β-keto-γ-fluorosubstituted sulfoxides giving rise to the corresponding oxiranes (Figure 1).[5] The synthetic opportunities associated with the epoxide ring and the sulfinyl group, render these compounds highly promising, versatile chiral building blocks for preparing a

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00709-1

Figure 1



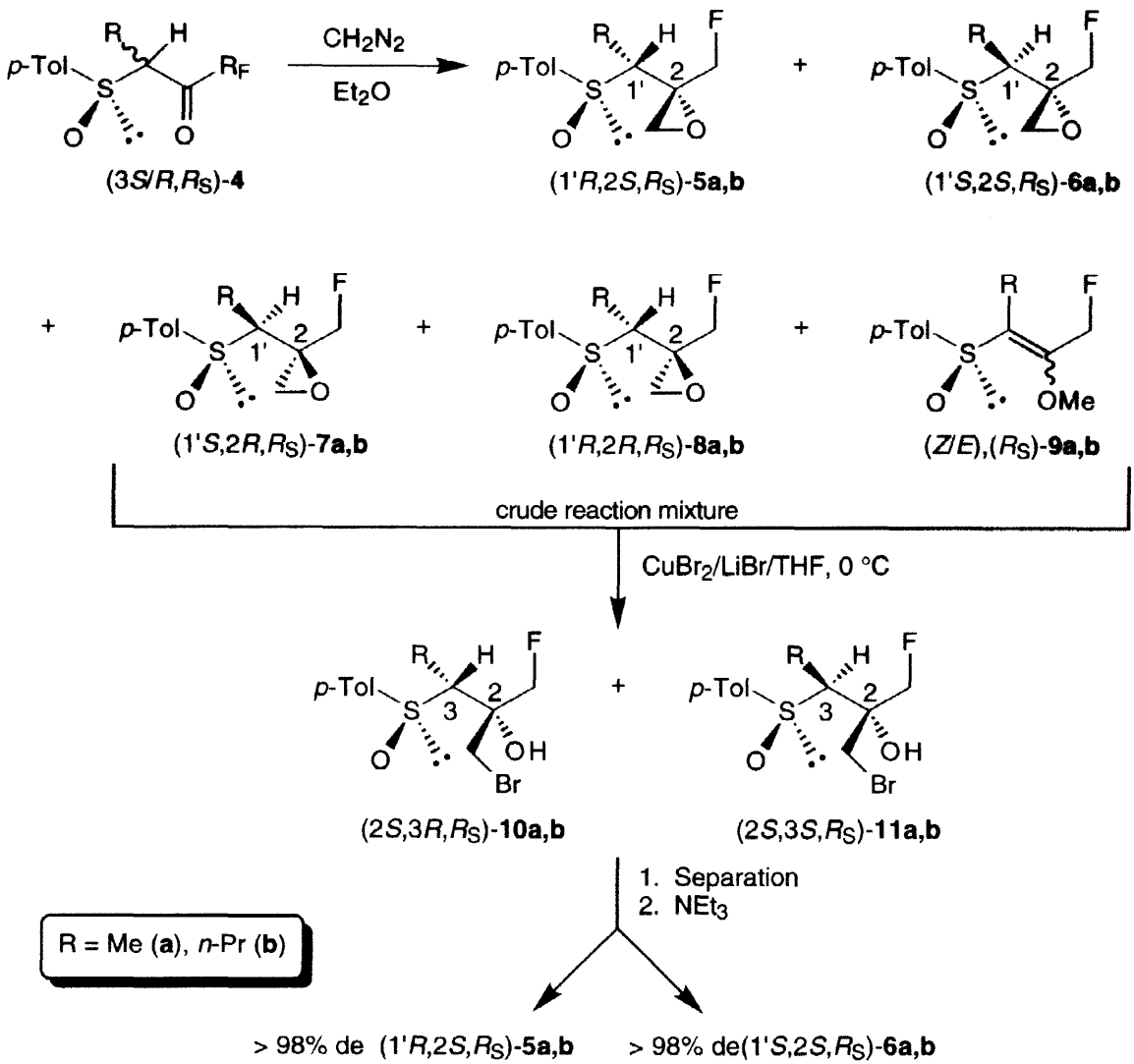
large number of enantiomerically pure, polyfunctional, fluorine-containing compounds. So far we have developed two types of chirons **1** ($R_F = CH_2F$) and **2** ($R_F = CH_2F$, CHF_2, CF_3, $CClF_2$, C_2F_5, n-C_7F_{15}) and demonstrated their efficient elaboration to the series of enantiopure fluorinated alcohols, amines, hydroxy and amino acids of biomedicinal importance.[5]

Expanding on this methodology, we have design new types of chirons **3** bearing an alkyl group in the position alpha to the sulfoxide function. The presence of the alkyl substituent would render compounds of type **3** even more versatile chirons, as compared with **1** and **2**, since apart from the elaboration of the epoxide ring, the alkyl group could be involved in the *syn*-elimination reaction to give the corresponding C-C double bound, an additional functionality capable of further synthetic elaboration. The preliminary study[6] into the reactions between the α-substituted β-keto-γ-fluoro sulfoxides and diazomethane has shown that the targeted epoxides of type **3** (Figure 1) could be prepared *via* this route in high chemical yields and synthetically useful levels of diastereoselectivity (over 70% de). However, exploration of the synthetic potential of chirons **3** in full was substantially restricted by the difficulties in their isolation and purification in optically pure form. In this paper we present a new and efficient procedure for preparing enantiomerically pure epoxides **3** and demonstrate their synthetic versatility with a series of key transformations of the epoxide ring and the sulfinyl group.

RESULTS AND DISCUSSION

The reaction between a diastereomeric mixture of α-alkyl-β-keto-γ-fluoro sulfoxides (3*S*/*R*,R_S)-**4a,b** (thermodynamic ratio *ca* 65/35, respectively) and diazomethane was shown to proceed cleanly in a diethyl ether solution at 0 °C, giving rise to a mixture of epoxides (1'*R*,2*S*,R_S)-**5a,b** and (1'*S*,2*S*,R_S)-**6a,b** as the dominant reaction products (86%), along with two minor diastereomeric oxiranes (1'*S*,2*R*,R_S)-**7a,b** and (1'*R*,2*R*,R_S)-**8a,b**, and (*Z*,*E*)-enol ethers **9a,b** as well (Scheme 1).[6] The stereochemistry of the newly-formed stereogenic center, C2 of the oxirane ring, was found to be overwhelmingly controlled by the chiral sulfoxide moiety affording (2*S*) configured epoxides in up to 72% dc regardless of the diastereomeric composition of starting keto

Scheme 1



sulfoxide.[7] Since the epoxides **5**,**6** are considered to be precursors to sulfur-free biologically relevant targets, the stereochemistry of the C1' stereogenic center in products **5** and **6** might be cleared upon further elaboration and thus is synthetically meaningless. Therefore, the use of readily available thermodynamic mixture of diastereomers (3*S*/*R*,*R*S)-**4a**,**b** to afford (2*S*) configured epoxides **5** and **6** in high chemical yield and respectable diastereoselectivity seemed to be reasonable and preparatively-attractive synthetic route. However, the similarity in chromatographic behavior of the main **5**,**6** and minor **7**,**8** epoxides turned out to be a serious drawback of the method, necessitating a series of time-consuming chromatographic separations of the resultant mixture to get the targeted epoxides **5** and **6** in diastereo- and enantiomerically pure form. To overcome this problem we decided to search for suitable derivatives of the target epoxides through which separation of the diastereomers could be accomplished efficiently on a preparative scale.

Synthesis of diastereo- and enantiomerically pure epoxides (1'*R*,2*S*,*R*S)-5a,b and (1'*S*,2*S*,*R*S)-6a,b. From the synthetic point of view preparation of the epoxides **5** and **6** through the corresponding derivatives could be preparatively viable provided the following criteria are met: the derivatives

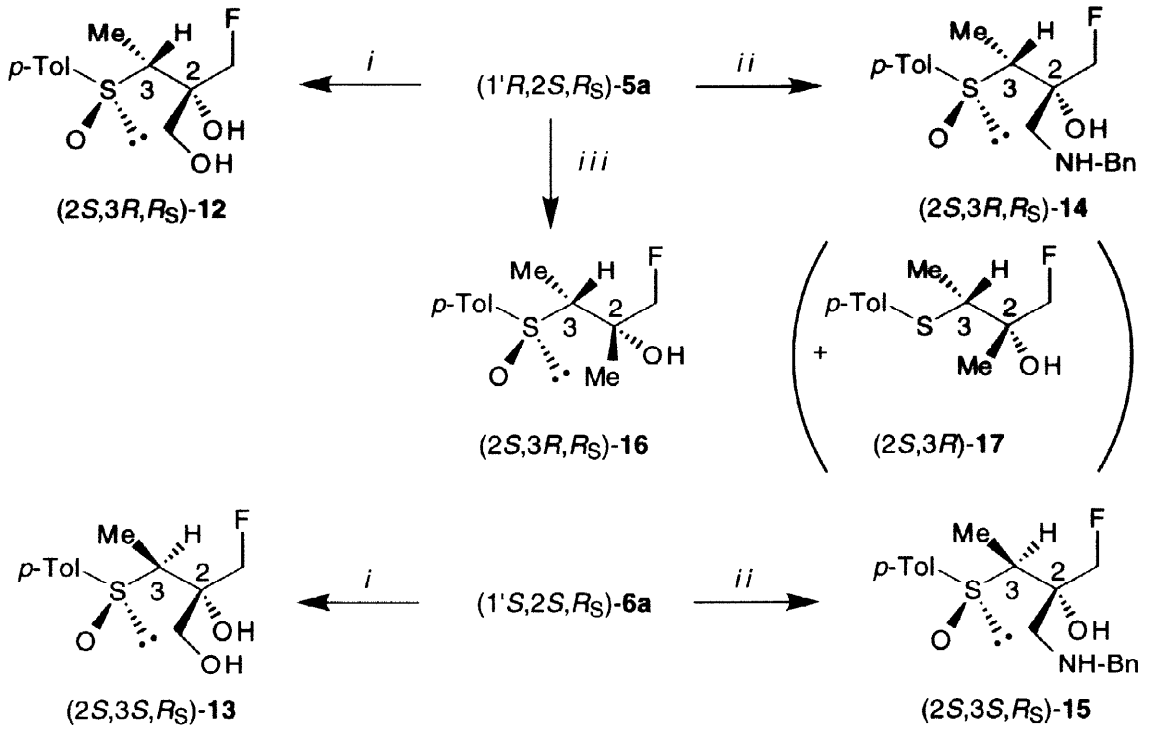
should be (1) obtained directly from the reaction mixture in high chemical yield; (2) readily separable crystalline compounds; (3) readily convertible back to the epoxides; and (4) stereochemically stable to all chemical transformations involved. Among various synthetic options we found that the corresponding bromohydrins perfectly suit the requirements set for the intermediates to perform preparation of the epoxides **5** and **6** in optically pure form. Thus, treatment of the crude mixture, resulting from the reaction between keto sulfoxide **4a** or **4b** and diazomethane, with $CuBr_2$/LiBr in THF at 0 °C gave rise to bromohydrins (2*S*,3*R*,*R*S)-**10a,b** and (2*S*,3*S*,*R*S)-**11a,b** along with the corresponding derivatives of the minor epoxides and unreacted enol ethers **9a,b** (Scheme 1). A single flash chromatography (FC) of this mixture of products allowed us to isolate the target diastereo- and enantiomerically pure bromohydrins (2*S*,3*R*,*R*S)-**10a,b** and (2*S*,3*S*,*R*S)-**11a,b** in 22% (**10a**), 37% (**11a**), 23% (**10b**) and 33% (**11b**) yields. The absolute configurations of compounds (2*S*,3*R*,*R*S)-**10a** and (2*S*,3*S*,*R*S)-**11a** were determined previously by X-ray analysis.[6] Recyclization of bromohydrins **10a,b** and **11a,b** to afford the final epoxides (1'*R*,2*S*,*R*S)-**5a,b** and (1'*S*,2*S*,*R*S)-**6a,b** was accomplished merely by dissolving compounds **10a,b**, **11a,b** in NEt_3 followed by stirring of the resultant solutions for 5 h at ambient temperature. According to NMR analysis of crude mixtures the reactions occurred cleanly to give only the epoxides **5a,b** and **6a,b**, which were isolated by FC in excellent chemical yields (90-95%).

Having thus developed a reliable protocol for preparing oxiranes **5a,b** and **6a,b** in optically pure form we set about exploration of their transformations to a series of polyfunctional, differently-substituted tertiary α-(fluoromethyl)carbinols, useful chiral building blocks for new enantiomerically-pure fluorinated compounds of biomedicinal importance.

Elaboration of the synthons 5a and 6a. Despite the fact that diastereomers **5a** and **6a** upon elaboration to sulfur-free derivatives might give the final compounds containing one stereogenic center of the same absolute configuration, we studied reactions of each **5a** and **6a** separately to obtain stereochemically individual products capable of proper characterization. Considering compounds **5a** and **6a** one could envision at least three reaction sites to be involved in further transformations: 1) the epoxide ring; 2) the sulfoxide group; and 3) the carbon atom bearing the alkyl and the sulfoxide groups. Our experience in the chemistry of synthons **1** and **2** (Figure 1) suggested that to provide complete regiodiscrimination between the possible reaction sites in the molecules of this type, the highly reactive epoxide ring should be elaborated prior to the synthesis of targeted sulfur-free compounds. Following this strategy we investigated first ring-opening reactions of **5a** and **6a**, to introduce oxygen and nitrogen functionalities, as well as a reduction of the epoxide ring.

Epoxide ring-opening reactions. Since under basic reaction conditions an epoxide ring having in α-position an acidic CH group prone to rearrangement to give open-chained allylic alcohols,[5] we applied an acidic catalyst to promote the reaction of **5a** and **6a** with water. Treatment of a THF solution of epoxide (1'*R*,2*S*,*R*S)-**5a** with water in the presence of catalytic amounts of perchloric acid gave cleanly the desired diol (2*S*,3*R*,*R*S)-**12** isolated by FC in 70% yield (Scheme 2). Starting with diastereomer (1'*S*,2*S*,*R*S)-**6a** the corresponding dihydroxy derivative (2*S*,3*S*,*R*S)-**13** was prepared under the same reaction conditions in 65% yield. Both reactions proceeded with a low rate, requiring 5 d at rt for completion. Ring-opening of **5a** and **6a** with benzylamine was found to occur with higher reaction rate (2 d at rt for completion) to afford the corresponding amino alcohols (2*S*,3*R*,*R*S)-**14** and (2*S*,3*S*,*R*S)-**15** in excellent isolated yields; 90 and 95%, respectively. Reduction of the epoxide ring, ring-opening with a hydride anion, was studied using (1'*R*,2*S*,*R*S)-**5a**

Scheme 2



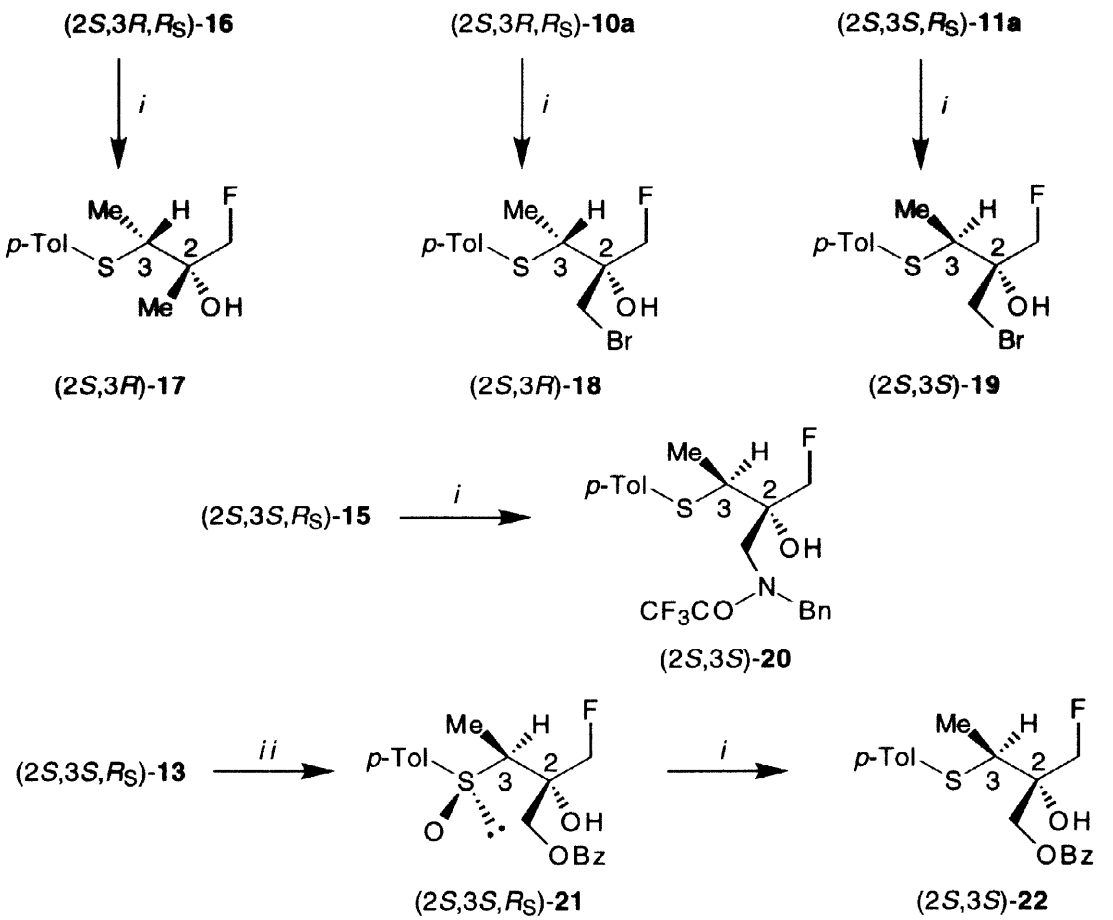
Key: (*i*) $HClO_4$, H_2O/THF, rt, 5 d; (*ii*) $BnNH_2$, THF, rt, 2 d; (*iii*) $LiAlH_4$, THF, -70 °C, 2 h

diastereomer. Treatment of **5a** in a THF solution with a suspension of $LiAlH_4$ for 2 h at -70 °C gave rise to the desired tertiary alcohol (2*S*,3*R*,R_S)-**16** isolated in 93% yield. Along with compound **16** the corresponding sulfenyl derivative (2*S*,3*R*)-**17**, resulting from the reduction of the sulfinyl group, was obtained in a minute amount (4%). It worth noting that the ring-opening reactions of diastereomeric oxiranes **5a** and **6a** with water and benzylamine, and **5a** with $LiAlH_4$ proceeded with complete regioselectivity involving attack by the incoming nucleophile exclusively on the less substituted carbon atom of the epoxide ring.

To afford the targeted sulfur-free compounds, three ways for removal of the sulfoxide group were studied: the reductive desulfurization, *Pummerer* rearrangement and *syn*-elimination reactions.

Reductive desulfurization. The most reliable protocol for removal of a sulfoxide group involves a two-reductive-step procedure; first, transformation of a sulfinyl to a thio group followed by a desulfenylation reaction to afford sulfur-free derivatives.[8] For the first step we used the *Oae* procedure,[9] which in our experience proved to be the method of choice for reducing a sulfoxide to a sulfide group. The reduction of four types of the ring-opened products, including bromohydrins **10a** and **11a**, was studied (Scheme 3). Treatment of tertiary carbinol (2*S*,3*R*,R_S)-**16** in a acetone solution with NaI and trifluoroacetic anhydride for 20 min at -20 °C afforded the corresponding sulfenyl derivative (2*S*,3*R*)-**17** in excellent isolated yield (97%). Under the same reaction conditions both diastereomeric bromohydrins (2*S*,3*R*,R_S)-**10a** and (2*S*,3*S*,R_S)-**11a** were cleanly reduced to give still-diastereomeric derivatives (2*S*,3*R*)-**18** and (2*S*,3*S*)-**19** in 85 and 85% yield, respectively. The reduction of amino-alcohol (2*S*,3*S*,R_S)-**15** was accompanied by trifluoroacetylation of the amino group giving rise to amide (2*S*,3*S*)-**20** in high isolated yield (83%). For the reduction of diol (2*S*,3*S*,R_S)-**13**, to avoid

Scheme 3



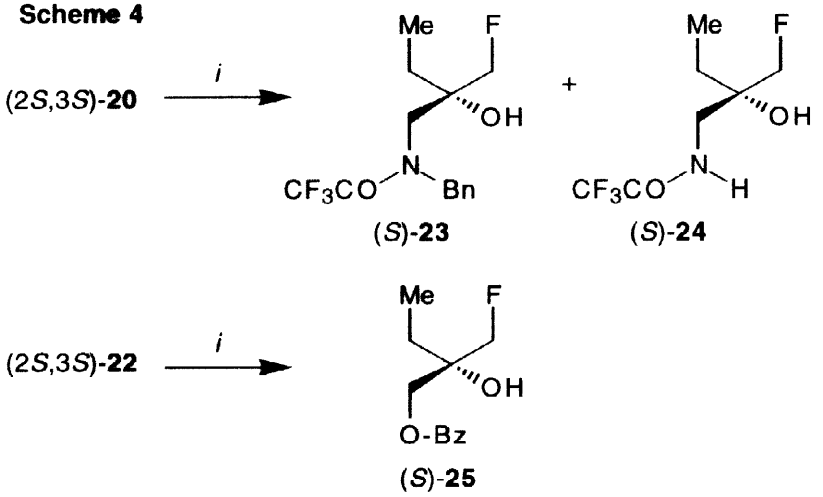
Key: (*i*) NaI, $(CF_3CO)_2O$, acetone, -20 °C; (*ii*) $PhCO_2H$, DCC, DMAP, CH_2Cl_2, rt

undesirable complications associated with a trifluoroacetylation of the primary hydroxy group, we first prepared the corresponding *O*-benzoyl derivative (2*S*,3*S*,R_S)-**21** by treatment of compound **13** with benzoic acid in the presence of DCC and DMAP in methylene chloride at rt. The reduction of thus protected **21** afforded sulfenyl derivative (2*S*,3*S*)-**22** in excellent isolated yield (98%).

The second step, a reductive desulfenylation reaction to afford sulfur-free derivatives, was performed using the standard reaction conditions[10] for *Raney* nickel-promoted hydrogenolysis (Scheme 4). The reduction of amido-alcohol (2*S*,3*S*)-**20** in an ethanol solution in the presence of *Raney*-Ni under hydrogen atmosphere at 80 °C was found to proceed with a low reaction rate and to be complicated with a partial hydrogenolysis of N-Bn bond. The reaction was completed in 24 h, giving rise to two sulfur-free products (*S*)-**23** and (*S*)-**24**, which were isolated by FC in 38 and 22% yield. By contrast, the hydrogenolysis of protected diol (2*S*,3*S*)-**22**, under the same reaction conditions, occurred with very high reaction rate, affording the only reaction product (*S*)-**25** in high isolated yield (89%).

Pummerer *rearrangement*. The *Pummerer* rearrangement is a very useful method for transformation of sulfoxides to sulfides or various oxygenated derivatives.[11] For example, α-unsubstituted chirons **2** (Figure 1) were efficiently transformed *via Pummerer* rearrangement to the corresponding primary alcohols or carboxylic

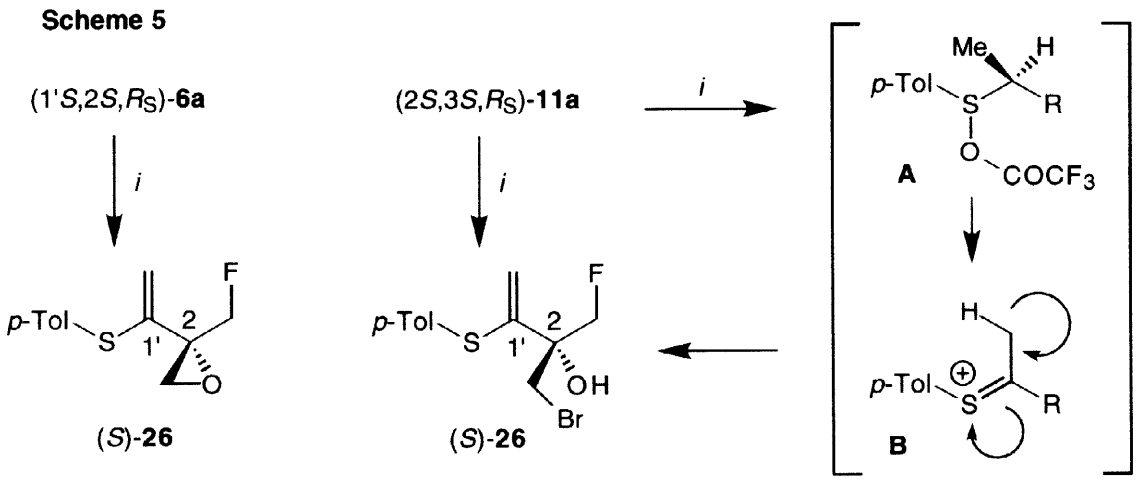
Scheme 4



Key: (*i*) *Raney*-Ni/H_2, ethanol, 80 °C

acids under reductive or oxidative conditions, respectively.[5b,e,i] The presence of a methyl group in the α-position to the sulfoxide group in the chirons under study was found to interfere with a normal course of the *Pummerer* rearrangement causing unusual reaction outcome.[12] The reaction was studied using oxirane **6a** and its ring-opened derivative **11a** as starting materials (Scheme 5). Treatment of epoxide (1'*S*,2*S*,*R*S)-**6a** in an acetonitrile solution with a trifluoroacetic anhydride in the presence of *sym*-collidine gave vinyl sulfide (*S*)-**26** as a main reaction product in 44% yield. The same chemical result, a formation of the corresponding vinyl sulfide, was observed in the reaction of bromohydrin (2*S*,3*S*,*R*S)-**11a**. However, the transformation of **11a** to sulfide (*S*)-**27** was accompanied by formation of a sizable amount of by-products causing low isolated yield (20%) of vinyl sulfide (*S*)-**27**. A plausible mechanistic rationale for the observed reaction outcome would involve first the formation of thionium ion **B**, a typical *Pummerer* intermediate,[11c] *via* trifluoroacetylation of the sulfoxide oxygen to give the product **A**, followed by α-deprotonation by a *sym*-collidine and the elimination of trifluoroacetic acid. Elimination of one of the methyl protons seems to be a more favorable process than attack of trifluoroacetate ion on thionium ion **B**, which would lead to regular reaction products.

Scheme 5

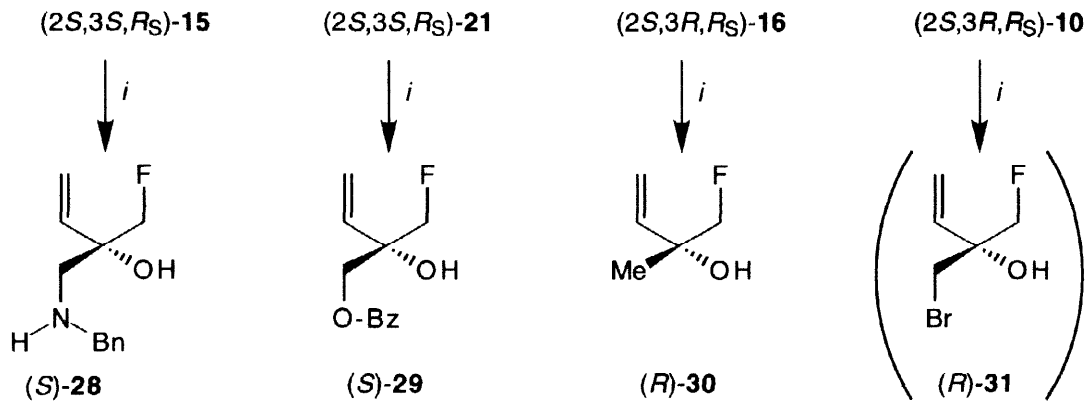


Key: (*i*) $(CF_3CO)_2O$, CH_3CN, -20 °C to rt

syn-*Elimination reactions*. Finally, thermal *syn*-elimination reactions of the *p*-tolyl sulfoxide group, leading to sulfur-free vinyl derivatives,[13] were studied using ring-opened derivatives (2*S*,3*R*,*R*S)-**10a**, (2*S*,3*S*,*R*S)-**15**, (2*S*,3*R*,*R*S)-**16** and (2*S*,3*S*,*R*S)-**21** as starting compounds (Scheme 6). We found that the

desired elimination of the *p*-tolyl sulfoxide group from amino-alcohol **15** to afford vinyl derivative (*S*)-**28** smoothly occurred upon short heating (10 min at 150 °C) of a solution of compound **15** in *p*-xylene. Amino-alcohol (*S*)-**28** was isolated by FC in 80% yield. Similarly, protected diol **21** and alcohol **16** were cleanly transformed upon heating in *p*-xylene solution to vinyl derivatives (*S*)-**29** and (*R*)-**30** in high chemical yields (78 and 73%, respectively). While compounds (*S*)-**28** and (*S*)-**29** were isolated by FC, volatile allyl alcohol (*R*)-**30** was obtained by fractional distillation. In contrast, heating a solution of bromohydrin **10a** in *p*-xylene resulted in a partial decomposition of the starting compound giving rise to a mixture of products among which the targeted vinyl derivative **31**, *p*-tolyl-[(4-methylphenyl)sulfenyl]sulfoxide, and 2-fluoromethyl-3-[(4-methylphenyl)sulfenyl]-butan-1,2-diol were detected by NMR. Presumably, under the reaction conditions employed bromohydrin **10a** could undergo a cyclization to give an epoxide and hydrobromic acid, two highly reactive species capable of further thermal and catalytic transformations.

Scheme 6



Key: (*i*) *p*-Xylene, 150 °C, 10 min

As one can see, the *syn*-elimination reaction under study, not available to the previously reported chirons **1** and **2** (Figure 1), is an attractive synthetic method for preparing interesting compounds of type (*S*)-**28**, (*S*)-**29** and (*R*)-**30** bearing four different functionalities on the stereogenic carbon atom.

In conclusion, we found that (2*S*)-2-fluoromethyl-2-(1'-*p*-tolylsulfinyl)alkyl oxiranes, prepared by the reaction between (R_S)-α-alkyl-β-keto-γ-fluoro sulfoxides and diazomethane, can be efficiently obtained in diastereomerically pure states *via* formation, purification and recyclization of the corresponding bromohydrins. The synthetic value of these oxiranes for preparing various biologically relevant chiral building blocks was demonstrated *via* reductive desulfurization, *Pummerer*, ring-opening and *syn*-elimination reactions. The presence of a methyl group in the α-position to the sulfoxide group in the starting compounds was found to interfere with a normal course of the *Pummerer* rearrangement giving rise to the corresponding vinyl sulfides in low chemical yield. By contrast, the thermal *syn*-elimination reaction of the *p*-tolyl sulfoxide group provided an efficient entry to the sulfur-free vinyl derivatives.

Acknowledgment. V. A. S. thanks National Research Council (C.N.R.) - Comitato Tecnologico and Progetto Finalizzato Chimica Fine for a Visiting Professor Fellowship.

EXPERIMENTAL SECTION

General. For standard laboratory praxis and techniques see the related paper, ref. 5c. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by ^1H and ^{19}F NMR spectrometry. All new compounds were characterized by ^1H NMR, ^{19}F NMR, and elemental analysis.

Synthesis of 2-fluoromethyl-2-[1'-(4-methylphenyl)sulfinyl]ethyl (1'*S*,2*S*,*R*$_S$)-5a, (1'*R*,2*S*,*R*$_S$)-6a and (*R*$_S$)-2-fluoromethyl-2-[1'-(4-methylphenyl)sulfinyl]-*n*-butyl oxiranes (1'*S*,2*S*,*R*$_S$)-5b, (1'*R*,2*S*,*R*$_S$)-6b. *Reactions of β-keto sulfoxides 4a,b with diazomethane.* General procedure. An ethereal solution of CH_2N_2 (*c.a.* 0.5M) was added portion-wise to a stirred solution of β-keto sulfoxides **4a,b** (13.5 mmol), taken as thermodynamic mixture of (3*S*,*R*$_S$) and (3*R*,*R*$_S$) diastereomers (ca. 65/35, respectively) in methanol (80 mL) at 0 °C up to persistence of the CH_2N_2 yellow color. The reaction was monitored by TLC and upon completion, N_2 was bubbled through the reaction solution to remove excess diazomethane. The solvent was evaporated *in vacuo* and the resultant mixture of products was used for preparation of bromohydrines (2*S*,3*R*,*R*$_S$)-**10a,b** and (2*S*,3*S*,*R*$_S$)-**11a,b**.

Synthesis of Bromohydrins 10a,b and 11a,b. **General procedure.** $CuBr_2$ (19.9 mmol) and LiBr (40.0 mmol) were dissolved in THF (30 mL) at 0 °C to afford a dark-green solution that was warmed up to rt. The crude mixture of epoxides, obtained from the reaction of β-keto sulfoxides **4a,b** with diazomethane (13.5 mmol), dissolved in the same solvent (10 mL), was added dropwise and the resultant mixture was stirred for 4 h at ambient temperature. The reaction was monitored by TLC and upon completion, treated with phosphate buffer (15 mL, pH = 7). The products were extracted by $CHCl_3$ (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford an oily residue that was flash chromatographed (*c*-hexane/ethyl acetate 4/1 for compounds **10a** and **11a**, chloroform/ethyl acetate 1/1 for **10b** and **11b**) to give the corresponding bromohydrins listed below.

(2*S*,3*R*,*R*$_S$)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]-butan-2-ol (10a).[6] Yield 22%; R_f = 0.45; $[\alpha]_D^{20}$ +183.1 (*c* 0.7, $CHCl_3$); $[\alpha]_{365}^{20}$ +916.0 (*c* 0.7, $CHCl_3$); mp 115-116 °C (*i*-Pr ether); ^1H NMR ($CDCl_3$) δ 1.01 (3H, dd, *J* = 7.4 and 1.9 Hz), 2.46 (3H, s), 3.30 (1H, qd, *J* = 7.4 and 1.2 Hz), 3.61 (1H, d, *J* = 11.1 Hz), 3.72 (1H, ddd, *J* = 11.1, 2.9 and 1.2 Hz), 4.61 (1H, ddd, *J* = 46.7, 10.5 and 1.2 Hz), 5.05 (1H, dd, *J* = 47.5 and 10.5 Hz), 5.87 (1H, br.s), 7.38, 7.69 (4H, m); ^{19}F NMR ($CDCl_3$) δ -222.99 (1F, dd, *J* = 47.5 and 46.7 Hz).

(2*S*,3*S*,*R*$_S$)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]-butan-2-ol (11a).[6] Yield 37%; R_f = 0.35; $[\alpha]_D^{20}$ +139.2 (*c* 1.8, $CHCl_3$); $[\alpha]_{365}^{20}$ +721.0 (*c* 1.8, $CHCl_3$); mp 65.4-66.4° C (*i*-Pr ether/*n*-hex 1:1); ^1H NMR ($CDCl_3$) δ 1.10 (3H, d, *J* = 7.1 Hz), 2.42 (3H, s), 2.98 (1H, qd, *J* = 7.1 and 2.2 Hz), 3.65 (1H, br.s), 3.67 (1H, dd, *J* = 11.2 and 1.7 Hz), 3.94 (1H, dd, *J* = 11.2 and 1.8 Hz), 4.77 (1H, dd, *J* = 46.8 and 10.0 Hz), 4.83 (1H, dd, *J* = 46.8 and 10.0 Hz), 7.33, 7.44 (4H, m); ^{19}F NMR ($CDCl_3$) δ -230.63 (1F, t, *J* = 46.8 Hz).

Apart from two major products, the corresponding (2*R*,3*S*,*R*$_S$)-configured bromohydrin was isolated in 18% yield; R_f = 0.34; $[\alpha]_D^{20}$ +104.1 (*c* 0.8, $CHCl_3$), $[\alpha]_{365}$ +505.9 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.07 (3H, d, *J* = 7.1 Hz), 2.42 (3H, s), 3.02 (1H, qd, *J* = 7.1 and 1.3 Hz), 3.62 (1H, br.s), 3.89 (1H, dd, *J* =

11.2 and 1.7 Hz), 3.99 (1H, dd, J = 11.2 and 2.2 Hz), 4.62 (1H, dd, J = 46.6 and 9.8 Hz), 4.69 (1H, dd, J = 47.0 and 9.8Hz), 7.33, 7.44 (4H, m); ^{19}F NMR ($CDCl_3$) δ -232.66 (1F, dd, J = 47.0 and 46.6Hz); Anal. Calcd for $C_{12}H_{16}BrFO_2S$: C,44.59; H,4.99; Br,24.72; F,5.88. Found: C,44.60; H,4.96; Br,24.70; F,5.91.

(2*S*,3*R*,*R*$_S$)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]-hexan-2-ol (10b). Yield 23%; R_f = 0.70 (*n*-hexane/ethyl acetate 4:1); $[\alpha]_D^{20}$ +158.0 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.5-1.7 (7H, m), 2.45 (3H, s), 3.13 (1H, br.t), 3.65 (1H, d, J = 11.0Hz), 3.73 (1H, ddd, J = 11.0, 2.3 and 1.2Hz),), 4.66 (1H, dd, J = 46.6 and 10.1Hz), 4.90 (1H, dd, J = 47.1 and 10.1Hz), 5.88 (1H, br.s), 7.37, 7.68 (4H, m); ^{19}F NMR ($CDCl_3$) δ -225.25 (1F, dd, J = 47.1 and 46.6Hz); Anal. Calcd for $C_{14}H_{20}BrFO_2S$: C,47.87; H,5.74; Br,22.75; F,5.41. Found: C,47.95; H,5.70; Br,22.70; F,5.38.

(2*S*,3*S*,*R*$_S$)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]-hexan-2-ol (11b). Yield 33.0%; R_f = 0.52; $[\alpha]_D^{20}$ +103.3 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.61 (3H, t, J = 7.2Hz), 1.01-1.92 (4H, m), 2.42 (3H, s), 2.86 (1H, m, J = 11.8, 3.5 and 2.5Hz), 3.67 (1H, br.s), 3.69 (1H, dd, J = 11.2 and 1.6Hz),), 3.93 (1H, dd, J = 11.2 and 1.8Hz), 4.77 (1H, dd, J = 46.8 and 10.1Hz), 4.85 (1H, dd, J = 46.8 and 10.1Hz), 7.33, 7.47 (4H, m); ^{19}F NMR ($CDCl_3$) δ -230.12 (1F, t, J = 46.8Hz); Anal. Calcd for $C_{14}H_{20}BrFO_2S$: C,47.87; H,5.74; Br,22.75; F,5.41. Found: C,47.90; H,5.75; Br,22.76; F,5.43.

Apart from two major products the corresponding (2*R*,3*S*,*R*$_S$)-configured bromohydrin was isolated in 10.0% yield; R_f = 0.49; $[\alpha]_D^{20}$ +64.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.5-2.0 (7H, m), 2.43 (3H, s), 2.85 (1H, m), 3.61 (1H, br.s), 3.92 (1H, dd, J = 11.4 and 1.8Hz), 3.99 (1H, dd, J = 11.4 and 2.0Hz), 4.61 (1H, dd, J = 46.8 and 9.8Hz), 4.67 (1H, dd, J = 47.1 and 9.8Hz), 7.35, 7.47 (4H, m); ^{19}F NMR ($CDCl_3$) δ -233.00 (1F, dd, J = 47.1 and 46.8Hz); Anal. Calcd for $C_{14}H_{20}BrFO_2S$: C,47.87; H,5.74; Br,22.75; F,5.41. Found: C,47.91; H,5.70; Br,22.77; F,5.38.

Synthesis of Epoxides 5a,b and 6a,b from Bromohydrins 10a,b and 11a,b. **General procedure**. The optically pure bromohydrin **10a**,**b** and **11a**,**b** (3.1 mmol) was dissolved in triethylamine (TEA) (20 mL) and the resultant mixture was stirred at ambient temperature under N_2 for 5 h. The reaction was monitored by TLC and upon completion an excess of TEA was evaporated *in vacuo* and the target oxirane was purified by FC using *n*-hexane/ethyl acetate 65/35 to isolate compounds **5a** and **6a**, and chloroform/ethyl acetate 10/1 for **5b** and **6b**.

From (2*S*,3*R*,*R*$_S$)-**10a**, (1'*R*,2*S*,*R*$_S$)-**5a**[6] was prepared in 95% yield: mp 84-85°C (*i*-Pr ether); R_f = 0.35; $[\alpha]_D^{20}$ +231.6 (*c* 0.5, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 7.3Hz), 2.44 (3H, br.s), 2.91 (1H, d, J = 4.3Hz), 3.07 (1H, dd, J = 5.1 and 4.3Hz), 3.33 (1H, q, J =7.3Hz), 4.35 (1H, dd, J = 47.5 and 10.5Hz), 4.70 (1H, dd, J = 47.0 and 10.5Hz), 7.35, 7.58 (4H, m); ^{19}F NMR ($CDCl_3$) δ -230.09 (1F, dd, J = 47.5 and 47.0Hz).

From bromohydrin (2*S*,3*S*,*R*$_S$)-**11a** oxirane (1'*S*,2*S*,*R*$_S$)-**6a**[6] was obtained in 90% yield; R_f = 0.35; $[\alpha]_D^{20}$ +185.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 7.6Hz), 2.42 (3H, s), 2.77 (1H, q, J = 7.6Hz), 2.88 (1H, d, J = 4.2Hz), 3.03 (1H, dd, J = 4.9 and 4.2Hz), 4.49 (1H, dd, J = 47.5 and 10.6Hz), 4.63 (1H, dd, J = 46.9 and 10.6Hz), 7.33, 7.50 (4H, m); ^{19}F NMR ($CDCl_3$) δ -229.60 (1F, dd, J = 47.5 and 46.9Hz).

From (2*S*,3*R*,*R*$_S$)-**10b**, (1'*R*,2*S*,*R*$_S$)-**5b** was prepared in 95% yield: R_f = 0.15 (*n*-hexane/ethyl acetate 4/1); $[\alpha]_D^{20}$ +177.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.80-1.00 (3H, m), 1.20-1.65 (4H, m), 2.43 (3H, br.s), 2.85 (1H, d, J = 4.3Hz), 3.03 (1H, dd, J = 7.5 and 5.5Hz), 3.17 (1H, dd, J = 5.4 and 4.3Hz), 4.18

(1H, dd, J = 47.1 and 10.6Hz), 4.38 (1H, dd, J = 47.8 and 10.6Hz), 7.35, 7.56 (4H, m); ^{19}F NMR ($CDCl_3$) δ -229.41 (1F, dd, J = 47.8 and 47.1Hz).

From (2*S*,3*S*,*R*$_S$)-**11b**, (1'*S*,2*S*,*R*$_S$)-**6b**[6] was obtained in 93% yield; R_f = 0.43; $[\alpha]_D^{20}$ +164.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.1Hz), 1.35-1.90 (4H, m), 2.41 (3H, br.s), 2.57 (1H, dd, J = 9.0 and 4.5Hz), 2.71 (1H, dd, J = 4.4 and 4.3Hz), 2.83 (1H, d, J = 4.3Hz), 4.49 (1H, dd, J = 47.0 and 10.0Hz), 4.51 (1H, dd, J = 47.0 and 10.0Hz), 7.32, 7.51 (4H, m); ^{19}F NMR ($CDCl_3$) δ -229.84 (1F, t, J = 47.0Hz).

(2*S*,3*R*,*R*$_S$)-2-Fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-1,2-diol (12). To a stirred solution of oxirane (1'*R*,2*S*,*R*$_S$)-**5a** (400 mg, 1.65 mmol) in a THF/H_2O (1/1; vol) (10 mL), $HClO_4$ (70%, 80 μL, 0.085 mmol) was added. The reaction was monitored by TLC and upon completion (5 d at rt), the reaction mixture was evaporated *in vacuo* to dryness. The targeted diol **12** was purified by FC (*n*-hexane/ethyl acetate 1/9). Yield 65%; R_f = 0.35; $[\alpha]_D^{20}$ +113.4 (*c* 0.5, $CHCl_3$); $[\alpha]_{365}^{20}$ +769.2 (*c* 0.5, $CHCl_3$); mp 107-109 °C (*i*-Pr ether/ethyl acetate 1/1); ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, dd, J = 7.3 and 1.5 Hz), 2.44 (3H, br.s), 2.78 (1H, br.dd, J = 7.9 and 5.6 Hz), 3.21 (1H, br.q, J = 7.3 Hz), 3.67 (1H, br.dd, J = 11.5 and 5.6 Hz), 3.76 (1H, br.dd, J = 11.5 and 7.9 Hz), 4.58 (1H, br.dd, J = 46.9 and 10.0 Hz), 4.85 (1H, dd, J = 47.3 and 10.0 Hz), 5.83 (1H, br.s), 7.38-7.67 (4H, m); ^{13}C NMR (all dec, $CDCl_3$) δ 9.25 (s), 21.50 (s), 64.32 (d, $^3J_{C,F}$ = 5.6 Hz), 64.78 (s), 76.61 (d, $^2J_{C,F}$ = 17.5 Hz), 85.10 (d, $^1J_{C,F}$ = 173.9 Hz), 127.77 (s), 131.04 (s), 139.50 (s) 144.41(s); ^{19}F NMR ($CDCl_3$) δ -227.98 (1F, br.dd, J = 47.3 and 46.9 Hz). Anal. Calcd for $C_{12}H_{17}FO_3S$: C, 55.36; H, 6.58; F, 7.30. Found: C, 55.30; H, 6.57; F, 7.32.

(2*S*,3*S*,*R*$_S$)-2-Fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-1,2-diol (13). Starting from epoxide (1'*S*,2*S*,*R*$_S$)-**6a** diol (2*S*,3*S*,*R*$_S$)-**13** was prepared in 70% yield, according to the procedure described for (2*S*,3*R*,*R*$_S$)-**12**. R_f = 0.35; $[\alpha]_D^{20}$ +138.7 (*c* 0.4, $CHCl_3$); $[\alpha]_{365}^{20}$ +665.3 (*c* 0.4, $CHCl_3$); mp 91-93 °C (*i*-Pr ether/ethyl acetate 1/1); ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, d, J = 7.2 Hz), 2.42 (3H, br.s), 2.88 (1H, dq, J = 1.5 and 7.2 Hz), 3.48 (1H, ddd, J = 11.7, 7.5 and 1.6 Hz), 3.92 (1H, ddd, J = 11.7, 5.0 and 1.7 Hz), 3.96 (1H, br.dd, J = 7.5 and 5.0 Hz), 4.02 (1H, br.s), 4.48 (1H, dd, J = 47.5 and 9.9 Hz), 4.53 (1H, dd, J = 47.0 and 9.9 Hz), 7.36-7.40 (4H, m); ^{13}C NMR (all dec, $CDCl_3$) δ 3.82 (s), 21.3 (s), 63.68 (d, $^3J_{C,F}$ = 5.6 Hz), 65.73 (d, $^3J_{C,F}$ = 3.9 Hz), 76.53 (d, $^2J_{C,F}$ = 16.7 Hz), 85.86 (d, $^1J_{C,F}$ = 173.9 Hz), 125.27 (s), 130.99 (s), 140.29 (s) 142.67 (s); ^{19}F NMR ($CDCl_3$) δ -232.96 (1F, br.dd, J = 47.5 and 47.0 Hz). Anal. Calcd for $C_{12}H_{17}FO_3S$: C, 55.36; H, 6.58; F, 7.30. Found: C, 55.32; H, 6.60; F, 7.27.

(2*S*,3*R*,*R*$_S$)-1-(*N*-Benzyl)amino-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-2-ol (14). Neat benzylamine (2.5 mmol) was added to a solution of oxirane (1'*R*,2*S*,*R*$_S$)-**5a** (1.0 mmol) in THF (2 mL) at rt. The reaction was monitored by TLC and upon completion (48 h) the solvent was evaporated *in vacuo* to afford amino derivative (2*S*,3*R*,*R*$_S$)-**14**. After purification by FC (*c*-hexane/ethyl acetate 2/3) compound **14** was obtained in 95% yield; $[\alpha]_D^{20}$ +105.3 (*c* 1.1, $CHCl_3$); mp 92-93 °C (*i*-Pr ether); ^{1}H NMR [$CDCl_3(D_2O)$] δ 0.90 (3H, dd, J = 7.4 and 1.6 Hz), 2.44 (3H, br.s), 2.76 (1H, br.s, J = 11.8 Hz), 2.85 (1H, dd, J = 11.8 and 1.8Hz), 3.34 (1H, br.q, J = 7.4 Hz), 3.74, 3.86 (2H, br.d, J = 13.2 Hz), 4.54 (1H, dd, J = 47.1 and 9.8 Hz), 4.86 (1H, dd, J = 47.4 and 9.8 Hz), 7.2-7.7 (9H, m); ^{19}F NMR ($CDCl_3$) δ -225.45 (1F, br.dd, J = 47.4

and 47.1 Hz); Mass (EI): 350(M^+), 330(M^+-HF). Anal. Calcd for $C_{19}H_{24}FNO_2S$: C, 65.30; H, 6.92; N, 4.08. Found: C, 65.25; H, 6.90; N, 4.07.

(2*S*,3*S*,*R*$_S$)-1-*N*-(Benzyl)amino-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-2-ol (15). From epoxide (1'*S*,2*S*,*R*$_S$)-**6a** amino derivative (2*S*,3*S*,*R*$_S$)-**15** was obtained in 90% yield, according to the procedure described for preparation of diastereomer (2*S*,3*R*,*R*$_S$)-**14**; $[\alpha]_D^{20}$ +101.6 (*c* 0.9, $CHCl_3$); mp 103-104 °C (*i*-Pr ether); ^{1}H NMR [$CDCl_3(D_2O)$] δ 0.97 (3H, br.d, *J* = 7.1 Hz), 2.41 (3H, br.s), 2.60 (1H, br.d, *J* = 13.1 Hz), 2.83 (1H, dd, *J* = 7.1 and 1.2 Hz), 3.12 (1H, dd, *J* = 13.1 and 1.3 Hz), 3.86, 3.91 (2H, br.d, *J* = 13.8 Hz), 4.38 (1H, dd, *J* = 47.5 and 9.7 Hz), 4.45 (1H, dd, *J* = 47.8 and 9.7 Hz), 7.2-7.5 (9H, m); ^{19}F NMR ($CDCl_3$) δ -229.48 (1F, br.dd, *J* = 47.8 and 47.5 Hz). Anal. Calcd for $C_{19}H_{24}FNO_2S$: C, 65.30; H, 6.92; N, 4.08. Found: C, 65.27; H, 6.93; N, 4.06.

(2*S*,3*R*,*R*$_S$)-2-Fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-2-ol (16). To a solution of oxirane (1'*R*,2*S*,*R*$_S$)-**5a** (400 mg, 1.65 mmol) in THF (5 mL) stirred at -70 °C under N_2 atmosphere, a suspension of $LiAlH_4$ (80 mg, 2.11 mmol) in the same solvent (5 mL) was added portionwise. After 2 h, the mixture was poured into an ice/water bath and the pH was adjusted to 7 by adding 1*N* HCl. The product was extracted with diethyl ether and after evaporation of the solvent *in vacuo* purified by FC (*n*-pentane/ethyl ether 2/3). Yield of (2*S*,3*R*,*R*$_S$)-**16** 93%; R_f = 0.35; $[\alpha]_D^{20}$ +181.8 (*c* 1.0, $CHCl_3$); mp 63-64 °C (*i*-Pr ether); ^{1}H NMR ($CDCl_3$) δ 0.98 (3H, dd, *J* = 7.3 and 1.4 Hz), 1.34 (3H, br.d, *J* = 2.3 Hz), 2.44 (3H, br.s), 3.02 (1H, q, *J* = 7.3 Hz), 4.57 (1H, dd, *J* = 47.0 and 9.9 Hz), 4.83 (1H, dd, *J* = 48.0 and 9.9Hz), 5.70 (1H, br.s), 7.36-7.47 (4H, m); ^{19}F NMR ($CDCl_3$) δ -222.66 (1F, dd, *J* = 48.0 and 47.0 Hz); Anal. Calcd for $C_{12}H_{17}FO_2S$: C, 58.99; H, 7.01; F, 7.77. Found: C, 59.03; H, 7.03; F, 7.74.

Apart from compound (2*S*,3*R*,*R*$_S$)-**16** about 4% of the corresponding sulfenyl derivative (2*S*,3*R*)-**17** was isolated. For physical properties and NMR data see below the corresponding protocol in the paragraph "*Reduction of sulfoxide into sulfide group*".

***Reduction of sulfoxide into sulfide group.* General procedure.** NaI (2.0 mmol) and the substrates (1.0 mmol) were suspended in acetone (10 mL) under N_2 atmosphere and stirred at -20 °C for 10 min. Then a solution of $(CF_3CO)_2O$ (3.0 mmol) in the same solvent (5 mL) was added dropwise and stirring was continued at the same temperature for 20 min. Saturated solutions of Na_2SO_3 and $NaHCO_3$ (1:1 vol) were added and the organic layers were extracted with ethyl ether, dried over Na_2SO_4, filtered and evaporated *in vacuo* to dryness. The targeted products were purified by FC.

(2*S*,3*R*)-2-Fluoromethyl-3-[(4-methylphenyl)sulfenyl]butan-2-ol (17). Starting from (2*S*,3*R*,*R*$_S$)-**16**, after FC (*n*-hexane/ethyl ether 7/3) sulfenyl derivative **17** was obtained in 97% yield; R_f = 0.50; $[\alpha]_D^{20}$ -42.7 (*c* 1.0, $CHCl_3$); $[\alpha]_{365}^{20}$ -169.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, *J* = 2.5 Hz), 1.41 (3H, br.d, *J* = 7.1 Hz), 2.34 (3H, br.s), 2.56 (1H, br.s), 3.26 (1H, q, *J* = 7.1 Hz), 4.36 (1H, dd, *J* = 47.6 and 9.4 Hz), 4.55 (1H, dd, *J* = 47.5 and 9.4 Hz), 7.11, 7.35 (4H, m); ^{19}F NMR ($CDCl_3$) δ -229.22 (1F, dd, *J* = 47.6 and 47.5 Hz). Anal. Calcd for $C_{12}H_{17}FOS$: C, 63.12; H, 7.50; F, 8.32. Found: C, 63.10; H, 7.51; F, 8.30.

(2*S*,3*R*)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfenyl]hexan-2-ol (18). Starting from (2*S*,3*R*,*R*$_S$)-**10a** sulfenyl derivative (2*S*,3*R*)-**18** was obtained in 85% yield; R_f = 0.35 (*n*-hexane/ethyl ether 85/15); $[\alpha]_D^{20}$ +21.8 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, dd, *J* = 7.2 and 1.2Hz), 2.34 (3H,

s), 2.71 (1H, br.s), 3.51 (1H, q, J = 7.2Hz), 3.74 (1H, dd, J = 10.8 and 1.8Hz), 3.80 (1H, dd, J = 10.8 and 2.0Hz), 4.54 (1H, d, J = 46.7Hz), 4.56 (1H, d, J = 46.7Hz), 7.14, 7.38 (4H, m); ^{19}F NMR ($CDCl_3$) δ -230.40 (1F, t, J = 46.7Hz); Anal. Calcd for $C_{12}H_{16}BrFOS$: C, 46.91; H, 5.25; Br, 26.01; F, 6.18. Found: C, 46.93; H, 5.24; Br, 26.04; F, 6.15.

(2*S*,3*S*)-1-Bromo-2-fluoromethyl-3-[(4-methylphenyl)sulfenyl]hexan-2-ol (19). Starting from (2*S*,3*S*,R_S)-**11a**, sulfenyl derivative (2*S*,3*S*)-**19** was obtained in 80% yield; R_f = 0.35 (*n*-hexane/ethyl ether 4/1); $[\alpha]_D^{20}$ +52.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, d, J = 7.1Hz), 2.34 (3H, s), 2.63 (1H, br.s), 3.46 (1H, dd, J = 7.1 and 1.2Hz), 3.60 (1H, dd, J = 10.7 and1.8Hz), 3.77 (1H, dd, J = 10.7 and 1.9Hz), 4.63 (1H, dd, J = 46.7 and 9.7Hz), 4.67 (1H, dd, J = 46.7 and 9.7Hz), 7.13, 7.36 (4H, m); ^{19}F NMR ($CDCl_3$) δ -232.24 (1F, t, J = 46.7Hz); Anal. Calcd for $C_{12}H_{16}BrFOS$: C, 46.91; H 6.18. Found: C, 46.90; H, 5.23; Br, 26.03; F, 6.16.

(2*S*,3*S*)-1-(*N*-Benzyl-*N*-trifluoroacetyl)amino-2-fluoromethyl-3-[(4-methylphenyl)-sulfenyl]butan-2-ol (20). Starting from (2*S*,3*S*,R_S)-**15**, after FC (*n*-hexane/ethyl acetate 4/1) compound (2*S*,3*S*)-**20** was obtained in 83% yield; $[\alpha]_D^{20}$ +38.1 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.37 (3H, br.d, J = 7.2 Hz), 2.31 (3H, br.s), 3.34 (1H, dq, J = 7.2 and 1.4 Hz), 3.53 (1H, dd, J = 14.7 and 3.4 Hz), 3.70 (1H, br.d, J = 14.7 Hz), 3.76 (1H, br.s), 4.47, 4.57 (2H, dd, J = 47.0 and 9.9 Hz), 4.79, 4.99 (2H, br.d, J = 16.7 Hz), 7.1-7.5 (9H, m); ^{19}F NMR ($CDCl_3$) δ -229.82 (1F, br.t, J = 47.0 Hz), -69.08 (3F, s). Anal. Calcd for $C_{21}H_{23}F_4O_2S$: C, 58.73; H, 5.40; N, 3.26. Found: C, 58.70; H, 5.42; N, 3.27.

(2*S*,3*S*,R_S)-1-(*O*-Benzoyl)-2-fluoromethyl-3-[(4-methylphenyl)sulfinyl]butan-1,2-diol (21). To a stirred solution of diol (2*S*,3*S*,R_S)-**13** (100 mg, 0.384 mmol) in CH_2Cl_2 (6 mL), neat benzoic acid (52 mg, 0.422 mmol) and DCC (87 mg, 0.422 mmol) were added. After 5 min under stirring at rt, a catalytic amount of DMAP (5 mg) was added. Immediately, a white precipitate was formed. After 1 h, the white precipitate was filtered and the filtrate was evaporated to dryness *in vacuo*. The targeted *O*-benzoyl derivative (2*S*,3*S*,R_S)-**21** was purified by FC (*n*-hexane/ethyl acetate 2/3). Yield 93%; R_f = 0.35; $[\alpha]_D^{20}$ +93.7 (*c* 0.5, $CHCl_3$); $[\alpha]_{365}^{20}$ +473.7 (*c* 0.5, $CHCl_3$); mp 90-91 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, br.d, J = 7.2 Hz), 2.42 (3H, br.s), 2.91 (1H, dq, J = 2.3 and 7.2Hz), 3.88 (1H, br.s), 4.54 (1H, dd, J = 12.0 and 1.4 Hz), 4.68 (1H, dd, J = 12.0 and 1.6 Hz), 4.80 (1H, dd, J = 47.0 and 10.0 Hz), 4.92 (1H, dd, J = 46.9 and 10.0 Hz), 7.3-8.2 (9H, m); ^{19}F NMR ($CDCl_3$) δ -230.07 (1F, br.dd, J = 47.0 and 46.9 Hz). Anal. Calcd for $C_{19}H_{21}FO_4S$: C, 62.62; H, 5.81; F, 5.21. Found: C, 62.65; H, 5.83; F, 5.20.

(2*S*,3*S*)-1-(*O*-Benzoyl)-2-fluoromethyl-3-[(4-methylphenyl)sulfenyl]butan-1,2-diol (22). Compound (2*S*,3*S*)-**22** was prepared according to the general procedure described above for reduction of a sulfoxide into a sulfide group. Starting from (2*S*,3*S*,R_S)-**21**, (2*S*,3*S*)-**22** was obtained, after FC (*n*-hexane/ethyl acetate 7/3), in 98% yield; R_f = 0.45; $[\alpha]_D^{20}$ +33.5 (*c* 1.0, $CHCl_3$); $[\alpha]_{365}^{20}$ +111.4 (*c* 1.0, $CHCl_3$); yellowish oil; ^{1}H NMR ($CDCl_3$) δ 1.49 (3H, br.d, J = 7.3 Hz), 2.31 (3H, br.s), 3.02 (1H, br.s), 3.47 (1H, dq, J = 7.3 and 1.3 Hz), 4.47 (1H, dd, J = 11.0 and 1.7Hz), 4.57 (1H, dd, J = 11.9 and 1.8 Hz), 4.64 (2H, d, J = 47.0 Hz), 7.0-8.1 (9H, m); ^{19}F NMR ($CDCl_3$) δ -233.16 (1F, br.t, J = 47.0 Hz). Anal. Calcd for $C_{19}H_{21}FO_3S$: C, 65.49; H, 6.07; F, 5.45. Found: C, 65.43; H, 6.10; F, 5.41.

Hydrogenolytic removal of the sulfenylic moiety. **General procedure.** The sulfenyl derivative **20**, **22** (1.0 mmol) was dissolved in ethanol (5 mL) and *Raney*-Ni was added (three times wt.). The

mixture was stirred at reflux under H_2 atm, then the black powder was removed by filtration. The filtrate was concentrated *in vacuo* and the residual product was purified by FC. Initially, the column was packed in *n*-pentane or *n*-hexane using further a gradient elution in the solvents indicated for each case.

(*S*)-1-(*N*-Benzyl-*N*-trifluoroacetyl)amino-2-fluoromethylbutan-2-ol (23) and (*S*)-1-(*N*-trifluoroacetyl)amino-2-fluoromethylpropan-2-ol (24). Starting from (2*S*,3*S*)-**20**, after 24 hrs the substrate disappeared. Flash chromatographic separation in *n*-hexane/ethyl acetate 7/3 gave two different products in enantiomerically pure form. (*S*)-**23**: 38% yield; R_f = 0.40; $[\alpha]_{365}^{20}$ +6.81 (*c* 0.5, $CHCl_3$); yellowish oil; ^1H NMR ($CDCl_3$) δ 0.94 (3H, t, *J* = 7.6Hz), 1.56 (2H, dq, *J* = 2.2 and 7.6Hz), 3.30 (1H, br.s), 3.42 (1H, br.d, *J* = 14.7Hz), 3.52 (1H, dd, *J* = 14.7 and 2.5Hz), 4.26, 4.30 (2H, dd, *J* = 47.5 and 9.6Hz), 4.76, 4.91 (2H, br.d, *J* = 16.4Hz), 7.1-7.5 (5H, m); ^{19}F NMR ($CDCl_3$) δ -229.10 (1F, br.t, *J* = 47.5Hz), -69.15 (3F, s). Anal. Calcd. for $C_{14}H_{17}F_4NO_2$: C, 54.72; H, 5.58; N, 4.56. Found: C, 54.70; H, 5.60; N, 4.58.

(*S*)-**24**: 22% yield; R_f = 0.30; $[\alpha]_{365}^{20}$ -16.7 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.97 (3H, t, *J* = 7.6Hz), 1.62 (2H, dq, *J* = 7.6 and 2.1Hz), 2.53 (1H, br.s), 3.50 (2H, d, *J* = 6.0Hz), 4.30, 4.35 (2H, dd, *J* = 47.2 and 2.5Hz), 6.82 (1H, br.s); ^{19}F NMR ($CDCl_3$) δ -233.18 (1F, br.t, *J* = 47.2Hz), -77.04 (3F, s). Anal. Calcd. for $C_7H_{11}F_4NO_2$: C, 38.72; H, 5.10; N, 6.54. Found: C, 54.70; H, 5.60; N, 4.58.

(*S*)-2-Fluoromethyl-1-(*O*-benzoyl)butan-1,2-diol (25). Starting from (2*S*,3*S*)-**22**, after 15 min, only one product was detected by TLC. Eluting from *n*-hexane up to *n*-hexane/ethyl ether 4/1 gave compound **25** in 89% yield; R_f = 0.35 (*n*-hexane/ethyl ether 9/1); $[\alpha]_D^{20}$ -2.60 (*c* 0.9, $CHCl_3$); $[\alpha]_{365}^{20}$ -4.81 (*c* 0.9, $CHCl_3$); yellowish oil; ^1H NMR ($CDCl_3$) δ 1.03 (3H, t, *J* = 7.5Hz), 1.70 (2H, dq, *J* = 1.4 and 7.5Hz), 2.42 (1H, br.s), 4.37 (2H, br.d, *J*=1.6Hz), 4.41 (1H, dd, *J* = 48.0 and 9.6Hz), 4.44 (1H, dd, *J* = 47.7 and 9.6Hz), 7.4-8.1 (5H, m); ^{19}F NMR ($CDCl_3$) δ -232.49 (br.dd, *J* = 48.0 and 47.7Hz). Anal. Calcd. for $C_{11}H_{15}FO_3$: C, 61.67; H, 7.06; F, 9.33. Found: C, 61.63; H, 7.04; F, 9.31.

Pummerer *rearrangement*. General procedure. TFAA (2.0 mmol) in CH_3CN (0.6 mL) was added dropwise to a stirred solution of the substrate (1.0 mmol) and *sym*-collidine (2.2 mmol) in the same solvent (5 mL) at -20 °C under N_2 atmosphere. The mixture was allowed to reach rt and, after disappearance of the starting compound (2 h, monitored by TLC) the pH of the solution was adjusted to 6 by addition of neat K_2CO_3. The resultant mixture was cooled to 0 °C and a solution of $HgCl_2$ (1.5 mmol) in acetonitrile (5 mL) was added portionwise. Upon completion of the reaction (about 24 h) the yellow precipitate was centrifuged and a clear solution was concentrated *in vacuo* and poured into a flash chromatographic column packed in *n*-pentane. Gradient elution using *n*-pentane/ethyl ether mixtures from 95/5 to 1/1 allowed the isolation of the main reaction products.

(*S*)-2-Fluoromethyl-2-[1'-(4-methylphenyl)sulfenyl]ethenyl oxirane (26). Starting from (1'*S*,2*S*,R_S)-**6a**, compound (*S*)-**26** was obtained in 44% yield; R_f = 0.35 (*n*-pentane/ethyl ether 95/5); yellowish oil; $[\alpha]_D^{20}$ -12.2 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.36 (3H, br.s), 2.82 (1H, dd, *J* = 5.3 and 4.6 Hz), 2.89 (1H, d, *J* = 5.3 Hz), 4.53 (1H, dd, *J* = 47.0 and 10.5 Hz), 4.78 (1H, dd, *J* = 47.6 and 10.5 Hz), 5.12, 5.61 (2H, br.s), 7.19-7.37 (4H, m); ^{19}F NMR ($CDCl_3$) δ -228.27 (1F, br.dd, *J* = 47.6 and 47.0Hz). Anal. Calcd for $C_{12}H_{13}FOS$: C, 65.26; H, 5.84; F, 8.47. Found: C, 65.28; H, 5.82; F, 8.45.

(*S*)-4-Bromo-3-fluoromethyl-2-[(4-methylphenyl)sulfenyl]but-1-en-3-ol (27). Starting from bromohydrin (2*S*,3*S*,R_S)-**11a**, the main reaction product, isolated in 20% yield, was compound (*S*)-**27**; R_f = 0.35 (*n*-pentane/ethyl ether 95/5); yellowish oil; $[\alpha]_D^{20}$ -6.70 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.36

(3H, br.s), 2.81 (1H, br.s), 3.78 (1H, dd, J = 10.9 and 1.1Hz), 3.87 (1H, dd, J = 10.9 and 1.5Hz), 4.58 (1H, dd, J = 47.2 and 10.3 Hz), 4.62 (1H, dd, J = 47.2 and 10.3Hz), 4.94, 5.60 (2H, m), 7.19, 7.38 (4H, m); ^{19}F NMR ($CDCl_3$) δ -230.50 (1F, br.t, J = 47.2). Mass (EI): 304 (M^+), 224 (M^+-Br^+), 149 (*p*-TolSCH=CH_2^+), 137 (*p*-TolSCH_2^+), 123 ($C_7H_7S^+$), 91 ($C_7H_7^+$), 79 (Br^+). Anal. Calcd for $C_{11}H_{14}BrFOS$: C, 45.06; H, 4.81; Br, 27.25; F, 6.48. Found: C, 45.03; H, 4.78; Br, 27.21; F, 6.51.

Thermal syn-elimination of sulfoxide group. **General procedure.** A solution of substrate (1.0 mmol) in *p*-xylene (20 mL) was heated at 150 °C under N_2 atmosphere for 10 min. Then the solution was concentrated *in vacuo* and the residue was purified by FC. Initially, the column was packed in *n*-pentane or *n*-hexane using further a gradient elution in the solvents indicated for each case.

(*S*)-(*N*-Benzyl)-3-fluoromethyl-1-buten-3-ol (28). After heating of starting (2*S*,3*S*,R_S)-**15** at 150 °C under N_2 atmosphere for 8 hrs, product **28** was obtained in 80% yield. Flash chromatographic purification was performed in *n*-hexane/ethyl acetate 7/3; $[\alpha]_D^{20}$ -14.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.35 (2H, br.m), 2.72 (1H, dd, J = 12.2 and 1.3Hz), 2.87 (1H, dd, J = 12.2 and 1.0Hz), 3.85 (2H, br.s), 4.28, 4.30 (2H, dd, J = 48.5 and 9.6Hz), 5.28, 5.50 (2H, m), 5.80 (1H, dd, J = 17.5 and 10.8Hz), 7.2-7.5 (5H, m); ^{19}F NMR ($CDCl_3$) δ -229.17 (br.t, J = 48.5Hz). Anal. Calcd for $C_{12}H_{16}FNO$: C, 68.87; H, 7.71; N, 6.69. Found: C, 68.83; H, 7.73; N, 6.67.

(*S*)-3-Fluoromethyl-4-(*O*-benzoyl)but-1-en-3,4-diol (29). Starting from (2*S*,3*S*,R_S)-**21**, eluting from *n*-hexane up to *n*-hexane/ethyl acetate 4/1, compound **29** was isolated in 78% yield; R_f = 0.35; $[\alpha]_D^{20}$ -9.48 (*c* 1.0, $CHCl_3$); $[\alpha]_{365}^{20}$ -33.5 (*c* 1.0, $CHCl_3$); yellowish oil; ^{1}H NMR ($CDCl_3$) δ 2.76 (1H, br.s), 4.44 (2H, br.d, J = 1.5Hz), 4.45 (2H, d, J = 48.1Hz), 5.40, 5.60 (2H, m,), 5.98 (1H, dd, J = 17.0 and 10.7Hz), 7.4-8.1 (9H, m); ^{19}F NMR ($CDCl_3$) δ -230.34 (t, J = 48.1Hz). Anal. Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17; F, 8.95. Found: C, 62.23; H, 6.15; F, 8.91.

(*R*)-3-Fluoromethylbut-1-en-3-ol (30). Starting from (2*S*,3*R*,R_S)-**16**, compound **30** was obtained in 73% yield following a different purification procedure. The residue was submitted to fractional distillation under ambient pressure and the product was collected at 110 °C, in a mixture with *p*-xylene. A further distillation afforded **30** in pure form: bp 78°C; $[\alpha]_D^{20}$ +5.85 (*c* 3.0, $CHCl_3$); $[\alpha]_{365}^{20}$ +23.7 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J = 2.3Hz), 2.02 (1H, br.s), 4.22 (1H, dd, J = 47.7 and 9.1Hz), 4.26 (1H, dd, J = 47.7 and 9.1Hz), 5.21, 5.38 (2H, m), 5.90 (1H, dd, J = 17.2 and 10.7Hz); ^{19}F NMR ($CDCl_3$) δ -227.13 (tq, J = 47.7 and 2.3Hz). Anal. Calcd for C_5H_9FO: C, 57.69; H, 8.65; F, 18.27. Found: C, 57.63; H, 18.37; F, 8.91.

(*R*)-4-Bromo-3-fluoromethylbut-1-en-3-ol (31). Starting from (2*S*,3*R*,R_S)-**10a**, after 15 min the substrate disappeared and the clear solution became dark-brown. Eluting from *n*-pentane up to *n*-pentane/ethyl ether 4/1, compound **31** was isolated in 32% yield, contaminated in about 1/1 ratio, by *p*-tolyl-[(4-methylphenyl)sulfenyl]sulfoxide: R_f = 0.35; yellowish oil; ^{1}H NMR ($CDCl_3$) δ 3.52 (1H, dd, J = 10.6 and 1.7Hz), 3.61 (1H, dd, J = 10.6 and 1.5Hz), 4.42 (2H, d, J = 47.3Hz), 5.39, 5.56 (2H, m), 5.94 (1H, dd, J = 17.4 and 10.7Hz); ^{19}F NMR ($CDCl_3$) δ -228.70 (br.t, J = 47.3Hz). As by-product, 2-(fluoromethyl)-3-[(4-methylphenyl)sulfenyl]-butan-1,2-diol was formed. ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, dd, J = 7.3 and 1.1Hz), 2.05 (1H, t, J = 6.5Hz), 2.34 (3H, br.s), 3.04 (1H, br.s), 3.41 (1H, br.q, J = 7.3Hz), 3.77 (2H, br.d, J = 6.5Hz), 4.48 (1H, dd, J = 47.4 and 9.6Hz), 4.53 (1H, dd, J = 47.3 and 9.6Hz), 7.14, 7.38 (4H, m); ^{19}F NMR ($CDCl_3$) δ -232.78 (br.dd, J = 47.4 and 47.3Hz).

REFERENCES AND NOTES

1 For general reviews on fluoro-organic compounds see: (a) Welch, J. T.; Eswarakrischnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y.; Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (d) *Fluorine-Containing Amino Acids: Synthesis and Properties*; Kukhar, V.P.; Soloshonok, V.A., Eds.; Wiley: Chichester, 1994. (e) *Organofluorine Chemistry: Principles and Commercial Applications*, Banks, R.E.; Smart, B.E.; Tatlow, J.C., Eds.; Plenum Press: New York, 1994. (f) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J.R.; Welch, J.T., Eds.; ACS Books, American Chemical Society: Washington, D.C., 1996. For recent publications see: (g) *Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards;* Resnati, G.; Soloshonok, V.A., Eds.; Tetrahedron Symposium-in-Print # 58; *Tetrahedron* **1996**, *52*, 1-330.

2 (a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, Tetrahedron Asymmetry Special Issue, Guest Editors: T. Hayashi and V. A. Soloshonok, *Tetrahedron: Asymmetry*, **1994**, *5*, # 6, 955-1126. (b) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: Chichester, scheduled to appear in 1998.

3 For discussion on stereochemical properties of fluorine substituents see: (a) ref. 3 (b). (b) Edwards, F. N. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum Press: New York, 1994, pp. 501-541. (c) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99. (d) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron*, **1996**, *52*, 12433. (e) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.*, **1997**, *62*, 3470. (f) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Letters*, **1997**, *38*, 4671. (g) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Letters*, **1997**, *38*, 4903. (h) Wipf, P.; Jung, J.-K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 764. (i) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.*, **1997**, *62*, 8288.

4 Bravo, P.; Zanda, M. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Chapter #4, Soloshonok, V. A., Ed.; Wiley: Chichester, scheduled to appear in 1998.

5 a) Arnone, A.; Bravo, P.; Cavicchio, G.; Frigerio, M.; Marchetti, V.; Viani, F.; Zappalà, C. *Tetrahedron Lett.* **1992**, *33*, 5609. b) Bravo, P.; Frigerio, M.; Soloshonok, V. A.; Viani, F. *Tetrahedron Lett.* **1993**, *34*, 7771. c) Bravo, P.; Farina, A.; Frigerio, M.; Meille, S.V.; Viani, F.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **1994**, *5*, 987. d) Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F. *Tetrahedron* **1994**, *50*, 13485. e) Bravo, P.; Frigerio, M.; Fronza, G.; Soloshonok, V.A.; Viani, F.; Cavicchio, G.; Fabrizi, G.; Lamba, D. *Can. J. Chem.* **1994**, *72*, 1769. f) Arnone, A.; Bravo, P.; Frigerio, M.; Salani, G.; Viani, F.; Zappalà, C.; Cavicchio, G.; Crucianelli, M. *Tetrahedron* **1995**, *51*, 8289.

6 Arnone, A.; Bravo, P.; Frigerio, M.; Meille, S. V.; Romita, V.; Viani, F.; Zappala, C.; Soloshonok, V. A.; Shishkin, O. V.; Struchkov, Yu. T. *Gazz. Chim. Ital.* **1997**, *127*, 826.

7 The reaction of diastereo- and enantiomerically pure keto sulfoxide (3*S*,*R*S)-**4a** gave a mixture of products of similar composition to that obtained in the reaction of thermodynamic (3*S*/*R*,*R*S)-**4a**. This result could be rationalized assuming that optically pure (3*S*,*R*S)-**4a** undergoes partial epimerization at the C2 stereogenic center under the conditions employed.

8 Grossert, J. S. In *The Chemistry of Sulphones and Sulphoxides*, Patai, S.; Rappoport, Z.; Stirling, C. J. H. Eds.; Wiley, Chichister, 1988, Chapter 20, p. 925.

9 Drabowicz, J.; Oae, S. *Synthesis*, **1977**, 404.

10 a) Pettit, G. R. *Org. React. (N.Y.)* **1966**, *12*, 356. b) Hauptmann, H.; Walter, W. F. *Chem. Rev.* **1962**, *62*, 347. c) Bonner, W. A.; Grimm, R. A. *Chem. Org. Sulfur Compd.* **1966**, *2*, 35. d) Trost, B. H. *Chem. Rev.* **1978**, *78*, 363.

11 (a) Pummerer, R. *Chem. Ber.* **1909**, *42*, 2282. (b) Kennedy, M.; McKervey, M. In *Comprehensive Organic Chemistry*; Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; vol. 7. (c) Russell, G.A.; Mikol, G.J. In *Mechanisms of Molecular Migration*; Thyagaragan, B.S., Ed.; Wiley: NY, 1968; vol. 1.

12 For other examples of vinyl sulfides formation from the corresponding sulfoxides under the conditions of Pummerer rearrangement, referred to as Pummerer elimination, see: (a) Bakuzis, P.; Bakuzis, M.F. *J. Org. Chem.* **1985**, *50*, 2569. (b) Durman, J.; Grayson, J.I.; Hunt, P.G.; Warren, S. *J. Chem. Soc. Perkin Trans. I* **1986**, 1939.

13 Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810.