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Synthesis of selectively fluorinated molecules from dimethylsulfoxide, fluoroacetic acid esters and diazomethane

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Abstract

Small, simple and polyfunctionalized fluorine-containing molecules were obtained through simple synthetic sequences, starting from cheap and readily available dimethylsulfoxide and fluorinated acetic acid esters. A comparison between the present results and those obtained when *p*-tolyl was one of the carbon ligands of sulfur shows a strict consistence in the stereocontrolling behaviour of the sulfoxide group acting as the chiral auxiliary in the two cases.

Keywords: Fluorinated molecules; Dimethyl sulfoxide; Synthesis; Stereocontrol

1. Introduction

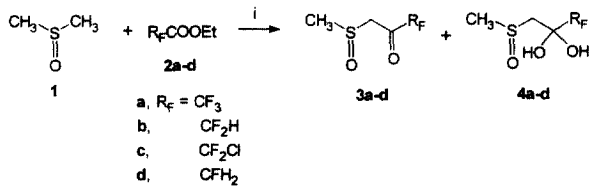
The high configuration stability at the stereogenic sulfur atom and the ability to transfer chirality from sulfur to carbon makes the sulfoxide group very efficient in bringing about diastereoselective auxiliary-induced reactions [1–4]. The stereogenicity of sulfoxide is linked to the steric and stereoelectronic features of the several groups surrounding the sulfur atom, that can differentiate the diastereotopic faces of a close or even a far reaction site [5,6]. Examples of the influence of the sulfoxide carbon ligands on the efficiency of the chirality transfer have been reported [7,8]. The modified Andersen procedure [9,10] for the preparation of enantiomerically pure sulfoxides, prompted us to synthesize a number of *p*-tolyl–alkyl or -aryl sulfoxides, useful and versatile chiral synthons for the preparation of fluorinated compounds [11,12]. In particular, methylene insertion on the keto group of β-keto-γ-fluoro sulfoxides by diazomethane [13] and the reduction to β-hydroxy-γ-fluoro sulfoxides of the same keto group by hydride-releasing species [14] are two efficient methods of transferring chirality from sulfur to carbon through 1,3-asymmetric induction.

In the present paper we describe the influence of a different carbon ligand at the sulfur atom on the diastereoselection of the two above mentioned synthetic procedures, the methyl substituent being employed instead of the *p*-tolyl. The presence of the smallest carbon ligand on sulfur simplifies the obtained chemical structures, in view of future planned MM2 calculation studies. Dimethyl sulfoxide was used as starting material, and the reactions of racemic β-keto-γ-fluorosubstituted sulfoxides were investigated.

2. Results and discussion

As shown in Scheme 1, the β-keto-γ-fluoro sulfoxides **3a–d** were obtained by condensation reaction of the α-sulfinyl anion of dimethylsulfoxide [15] (**1**) on commercially available fluorinated acetic esters **2a–d**: the acylation of the sodium anion of DMSO with trifluoro- **2a**, difluoro- **2b**, chlorodifluoro- **2c**, and monofluoro-ethyl acetate **2d** gave a mixture of β-keto sulfoxides isolated in keto form **3** or as *gem*-diol derivatives **4**. The ratio between the keto- and hydrate forms (**3/4**) is strictly dependent on the degree of fluorosubstitution, as shown in Table 1.

Chemical yields of the first synthetic step were excellent for trifluoro derivatives **3,4a**, good for the difluoro **3,4b** and



Scheme 1. Reaction conditions: i) NaH, 60–70°C.

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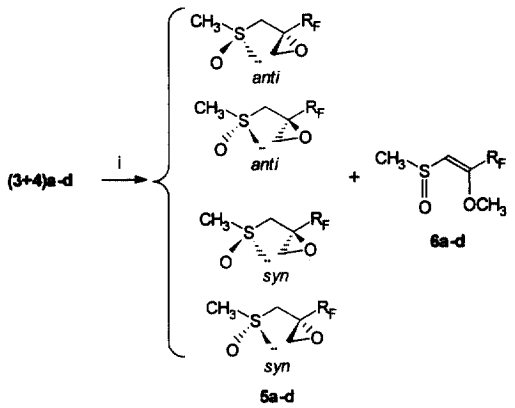
Table 1
Regio- and diastereoselectivity comparison between the results obtained on (3+4) substrates having methyl or *p*-tolyl at sulfur, respectively

Entry	R_F	Keto/*gem*-diol 3/4 ratio		Solvent [a]	Oxirane/enolether 5/6 ratio		*Anti*/*syn* 5 ratio	
		CH_3	*p*-Tolyl		CH_3	*p*-Tolyl	CH_3	*p*-Tolyl
1	CF_3	>3:97	>3:97	A	1.5:1.0	1.3:1.0	>97:3	>97:3
				B	5.2:1.0	5.2:1.0	>97:3	>97:3
2	CF_2H	1.0:2.0	1.0:3.0	A	13.4:1.0	4.6:1.0	80:20	83:17
				B	41.0:1.0	19:1.0	79:21	79:21
3	CF_2Cl	1.0:1.5	1.0:2.0	A	1.0:1.1	1.0:2.1	>97:3	>97:3
				B	4.5:1.0	7.3:1.0	>97:3	>97:3
4	CFH_2	>97:3	>97:3	A	20:1.0	4.6:1.0	62:38	94:6
				B	82:1.0	>97:3	69:31	80:20

[a] A, ethyl ether; B, methanol.



Scheme 2. Reaction conditions: i) CH_2N_2, ethyl ether or methanol, 0°C.

difluorochloro **3,4c** but only satisfying for the monofluoro sulfoxide **3,4d**, as a consequence of difficulties in the extraction procedures from the dipolar aprotic solvent/reagent (DMSO). The left side of Table 1 shows also that a substantial consistency of both keto/hydrate ratio data for tri-, di- and difluorochloro derivatives is shown between the methyl sulfoxide and the previously examined *p*-tolyl one [13].

2.1. Reaction of β-keto sulfoxides 3,4a–d with diazomethane

The reaction between fluorinated β-keto sulfoxides **3,4a–d** and diazomethane was carried out by dissolving the substrate in the appropriate solvent and adding an ethereal solution of freshly prepared CH_2N_2 as depicted in Scheme 2.

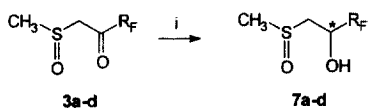
The right side of Table 1 summarizes the obtained results. In every case examined, the main reaction products were the racemic mixtures of the two enantiomeric epoxides **5** having 1,3-*anti* relationship between carbon and sulfur stereocentres. This behaviour is strictly in line with that already observed for *p*-tolyl-substituted sulfoxides and emphasizes a very high ketone diastereofacial preference (*Re* for **3a,b,d** and *Si* for **3c**)[1] for trifluoro **3a** and difluorochloro **3c** derivatives. In these cases, the solvent effect seems not to influence the stereochemical outcome of the attack, whilst it seems more important on the regiochemical outcome, as shown by the different oxirane/enolether **5/6** ratios observed in ethyl ether (A) vs. methanol (B).

The sulfoxide group has a great influence on the facial selectivity of the diazomethane attack and this behaviour is independent on the carbon ligand (methyl or *p*-tolyl) at sulfur. Moreover, also the degree of fluorination at γ-carbon seems to influence in some extent the diastereoselection of the reaction, the diastereoisomeric excess being directly proportional to the number of fluorine atoms of the molecule.

2.2. Reduction of β-keto sulfoxides 3,4a–d

The keto/diol **3/4** mixtures were reduced to alcohols **7a–d** following two different procedures depending on the fluorosubstitution degree (Scheme 3). Sodium borohydride was the reducing agent of choice for **a–c** substrates because it reacts smoothly also with the *gem*-diols. On the other hand, diisobutylaluminium hydride was an effective hydride-releasing agent for the reduction of **3d** (97% in the keto form).

Chemical yields, diastereoselection of the process and comparison with the results previously obtained for *p*-tolyl sulfur-ligand are shown in Table 2. A good consistency (methyl vs. *p*-tolyl) is observed: DIBAH showed a high diastereoselectivity for the *pro Re* face of the ketone **3d**, giving the alcohols **7d** in high diastereomeric excess (d.e. = 84%). The diastereo-facial preference was lower for the reducing agents ($NaBH_4$ and $LiBH_4$) that are active in aqueous medium and the preferred face of the ketones **3a–c** was opposite (*pro Si* for **3a,b** and *pro Re* for **3c**)[1] with respect to the DIBAH behaviour.



Scheme 3. Reaction conditions: i) a) $NaBH_4$, methanol, 0°C ($R_F = CF_3$, CF_2H, CF_2Cl); or b) diisobutyl aluminium hydride (DIBAH), THF, −60°C ($R_F = CFH_2$).

[1] The inversion of the stereochemical indicator (Re/Si) comes only from change in the order of decreasing atomic number due to the introduction of chlorine on the carbon joined to the stereocentre.

Table 2
Diastereoselectivity comparison between the results obtained on (3+4) substrates having methyl or *p*-tolyl at sulfur, respectively

Entry	R_F	Chemical yields (%) of 7	Alcohols 7	*Syn*/*anti* ratio
			CH_3	*p*-Tolyl
1	CF_3	86	62:38 [a]	70:30 [c] [16]
2	CF_2H	84	61:39 [a]	#
3	CF_2Cl	85	63:37 [a]	68:32 [c] [17]
4	CFH_2	84	8:92 [b]	2:98 [b] [18]

[a] $NaBH_4$ in methanol/water.
[b] DIBAH in THF.
[c] $LiBH_4$ in methanol/water.

3. Functional groups elaborations

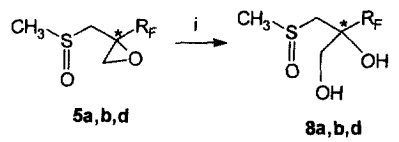
The above described oxiranes **5a–d** and alcohols **7a–d** are versatile intermediates for the synthesis of small polyfunctionalized fluorine-containing molecules. In particular, the oxiranes show three different reaction sites: i) the carbon atom α to the sulfoxide group, where the presence of the sulfinyl moiety enhances the acidity of its two protons; ii) the sulfoxide group, which shows a peculiar reactivity that can be used for synthetic purposes; iii) the carbon atoms of the oxirane ring, where the steric strain makes these carbons reactive towards nucleophilic and/or electrophilic ring opening agents. The reactivity of the second and of the third site are examined here.

3.1. Nucleophilic oxirane ring opening by oxygen nucleophile

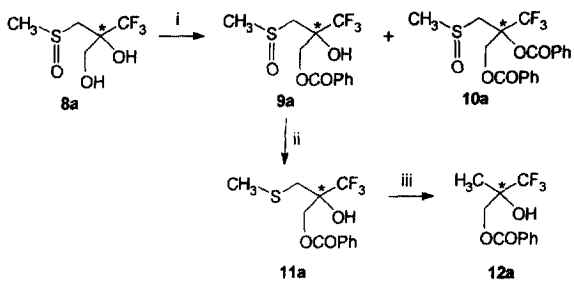
The oxirane-ring opening by water was studied on the trifluoro, difluoro and monofluoro derivatives **5a,b,d** as shown in Scheme 4. The acid catalysed reaction gave slowly but in good yields the diols **8a,b,d**.

3.2. Chemical elaborations at sulfur

The primary hydroxyl group of the diastereomerically pure trifluoro derivative **8a** was then selectively protected as the benzoyl ester **9a**. Treatement with trifluoroacetic anhydride and sodium iodide in dimethylketone [19] allowed the reduction of the sulfoxide to thio group affording the intermediate **11a**, that was subsequently desulfurized by using Raney-nickel under H_2 giving the 2-trifluoromethyl propan-1,2-diol **12a** (Scheme 5).



Scheme 4. Reaction conditions: i) $HClO_4$, H_2O/THF, rt.



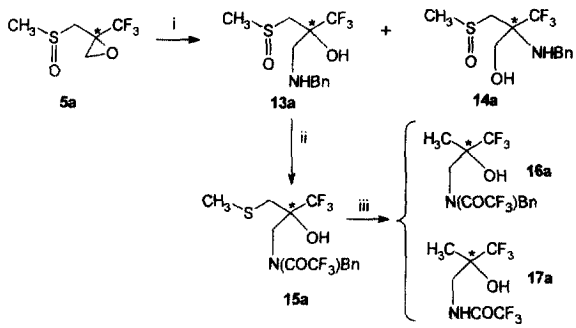
Scheme 5. Reaction conditions: i) PhCOOH, DCC, DMAP, CH_2Cl_2, rt; ii) NaI, $(CF_3CO)_2O$, acetone, −20°C; iii) Raney-Ni, ethanol, 80 °C (reflux).

3.3. Nucleophilic oxirane ring opening by nitrogen nucleophiles

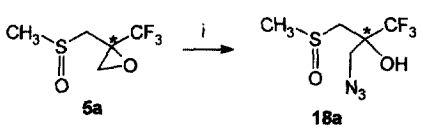
The diastereomerically pure sulfinyl oxirane **5a** was submitted to ring-opening reactions by nitrogen-nucleophilic species, such as benzylamine and sodium azide (Scheme 6).

The nucleophilic attack of benzylamine was fast, efficient and site-selective, leading in 4 h and in good chemical yields (82%) to the hydroxy-amino sulfoxide **13a** arising from the selective attack of nitrogen on the secondary carbon atom of the oxirane ring. Compound **14a**, deriving from the same nucleophilic attack on the tetrasubstituted carbon of the ring, formed only in traces (4%). Following the same described procedure for the desulfurization of **11a**, the methyl-trifluoromethyl-methylamino (*N*-benzyl-trifluoroacetyl-protected) carbinol **16a** or the debenzylated analog **17a** were obtained in good overall yields (90%) and in a ratio depending on the reaction conditions.

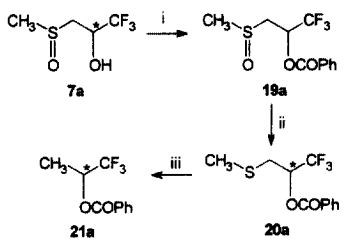
As depicted in Scheme 7, sodium azide also acted in a stereospecific way on the diastereomerically pure trifluoro derivative **5a**, giving exclusively the product **18a** (88% yield) arising from azide attack on the secondary carbon atom of the oxirane ring.



Scheme 6. Reaction conditions: i) benzylamine, rt; ii) $(CF_3CO)_2O$, NaI, acetone, −20°C; iii) Raney-Ni, ethanol, 80°C (reflux): ca. 45 min → **16a**; ca. 120 min → **17a**.



Scheme 7. Reaction conditions: i) NaN_3, NH_4Cl, ethanol, rt.



Scheme 8. Reaction conditions: i) PhCOOH, DCC, DMAP, CH_2Cl_2, rt; ii) $(CF_3CO)_2O$, NaI, acetone, −20°C; iii) Raney-Ni, ethanol, 80°C (reflux).

3.4. Chemical elaborations at sulfur

Finally, from the diastereomerically pure trifluoro derivative **7a**, the methyl–trifluoromethyl secondary alcohol-*O*-benzoyl protected **21a** was obtained in good overall yield. The synthetic sequence, shown in Scheme 8, is strictly analogous to the one described above for obtaining the derivatives **12a** and **16**, **17a**.

4. Conclusions

Several selectively fluorinated molecules have been obtained in racemic form from dimethylsulfoxide and fluorinated acetic esters, through the corresponding β-keto-γ-fluoro-substituted sulfoxides. The diastereoselectivity of methylene and hydride insertions on the keto moiety were studied and the results compared with those observed on the *p*-tolyl-containing analogues, showing a strict consistency between the two cases.

5. Experimental details

General. TLC are run on silica gel 60 F_{254} Merck; flash column chromatographies FC are performed with silica gel 60 (60–200 μm, Merck). ^1H, and ^{19}F spectra are recorded on a Bruker AC 250L spectrometer operating at 250 MHz in $CDCl_3$. ^{13}C spectra are recorded on a Bruker CXP 300. Chemical shifts are expressed in ppm (δ), using tetramethylsilane (TMS) as internal standard for ^1H nucleus ($\delta_H = 0.00$), whilst C_6F_6 is used as external standard ($\delta_F = -162.90$) for ^{19}F. Mass spectra are registered on a TSQ 70 Finnigan Mat three-stage quadrupole instrument. DIS (Direct Inlet System) is used for pure compounds. Infrared spectra are performed using a Perkin Elmer System 2000 FT-IR (Scan Range: 15600 cm^{-1}; Combined Scan Direction). Combustion microanalyses are performed by Redox SNC, Cologno Monzese (Milano). THF is freshly distilled from Na, diisopropylamine is freshly distilled from CaH_2; in all other cases, commercially available reagent-grade solvents are employed without purification. All reactions where an organic solvent is employed are performed under a nitrogen atmosphere, after flame-drying procedures of the glass apparatus.

5.1. Synthesis of fluorinated ketones (3 + 4)a–d

General. Sodium iodide (10 mmol, 55% mineral oil) is washed three times with *n*-hexane, DMSO (5 ml) is added and the mixture is heated at 65–70°C for 40 min. At room temperature, THF (10 ml) is added, the mixture is cooled at −20°C and the fluorinated ester (R_FCOOEt—0.5 eq) is added. After 30 min under stirring, the reaction mixture is poured into water/ice bath and pH is adjusted to 3–4 by adding dropwise a 1 N HCl solution. The solvent is evaporated and the organics are extracted with ethyl acetate (3 × 10 ml). The combined organics are dried over sodium sulfate, filtered and evaporated to dryness to give a residue that is purified by flash chromatography. Chemical yields, keto/*gem*-diol ratio of the obtained compounds and chemico-physical characterizations of **(3 + 4)a–d** are given in Table 3. The spectroscopic characterizations are reported below.

a) $R_F = CF_3$ (97% *gem*-diol **4a**); 1-(methylsulfinyl)-3,3,3-trifluoropropan-2,2-*gem*-diol (**4a**), ^1H NMR ($CDCl_3$), δ: 2.85 (s, 3H, CH_3), 2.95 (d, 1H, CH_aS, $J = 13.7$ Hz), 3.15 (d, 1H, CH_bS); ^{19}F NMR ($CDCl_3$), δ: −88.6 (d, 3F, CF_3, $J = 3.39$ Hz); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 39.90 (s, CH_2S), 56.23 (s, CH_3), 92.90 (q, COH, $J = 33.3$ Hz), 122.12 (q, CF_3, $J = 286.68$ Hz); IR(KBr), cm^{-1}: 3406.98, 3159.06[$C(OH)_2$], 1416.97, 1259.24, 1196.82, 1156.16, 1114.76, 1093.50, 1016.07, 968.79, 949.95; MS (*m/z*): 192. 1-(Methylsulfinyl)-3,3,3-trifluoropropanone **3a**: ^1H NMR ($CDCl_3$), δ: 2.82 (s, 3H, CH_3), 4.10 (m, 2H, CH_2S); ^{19}F NMR ($CDCl_3$), δ: −80.45 (s, 3F, CF_3, $J = 5.93$ Hz); elemental anal. for $C_4H_7O_3F_3S$. Found (%): C, 25.52; H, 3.77; S, 15.76; F, 28.08. Calculated (%) C, 25.00; H, 3.65; S, 16.67; F, 29.69.

b) $R_F = CF_2H$; 1-(methylsulfinyl)-3,3-difluoropropan-2,2-*gem*-diol (**4b**), ^1H NMR ($CDCl_3$), δ: 2.80 (s, 3H, CH_3), 2.97 (d, 1H, CH_aS, $J = 13.5$ Hz), 3.11 (d, 1H, CH_bS), 5.56 (t, 1H, $J = 55.05$ Hz); ^{19}F NMR ($CDCl_3$), δ: −134.4 (dd,

Table 3
Yields, keto/*gem*-diol ratio and chemico-physical characterizations for **4a**, **(3 + 4)b/c**, and **3d**

R_F	Chemical yields (3 + 4%)	3/4 Ratio	Eluent	R_f	m.p. (°C) solvent
CF_3	93	>3:97	AcOEt/*n*-Hex 9:1	0.35	95–96 AcOEt/*n*-Hex
CF_2H	73	1.0:2.0	AcOEt	0.31	66–67 AcOEt/*n*-Hex
CF_2Cl	76	1.0:1.5	AcOEt/*n*-Hex 9:1	0.34	89–90 ethyl ether
CFH_2	57	>97:3	$CHCl_3$/MeOH 95:5	0.30	oil

1F, CF_bH, $J=55.05$ Hz), −136.3 (dd, 1F, CF_aH, $J=280.8$ and 53.95 Hz); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 14.17 (s, CH_3), 52.74 (s, CH_2S), 93.75 (t, COH, $J=59.18$ Hz), 113.63 (t, CHF_2, $J=249.7$ Hz). 1-(Methylsulfinyl)-3,3-difluoropropan-2-one (**3b**), ^1H NMR ($CDCl_3$), δ: 2.76 (s, 3H, CH_3), 3.92 (d, 1H, CH_aS, $J=15.12$ Hz), 4.23 (d, 1H, CH_bS,), 5.82 (t, 1H, CHF, $J=53.95$ Hz); ^{19}F NMR ($CDCl_3$), δ: −129.2 (d, 2F, CF_2H, $J=53.95$ Hz); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 21.06 (s, CH_3), 59.30 (d, CH_2S, $J=146.12$ Hz), 109.66 (t, CHF_2, $J=260.8$ Hz), 192 (s, CO). Spectroscopic data referred to the mixture **3b/4b**: IR(KBr), cm^{-1}: 1074.63 (C=O), 3376.71 [$C(OH)_2$]; MS (*m/z*): 156.

c) $R_F=CF_2Cl$; 1-(methylsulfinyl)-3-chloro-3,3-difluoropropan-2,2-*gem*-diol (**4c**), ^1H NMR ($CDCl_3$), δ: 2.8 (s, 3H, CH_3), 3.11 (d, 1H, CH_aS, $J=13.5$ Hz), 3.24 (d, 1H, CH_bS); ^{19}F NMR ($CDCl_3$), δ: −72.7 (d, 1F, CF_aCl, $J=163.7$ Hz), −71.9 (d, 1F, CF_bCl); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 40.0 (s, CH_3), 55.0 (s, CH_2S), 96.0 (t, COH, $J=27.7$ Hz), 128.0 (t, CF_2Cl, $J=279.28$ Hz). 1-(Methylsulfinyl)-3-chloro-3,3-difluoropropan-2-one (**3c**), ^1H NMR ($CDCl_3$), δ: 2.82 (s, 3H, CH_3), 4.10 (d, 1H, CH_aS, $J=15.4$ Hz), 4.22 (d, 1H, CH_bS); ^{19}F NMR ($CDCl_3$), δ: −70.2 (d, 1F, CF_aCl, $J=161.3$ Hz), −69.9 (d, 1F, CF_bCl), ^{13}C NMR ($CDCl_3$) (all dec.), δ: 40.0 (s, CH_3), 58.0 (s, CH_2S), 123.0 (t, CF_2Cl, $J=279.3$ Hz), 183.5 (t, CO, $J=33.3$ Hz); spectroscopic data referred to the mixture **3c/4c**: IR(KBr), cm^{-1}: 3403.21[$C(OH)_2$], 1403.59, 1220.79, 1115.06, 1096.67, 1019.71, 897.76; MS (*m/z*): 189.

d) $R_F=CFH_2$ (97% keto form **3d**); 1-fluoro-1-(methylsulfinyl)-propan-2-one (**3d**), ^1H NMR ($CDCl_3$), δ: 2.74 (s, 3H, CH_3), 3.74 (dd, 1H, CH_aS, $J=13.91$ and 3.48 Hz), 4.03 (dd, 1H, CH_bS, $J=2.71$ Hz), 4.92 (dd, 1H, CH_aF, $J=47.13$ and 17.0 Hz), 5.00 (dd, 1H, CH_bF, $J=47.13$ Hz); ^{19}F NMR ($CDCl_3$), δ: −226.53 (tdd, 1F, CFH_2, $J=47.13$, 3.48 and 2.71 Hz); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 39.0 (s, CH_3), 59.4 (s, CH_2S), 86.0 (d, CH_2F, $J=186.6$ Hz), 198.0 (s, CO); IR(KBr), cm^{-1}: 1023.86, 1733,70 (C=O); MS (*m/z*): 138; elemental anal. for $C_4H_7O_2FS$. Found (%): C, 34.70; H, 5.08; F, 13.78. Calculated (%) C, 34.77; H, 5.11; F, 13.75.

5.2. Synthesis of fluorinated epoxides 5a–d

General. A solution of diazomethane (ca. 0.5 M) in ethyl ether is added to a solution of keto/*gem*-diol **3/4** mixture (1.0 mmol) in the suitable solvent (5 ml) at 0°C up to persistence of the yellow colour. The reaction is kept under stirring at 0°C until all starting material disappeared (TLC monitoring), then the excess of diazomethane is removed by bubbling a stream of nitrogen inside the reaction solution, the solvent is evaporated and the crude purified by flash chromatography.

5.2.1. Methanol

After 1 h, the following results are obtained.

a) $R_F=CF_3$; flash purification (ethyl acetate/*n*-hexane 9:1) gives: 1-(methylsulfinyl)-2-methoxy-3,3,3-trifluoroprop-1-ene (**6a**) in 12% yield; $R_f=0.32$; ^1H NMR ($CDCl_3$), δ: 2.70 (s, 3H, CH_3), 4.07 (s, 3H, OCH_3), 6.23 (s, 1H, CH=C); ^{19}F NMR ($CDCl_3$), δ: −71.4 (s, 3F, CF_3); elemental anal. for $C_5H_7O_2F_3S$. Found (%): C, 31.90; H, 3.78; F, 30.28. Calculated (%) C, 31.92; H, 3.75; F, 30.29 along with (2*S*/*R*,*S*/R_S)-2-[(mehylsulfinyl)methyl]-2-(trifluoromethyl)oxirane (**5a**) in 62% yield: $R_f=0.30$, m.p. 57°C (isopropylether); ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 3.28 (d, 1H, CH_aS, $J=13.Hz$), 3.42 (d, 1H, CH_bS), 3.24 (d, 1 H, CH_aO, $J=3.5$ Hz), 3.43 (dq, 1H, CH_bO, $J=2.0$ Hz), ^{19}F NMR ($CDCl_3$), δ: −78.4 (d, 1F, CF_3, $J=2.0$ Hz); elemental anal. for $C_5H_7O_2F_3S$. Found (%): C, 31.95; H, 3.73; F, 30.24. Calculated (%) C, 31.92; H, 3.75; F, 30.29.

b) $R_f=CF_2H$; from flash purification in ethyl acetate/*n*-hexane 9:1 a mixture of oxiranes (2*S*/*R*,*S*/R_S)-**5b** ($R_f=0.35$, 76% yield) in 79:21 ratio, and one enolether **6b** is obtained. 3,3-Difluoro-1-(methylsulfinyl)-2-methoxy-prop-1-ene (**6b**): ^1H NMR ($CDCl_3$), δ: 2.75 (s, 3H, CH_3), 4.05 (s, 3H, OCH_3), 5.80 (t, 1H, CHF_2, $J=52.25$ Hz), 6.22 (s, 1H, CH=C); ^{19}F NMR ($CDCl_3$), δ: −122.5 (dd, 1 F, CF_aH, $J=301.65$ and 53.99 Hz), −120.4 (dd, 1F, CF_bH, $J=52.25$ Hz); elemental anal. for $C_5H_8O_2F_2S$. Found (%): C, 35.30; H, 4.78; F, 22.28. Calculated (%) C, 35.29; H, 4.74; F, 22.33. (2*R*/*S*,*S*/R_S)-2-(Difluoromehyl)-2-[(methylsulfinyl)methyl]-oxirane (**5b**) (main epoxide): ^1H NMR ($CDCl_3$), δ: 2.73 (s, 3H, CH_3), 3.06 (d, 1H, CH_aO, $J=4.24$ Hz), 3.19 (d, 1H, CH_aS, $J=14.3$ Hz), 3.31 (ddd, 1H, CH_bO, $J=1.94$ and 1.96 Hz), 3.33 (d, 1H, CH_bS), 5.65 (t, 2H, CHF_2, $J=54.85$ Hz); ^{19}F NMR ($CDCl_3$), δ: −125.52 (ddd, 1F, CF_aH, $J=295.2$, 54.85 and 1.76 Hz), −127.12 (ddd, 1F, CF_bH, $J=55.16$ and 4.1 Hz); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 40.2 (s, CH_3), 48.4 (s, CH_2O), 52.0 (s, CH_2S), 55.0 (t, CCF_2, $J=14.79$ Hz), 114.5 (t, CF_2, $J=246.0$ Hz); MS (*m/z*): 170. (2*R*/*S*,*S*/R_S)-**5b** (Minor epoxide): ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 3.08 (d, 1H, CH_aO, $J=4.25$ Hz), 3.09 (d, 1H, CH_aS, $J=13.13$ Hz), 3.19 (d, 1H, CH_bS), 3.19 (ddd, 1H, CH_bO, $J=1.16$ and 0.77 Hz), 5.67 (t, 2H, CHF_2, $J=54.86$ Hz); ^{19}F NMR ($CDCl_3$), δ: −125.52 (dd, 1F, CF_aH, $J=292.5$, 52.0 and 3.59 Hz), −124.3 (dd, 1F, CF_bH, $J=54.7$ and 2.69 Hz); elemental anal. for $C_5H_7O_2F_3S$. Found (%): C, 31.89; H, 3.70; F, 30.31. Calculated (%) C, 31.92; H, 3.75; F, 30.29.

c) $R_F=CF_2Cl$; after flash purification (ethyl acetate/*n*-hexane 9:1) the following compounds are obtained: 3-chloro-3,3-difluoro-1-(methylsulfinyl)-2-methoxy-prop-1-ene (**6c**): $R_f=0.32$; 15% yield; ^1H NMR ($CDCl_3$), δ: 2.76 (s, 3H, CH_3), 4.21 (s, 3H, OCH_3), 6.17 (s, 1H, CH=C); ^{19}F NMR ($CDCl_3$), δ: −58.8 (d, 1F, CF_aCl, $J=172.5$ Hz), −59.4 (d, 1F, CF_bCl); (2*S*/*R*, *S*/R_S)-2-(chlorodifluoromethyl)-2-[(methylsulfinyl)methyl]oxirane (**5c**): $R_f=0.30$; 78% yield; ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 3.34 (dd, 1H, CH_aS, $J=14.4$ and 2.87 Hz), 3.51 (d, 1H, CH_bS), 3.31 (d, 1H, CH_aO, $J=4.8$ Hz), 3.47 (dt, 1H, CH_bO, $J=2.1$ Hz); ^{19}F NMR ($CDCl_3$), δ: −66.0 (d, 2F, CF_2Cl, $J=2.1$ Hz); elemental anal. for $C_5H_7O_2ClF_2S$. Found (%):

C, 29.39; H, 3.50; F, 18.61. Calculated (%) C, 29.35; H, 3.45; F, 18.57.

d) $R_F = CFH_2$; from flash purification (chloroform/methanol 9:1) a mixture of epoxides **5d** (R_f = 0.35, 78% ratio) in 62:38 ratio is obtained. The enolether **6a** is formed in less than 5% and is characterized only through its ^{19}F NMR spectrum: 3-fluoro-1-(methylsulfinyl)-2-methoxy-prop-1-ene (**6a**): ^{19}F NMR ($CDCl_3$), δ: −220.4 (t, 1F, CFH_2, J = 48 Hz). (2*S*/*R*,*S*/R_S)-2-(Fluoromethyl)-2-[(methylsulfinyl)-methyl]oxirane (**5d**) (main epoxide): ^1H NMR ($CDCl_3$), δ: 2.70 (s, 3H, CH_3), 2.98 (d, 1H, CH_aS, J = 13.91 Hz), 3.33 (d, 1H, CH_bS), 2.94 (dd, 1H, CH_aO, J = 4.63 and 1.05 Hz), 3.16 (dd, 1H, CH_bO, J = 4.82 Hz), 4.40 (dd, 1H, CH_aF, J = 47.13 and 10.81 Hz), 4.71 (dd, 1H, CH_bF); ^{19}F NMR ($CDCl_3$), δ: −228.9 (td, 1F, CH_2F, J = 47.13 and 4.82 Hz); (2*R*/*S*,*S*/R_S)-**5d** (minor epoxide): ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 2.95 (dd, 1H, CH_aS, J = 13.13 and 0.78 Hz), 3.18 (d, 1H, CH_bS), 2.95 (dd, 1H, CH_aO, J = 4.25 and 1.31 Hz), 3.06 (dd, 1H, CH_bO, J = 4.81 Hz), 4.42 (dd, 1H, CH_aF, J = 46.74 and 10.82 Hz), 4.78 (dd, 1H, CH_bF, J = 47.51 Hz); ^{19}F NMR ($CDCl_3$), δ: −227.55 (td, 1F, CH_2F, J = 47.51 and 4.81 Hz); elemental anal. for $C_5H_9O_2FS$. Found (%): C, 39.49; H, 6.00; F, 12.51. Calculated (%) C, 39.46; H, 5.96; F, 12.48.

5.2.2. Ethyl ether

After 6 h the results reported in Table 2 and compared with those observed in methanol are reported.

5.3. Synthesis of alcohols 7 a–c

General. $NaBH_4$ (1.5 mmol) is added to a solution of keto/*gem*-diol **(3+4)a–c** (0.5 mmol) mixture in methanol (5 ml) at 0°C. The reaction is kept under stirring at 0°C to total used of the substrate, then a saturated solution of ammonium chloride is added, the organics are extracted with ethyl acetate (3×5 ml), dried on sodium sulfate, filtered and evaporated to dryness to give a residue that, after FC purification, gave the results listed in Table 4.

Each compound is characterized as follows.

a) $R_F = CF_3$, (2*S*/*R*,*S*/R_S)-1-(methylsulfinyl)-3,3,3-trifluoropropan-2-ol (**7a**): ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 2.87 (dd, 1H, CH_aS, J = 13.56 and 10.17 Hz), 2.99 (s, 1H, OH), 3.16 (dd, 1H, CH_bS, J = 2.03 Hz), 4.50–4.64 (m, 1H, C*H*OH, J = 6.11 Hz); ^{19}F NMR ($CDCl_3$), δ: −80.58 (d, 3F, CF_3 $^3J_{H-F}$ = 5.72 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 39.0 (s, CH_3), 50.0 (s, CH_2S), 64.5 (q, CCF_3, J = 31.44 Hz), 124.6 (q, CF_3, J = 281.13 Hz); (2*R*/*S*,*S*/R_S)-1-(methylsulfinyl)-3,3,3-trifluoropropan2-ol (**7a**): ^1H ($CDCl_3$), δ: 2.83 (s, 3H, CH_3), 2.93 (d, 1H, CH_aS, J = 12.89 Hz), 2.98 (d, 1H, CH_bS), 4.68–4.82 (m, 1H, C*H*OH, J = 6.78 and 2.04 Hz), 4.75 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$), δ: −80.28 (d, 3F, CF_3, J = 7.62 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 38.5 (s, CH_3), 54.5 (s, CH_2S), 64.8 (q, CCF_3, J = 31.44 Hz), 124.4 (q, CF_3, J = 282.98 Hz); IR (KBr), cm^{-1}: 3209.36, 1280.91, 1109.00, 984.87, 948.69, 670.28; MS (*m*/*z*): 176; elemental analysis for $C_4H_7O_2F_3S$. Found (%): C, 27.25; H, 4.14; S, 18.15; F, 32.18. Calculated (%) C, 27.27; H, 3.98; S, 18.18; F, 32.39.

Table 4
Reaction yields, diastereoselection and FC eluent of **7a–c**

R_F	Chemical yields (%)	*Syn–anti* 7 ratio	FC eluent	R_f	m.p. (°C)
CF_3	86	62:38	AcOEt/AcOH 95:5	0.38	87–88
CF_2H	84	61:39	AcOEt/AcOH 95:5	0.28	oil
CF_2Cl	85	63:37	AcOEt	0.33	54–55

b) CHF_2 (2*S*/*R*,*S*/R_S)-3,3-difluoro-1-(methylsulfinyl)-propan-2-ol (**7b**): ^1H NMR ($CDCl_3$), δ: 2.80 (s, 3H, CH_3), 2.90 (d, 1H, CH_aS, J = 11.0 Hz), 3.05 (dd, 1H, CH_bS, J = 2.75 Hz), 4.50 (m, 1H, C*H*OH), 4.60 (d, 1H, OH, J = 3.3 Hz,), 5.80 (t, 1H, CHF_2, J = 55.0 Hz); ^{19}F NMR ($CDCl_3$), δ: −133.4 (ddd, 1F, CF_aH, J = 197.5, 55.0 and 11.0 Hz), −128.7 (ddd, 1F, CF_bH, J = 55.0 and 8.5 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 39.50 (s, CH_3), 51.0 (s, CH_2S), 66.90 (t, *C*CF_2H, J = 24.04 Hz), 115.40 (t, CF_2H, J = 245.99 Hz); (2*R*/*S*,*S*/R_S)-3,3-difluoro-1-(methylsulfinyl)-propan-2-ol (**7b**): ^1H NMR ($CDCl_3$), δ: 2.80 (s, 3H, CH_3), 2.90 (d, 1H, CH_aS, J = 12.1 Hz), 2.98 (d, 1H, CH_bS), 4.40 (m, 1H, C*H*OH), 5.10 (d, 1H, OH, J = 5.5 Hz), 5.82 (t, 1H, CHF_2, J = 55.5 Hz); ^{19}F NMR ($CDCl_3$), δ: −132.5 (ddd, 1F, CF_aH, J = 200, 55.5 and 10.0 Hz), −128.8 (ddd, 1F, CF_bH, J = 55.5 and 6.0 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 38.50 (s, CH_3), 53.95 (s, CH_2S), 65.40 (t, *C*CF_2H, J = 24.04 Hz), 115.00 (t, CF_2H, J = 245.99 Hz); MS (*m*/*z*): 158; elemental analysis for $C_4H_8O_2F_2S$. Found (%): C, 30.35; H, 5.14; F, 24.08. Calculated (%) C, 30.37; H, 5.10; F, 24.02.

c) CF_2Cl; (2*R*/*S*,*S*/R_S)-3-chloro-3,3-difluoro-1-(methylsulfinyl)-propan-2-ol (**7c**): ^1H NMR ($CDCl_3$), δ: 2.83 (s, 3H, CH_3), 2.89 (d, 1H, CH_aS, J = 13.94 Hz), 3.24 (dd, 1H, CH_bS, J = 1.88 Hz), 4.50 (m, 1H, C*H*OH, J = 7.93 Hz), 5.97 (d, 1H, OH, J = 5.23 Hz); ^{19}F NMR ($CDCl_3$), δ: −65.0 (ddd, 1F, CF_aCl, J = 166.6, 7.93 and 1.79 Hz), −66.4 (dd, 1F, CF_bCl, J = 7.65 Hz); (2*R*/*S*,*S*/R_S)-3-chloro-3,3-difluoro-1-(methylsulfinyl)-propan-2-ol (**7c**): ^1H NMR ($CDCl_3$), δ: 2.73 (s, 3H, CH_3), 2.99 (d, 1H, CH_aS, J = 12.81 Hz), 3.08 (dd, 1H, CH_bS, J = 2.64 Hz), 4.50 (m, 1H, C*H*OH, J = 8.08 Hz), 6.43 (d, 1H, OH, J = 5.67 Hz); ^{19}F NMR ($CDCl_3$), δ: −65.3 (ddd, 1F, CF_aCl, J = 171.7, 8.08 and 1.80 Hz), −66.1 (dd, 1F, CF_bCl, J = 8.5 Hz); IR (KBr), cm^{-1}: 3177.70, 1106.54, 1005.83, 676.38; MS (*m*/*z*): 193; elemental analysis for $C_4H_7O_2F_2ClS$. Found (%): C, 25.77; H, 3.77; S, 16.65; F, 19.11; Cl, 17.81. Calculated (%) C, 24.94; H, 3.64; S, 16.63, F, 19.74, Cl, 18.42.

5.4. Synthesis of fluoromethylalcohol 7d

The ketone **3d** (0.5 mmol) is dissolved in THF (5 ml), the solution is cooled at −60°C under nitrogen and DIBAL-

H (4 mmol, 2 ml) is added by syringe. The THF solution is kept at −60°C for 4 h, then an aqueous solution of NH_4Cl is added and pH is adjusted to 2 by adding a 1 N HCl solution. After extraction with ethyl acetate and the usual work-up, a FC purification in chloroform/methanol 9:1 gives the alcohol **7d** [(2*S*/*R*,*S*/R_S)/(2*R*/*S*,*S*/R_S) = 92:8] in 84% global yield. The spectroscopic data follow.

d) CFH$_2$, (2*S*/*R*,*S*/R_s)-3-fluoro-1-(methylsulfinyl)-propan-2-ol (**7d**): ^{1}H NMR ($CDCl_3$), δ: 2.70 (s, 3H, CH_3), 2.78 (dd, 1H, CH_aS, J = 13.13 and 2.31 Hz), 2.99 (dd, 1H, CH_bS, J = 6.56 Hz), 4.32–4.60 (m, 3H, C*H*OH + CFH_2), 3.64 (m, 1H, OH); ^{19}F NMR ($CDCl_3$), δ: −230.2 (td, 1F, CH_2F, J = 45.5 and 19.5 Hz); (2*R*/*S*,*S*/R_S)-3-fluoro-1-(methylsulfinyl)-propan-2-ol (**7d**): ^{1}H NMR ($CDCl_3$), δ: 2.73 (s, 3H, CH_3), 2.90 (dd, 1H, CH_aS, J = 14.0 and 2.71 Hz), 2.97 (dd, 1H, CH_bS, J = 1.93 Hz), 3.87 (m, 1H, OH), 4.36–4.66 (m, 3H, C*H*OH + CFH_2); ^{19}F NMR ($CDCl_3$) δ: −231.45 (td, 1F, CFH_2, J = 48.1 and 19.5 Hz); elemental analysis for $C_4H_9O_2FS$. Found (%): C, 34.25; H, 6.44; F, 13.58. Calculated (%) C, 34.27; H, 6.47; F, 13.55.

5.5. Synthesis of 3-(methylsulfinyl)-2-(trifluoromethyl)-propan-1,2-diol (8a)

The oxirane (2*S*/*R*,*S*/R_S)-**5a** (0.53 mmol, 100 mg) is dissolved into a THF/H_2O 1:1 (4 ml) mixture and $HClO_4$ (2 eq., 96 μl) is added at rt. The reaction is kept five days, then the solvent is evaporated under reduced pressure and the organics are extracted with ethyl acetate (3×5 ml). The combined organic layers are dried over sodium sulfate, filtered and evaporated to dryness. The residue is purified by flash chromatography in ethyl acetate/methanol 97:3 to give (2*S*/*R*,*S*/R_S)-3-(methylsulfinyl)-2-(trifluoromethyl)-propan-1,2-diol (**8a**) in 56% yield: R_f = 0.35; ^{1}H NMR ($CDCl_3$), δ: 2.74 (s, 3H, CH_3), 3.12 (d, 1H, CH_aS, J = 13.75 Hz), 3.22 (t, 1H, CH_2OH, J = 0.6 Hz), 3.25 (d, 1H, CH_bS), 3.78 (d, 1H, CH_aO, J = 11.0 Hz), 3.86 (dd, 1H, CH_bO), 3.41 (s, 1H, COH); ^{19}F NMR ($CDCl_3$), δ: −81.6 (s, 3F, CF_3); elemental analysis for $C_5H_9O_3F_3S$. Found (%): C, 29.15; H, 4.44; F, 27.68. Calculated (%) C, 29.13; H, 4.40; F, 27.64.

Starting from *syn*-oxirane **5b**, 2-(difluoromethyl)-3-(methylsulfinyl)-propan-1,2-diol (**8b**) was obtained as a yellowish oil: ^{1}H NMR ($CDCl_3$), δ: 2.74 (s, 3H, CH_3), 3.05–3.20 (m, 2H, CH_2S), 3.70–3.80 (m, 2H, CH_2O), 6.0 (t, 1H, CHF_2); ^{19}F NMR ($CDCl_3$), δ: −134.0 (dd, 1F, CF_aH, J = 283.5 and 55.75 Hz), −132.3 (dd, 1F, CF_bH, J = 52.5 Hz); elemental analysis for $C_5H_{10}O_3F_2S$. Found (%): C, 31.95; H, 5.34; F, 20.18. Calculated (%) C, 31.91; H, 5.36; F, 20.19.

Starting from the 62:38 *anti/syn* diastereoisomeric mixture of oxiranes **5d**, a mixture of diols **8d** (R_f = 0.32, 12% yield) in 3:2 ratio is obtained: (2*S*/*R*,*S*/R_S)-2-(fluoromethyl)-3-(methylsulfinyl)-propan-1,2-diol (**8d**) (main diol): ^{1}H NMR ($CDCl_3$), δ: 2.92 (dd, 1H, CH_aS, J = 13.13 and 1.16 Hz), 3.10 (dd, 1H, CH_bS), 3.40 (br s, 2H, OH), 3.76 (dd, 1H, CH_aO, J = 11.98 and 2.32 Hz), 3.84 (dd, 1H, CH_bO, J = 1.54 Hz), 4.43 (ddd, 1H, CH_aF, J = 47.13, 9.65 and 2.3 Hz), 4.62 (ddd, 1H, CH_bF, J = 2.31 Hz); ^{19}F NMR ($CDCl_3$), δ: −232.5 (t, 1F, CH_2F, J = 47.13 Hz). (2*R*/*S*,*S*/R_S)-**8d** (Minor diol), ^{1}H NMR ($CDCl_3$), δ: 2.73 (s, 3H, CH_3), 3.03 (d, 2H, CH_2S, J = 1.54 Hz), 3.67 (dd, 1H, CH_aO, J = 11.59 and 1.93 Hz), 3.71 (dd, 1H, CH_bO), 4.23 (br s, 2H, OH), 4.33 (ddd, 1H, CH_aF, J = 47.13, 9.66 and 1.54 Hz), 4.52 (dd, 1H, CH_bF); ^{19}F NMR ($CDCl_3$), δ: −229.5 (t, 1F, CH_2F, J = 47.13 Hz); elemental analysis for $C_5H_{11}O_3FS$. Found (%): C, 35.25; H, 6.54; F, 11.18. Calculated (%) C, 35.28; H, 6.51; F, 11.16.

5.6. Synthesis of the benzoylic compounds 9a and 10a

Diol **8a** (1.0 mmol, 206 mg) is dissolved in methylene chloride (7.5 ml) at 0°C under nitrogen. Benzoic acid (1.0 mmol, 122 mg), DCC (1.1 mmol, 226 mg) and, 5 min after the last addition, DMAP (0.1 mmol, 12 mg) are added. The reaction mixture is kept 6 h under stirring at rt. A TLC monitoring shows the formation of two UV–visible spots. After filtration of the white solid, evaporation and flash chromatographic purification of the crude (ethyl acetate/*n*-hexane 4:1), 1-*O*-(benzoyl)-3-(methylsulfinyl)-2-(trifluoromethyl)-propan-1,2-diol (**9a**), is obtained in 80% yield; R_f = 0.35; m.p. = 86–87°C (isopropylether); along with 1,2-[*O*-(dibenzoyl)]-3-(methylsulfinyl)-2-(trifluoromethyl)-propan-1,2-diol (**10a**), R_f = 0.45; 5% yield; m.p. = 65–66°C (isopropylether); elemental analysis for $C_{12}H_{13}O_4F_3S$. Found (%): C, 27.25; H, 4.14; S, 18.15; F, 32.18. Calculated (%) C, 27.27; H, 3.98; S, 18.18; F, 32.39.

9a: ^{1}H NMR ($CDCl_3$), δ: 2.78 (s, 3H, CH_3), 3.18 (s, 2H, CH_2S), 4.59 (d, 1H, CH_aO, J = 11 Hz), 4.67 (d, 1H, CH_bO), 7.40–8.10 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$), δ: −79.2 (s, 3F, CF_3); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 40.05 (s, CH_3), 54.5 (s, CH_2S), 65.0 (s, CH_2O), 74.4 (q, COH, J = 27.74 Hz), 125.0 (q, CF_3, J = 288.53 Hz), 128.0–134.0 (s, ArC), 166.0 (s, CO); IR(KBr), cm^{-1}: 2927.23, 1690.89, 1278.33, 708.53; MS (*m*/*z*): 311; elemental analysis for $C_{12}H_{13}O_4F_3S$. Found (%): C, 46.45; H, 4.24; F, 18.38. Calculated (%) C, 46.45; H, 4.22; F, 18.37.

10a: ^{1}H NMR ($CDCl_3$), δ: 2.78 (s, 3H, CH_3), 3.78 (d, 1H, CH_aS, J = 12.6 Hz), 3.85 (d, 1H, CH_bS), 5.06 (dd, 1H, CH_aO, J = 13.7 and 3.8 Hz), 5.22 (dd, 1H, CH_bO, J = 1.9 Hz), 7.3–8.2 (m, 10H, Ar); ^{19}F NMR ($CDCl_3$), δ: −76.4 (s, 3F, CF_3); MS (*m*/*z*): 415; elemental analysis for $C_{18}H_{17}O_5F_3S$. Found (%): C, 53.75; H, 4.24; F, 14.18. Calculated (%) C, 53.73; H, 4.26; F, 14.16.

5.7. Synthesis of 1-[O-(benzoyl)]-3-(methylsulfenyl)-2-(trifluoromethyl)-propan-1,2-diol (11a)

NaI (3.0 mmol, 447 mg) is added to a solution of diol **9a** (1.0 mmol, 310 mg) in acetone (10 ml), the mixture is cooled at −20°C under nitrogen and trifluoroacetic anhydride (5.0 mmol, 706 μl) is added by syringe. After 10 min the reaction is complete (TLC monitoring). The reaction is quenched by

adding saturated solutions of Na_2SO_3 and $NaHCO_3$ (pH 7). The organics are extracted in diethyl ether and washed with water. After drying on sodium sulfate, filtration and evaporation, the residue is purified by flash chromatography (FC) in *n*-hexane/ethyl ether 85:15 to give **11a**: R_f=0.30; 78% yield; ^{1}H NMR ($CDCl_3$), δ: 2.23 (s, 3H, CH_3), 2.91 (d, 1H, CH_aS, J=14.68 Hz), 3.07 (d, 2H, CH_bS), 3.80 (br s, 1H, OH), 4.52 (dq, 1H, CH_aO, J=11.98 and 0.77 Hz), 4.66 (d, 1H, CH_bO), 7.40–7.55 (m, 3H, Ar), 8.0–8.1 (m, 2H, Ar); ^{19}F NMR ($CDCl_3$), δ: −80.25 (s, 3F, CF_3); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 18.0 (s, CH_3), 37.0 (s, CH_2S), 64.5 (s, CH_2O), 74.0 (q, COH, J=27.64 Hz), 125.0 (q, CF_3, J=286.68 Hz), 128.5–133.5 (s, ArC), 166.0 (s, CO); elemental analysis for $C_{12}H_{13}O_3F_3S$. Found (%): C, 54.95; H, 4.94; F, 21.78. Calculated (%) C, 54.95; H, 4.99; F, 21.73.

*5.8. Synthesis of 1-[O-(benzoyl)]-2-(trifluoromethyl)-propan-1,2-diol (**12a**)*

11a (0.5 mmol, 150 mg) is dissolved in ethanol (2 ml) and Raney-Ni (equal amount in weight) is added. The reaction is kept at reflux under vigorous stirring and H_2 atmosphere for 45 min. Then, Raney-Ni is filtered, ethanol is evaporated and the residue is purified by FC in *n*-hexane/ethyl ether 7:3: R_f=0.30; 68% yield; m.p.=54–55°C (isopropylether); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 3H, CH_3), 3.00 (s, 1H, OH), 4.40 (dq, 1H, CH_aO, J=11.97 and 1.16 Hz), 4.55 (d, 1H, CH_bO), 7.40–7.50 (m, 3H, Ar), 8.0–8.1 (m, 2H, Ar); ^{19}F NMR ($CDCl_3$) δ: −82.2 (s, 3F, CF_3); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 19.0 (s, CH_3), 66.0 (s, CH_2), 73.0 (q, COH, J=28.66 Hz), 124.15 (q, CF_3, J=284.86 Hz), 129.0–134.0 (s, ArC), 167.0 (s, CO); IR (KBr), cm^{-1}: 3455.35, 1701.61, 1283.57, 1189.74, 1156.33, 1127.52, 712.04; MS (m/z): 248; elemental analysis for $C_{11}H_{11}O_3F_3$. Found (%): C, 53.28; H, 4.45; F, 22.97. Calculated (%) C, 53.23; H, 4.47; F, 22.96.

*5.9. Reaction of opening of the oxirane **5a** with benzylamine*

The oxirane (*2S/R,S/R*$_S$)-**5a** (0.53 mmol, 100 mg) is dissolved in THF (2 ml) and benzylamine (10 mmol, 581 μl) is added at 0°C, under nitrogen. The reaction is kept under stirring for 4 h, then the solvent is evaporated under reduced pressure and the crude product is purified by FC in ethyl acetate to give: 2-[*N*-(benzylamino)]-3-(methylsulfinyl)-2-trifluoromethylpropan-1-ol (**14a**): R_f=0.38; 4% yield; ^{1}H NMR ($CDCl_3$), δ: 2.65 (s, 3H, CH_3), 2.87 (br s, 1H, OH), 3.21 (d, 1H, CH_aS, J=13.2 Hz), 3.24 (d, 1H, CH_bS), 3.48 (s, 2H, CH_2Ph), 3.93 (dd, 1H, CH_aO, J=13.5 and 4.0 Hz), 4.03 (dd, 1H, CH_bO, J=8.0 Hz), 7.2–7.4 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$) δ: −78.6 (s, 3F, CF_3); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 40.0 (s, CH_3), 49.0 (s, CH_2S), 60.0 (s, CH_2OH), 73.0 (q, CCF_3, J=26.5 Hz), 126.0–130.0 (s, ArC); elemental analysis for $C_{12}H_{16}O_2F_3NS$. Found (%): C, 48.83; H, 5.47; F, 19.32; N, 4.70. Calculated (%) C, 48.80; H, 5.46; F, 19.30; N, 4.74; and 1-[*N*-(benzylamino)]-3-(methylsulfinyl)-2-trifluoromethylpropan-2-ol (**13a**), R_f=0.34; 82% yield; ^{1}H NMR ($CDCl_3$) δ: 2.65 (s, 3H, CH_3), 2.96 (dd, 1H, CH_aN, J=14.0 and 0.8 Hz), 3.05 (d, 1H, CH_aS, J=13.5 Hz), 3.09 (d, 1H, CH_bS), 3.17 (dd, 1H, CH_aN, J=1.2 Hz), 3.84 (d, 1H, CH_aPh, J=13.6 Hz), 2.89 (d, 1H, CH_bPh), 7.2–7.4 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$) δ: −82.5 (s, 3F, CF_3); MS (m/z): 295 (M+1), 278 (M^+-H_2O), 228 ($M^+-CF_3^+$), 70 (CF_3^+); elemental analysis for $C_{12}H_{16}O_2F_3NS$. Found (%): C, 48.85; H, 5.44; F, 19.35; N, 4.78. Calculated (%) C, 48.80; H, 5.46; F, 19.30; N, 4.74.

*5.10. Synthesis of 1-[N-(benzyltrifluoroacetyl)]-2-hydroxy-3-(methylsulfenyl)-2-(trifluoromethyl)-propylamine (**15**)*

NaI (3.0 mmol, 447 mg) is added to a solution of *N*-benzylpropylamine **13a** (1.0 mmol, 294 mg) in acetone (10 ml), the mixture is cooled at −20°C under nitrogen. Trifluoroacetic anhydride (5.0 mmol, 706 μl) is added by syringe and, after 10 min, aqueous solutions of Na_2SO_3 and $NaHCO_3$ are dropped in. After the usual work-up, a FC purification in *n*-hexane/ethyl ether 85:15 gives **15** in 68% yield: R_f=0.30; ^{1}H NMR ($CDCl_3$), δ: 2.20 (s, 3H, CH_3), 2.70 (d, 1H, CH_aS, J=14.8 Hz), 3.00 (d, 1H, CH_bS), 3.40 (d, 1H, CH_bN, J=14.8 Hz), 4.15 (dd, 1H, CH_bN), 4.65 (d, 1H, CH_aPh, J=16.6 Hz), 4.75 (s, 1H, OH), 5.00 (d, 1H, CH_bPh), 7.10–7.45 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$), δ: −80.5 (s, 3F, CF_3), −69.3 (s, 3F, CF_3CO); ^{13}C NMR ($CDCl_3$) (all dec.), δ: 18.0 (s, CH_3), 38.5 (s, CH_2S), 48.0 (s, CH_2N), 52.5 (s, CH_2Ph), 76.0 (q, CCF_3, J=25.0 Hz), 120.5 (q, CF_3, J=280.0 Hz), 127.0–130.0 (s, ArC), 165.0 (s, CO); MS (m/z): 376; elemental analysis for $C_{14}H_{15}O_2F_6NS$. Found (%): C, 44.78; H, 4.04; F, 30.35; N, 3.78. Calculated (%) C, 44.80; H, 4.03; F, 30.37; N, 3.73.

5.11. Desulfenylation reaction

N-(Benzyltrifluoroacetyl)-propylamine **15a** (0.5 mmol, 188 mg) is dissolved in ethanol (4 ml) and Raney-Ni is added (same amount in weight). The reaction mixture is vigorously stirred at reflux for 1 h in a H_2 atmosphere. Raney-Ni is filtered with caution, the solvent evaporated and the crude purified by FC in *n*-pentane/ethyl ether 85:15 to give **16a** (R_f=0.30) in 56% yield together with **17a** (R_f=0.18) in 34% yield. 1-[*N*-(Benzyltrifluoroacetyl)]-2-hydroxy-2-(trifluoromethyl)-propylamine (**16a**): ^{1}H NMR ($CDCl_3$), δ: 1.35 (s, 3H, CH_3), 3.45 (d, 1H, CH_aN, J=14.69 Hz), 3.77 (d, 1H, CH_bN), 3.90 (br s, 1H, OH), 4.74 (d, 1H, CH_aPh, J=16.20 Hz), 4.90 (d, 1H, CH_bPh), 7.1–7.5 (m, 5H, Ar); ^{19}F NMR ($CDCl_3$), δ: −69.3 (s, 3F, CF_3CO), −83.1 (s, 3F, CF_3); elemental analysis for $C_{13}H_{13}O_2F_6N$. Found (%): C, 47.25; H, 3.94; F, 34.68; N, 4.28. Calculated (%) C, 47.42; H, 3.98; F, 34.62; N, 4.25. 2-Hydroxy-1-[*N*-(trifluoroacetyl)]-2-trifluoromethylpropylamine (**17a**): ^{1}H NMR ($CDCl_3$), δ: 1.40 (s, 3H, CH_3), 3.10 (br s, 1H, OH), 3.59 (dd, 1H, CH_aN, J=14.32 and 5.27 Hz), 3.71 (dd, 1H,

CH_bN, J=6.79 Hz), 6.80 (br s, 1H, NH); ^{19}F NMR ($CDCl_3$), δ: −77.2 (s, 3F, CF_3CO), −83.2 (s, 3F, CF_3); elemental analysis for $C_6H_7O_2F_6N$. Found (%): C, 47.25; H, 3.94; F, 34.68; N, 5.88. Calculated (%) C, 47.42; H, 3.98; F, 34.62; N, 5.86.

5.12. Synthesis of 1-azido-3-(methylsulfinyl)-2-(trifluoromethyl)-propan-2-ol (18a)

The oxirane (2*S*/*R*,*S*/R_S)-**5a** (0.53 mmol, 100 mg) is dissolved in absolute ethanol (2 ml) and a mixture of solid NaN_3 (1.2 eq, 41 mg) and NH_4Cl (1.0 eq, 28 mg) is added at 0°C under nitrogen. The reaction is kept under stirring at rt overnight, then the solvent is evaporated and the residue purified by FC in ethyl acetate/*n*-hexane 4:1 to give **18a** (107 mg, 88% yield): R_f=0.35; ^1H NMR ($CDCl_3$), δ: 2.65 (s, 3H, CH_3), 2.93 (d, 1H, CH_aS, J=12.65 Hz), 3.22 (d, 1H, CH_bS), 3.44 (d, 1H, CH_aN, J=12.10 Hz), 3.70 (d, 1H, CH_bN), 5.90 (br s, 1H, OH); ^{19}F NMR ($CDCl_3$), δ: −80.03 (s, 3F, CF_3); ^{13}C NMR ($CDCl_3$) (all dec), δ: 40.05 (s, CH_3), 53.0 (s, CH_2S), 54.0 (s, CH_2N_3), 75.9 (q, CCF_3, J=28.66 Hz), 124.50 (q, CF_3, J=287.61 Hz); IR (KBr), cm^{-1}: 3420.39, 2115.08 (C–N_3), 1177.23, 1017.62; MS (*m*/*z*): 232 (M^+ + 1); elemental analysis for $C_5H_8O_2F_3N_3S$. Found (%): C, 26.09; H, 3.50; S, 13.91; F, 24.62; N, 18.11. Calculated (%) C, 25.97; H, 3.49; S, 13.86; F, 24.65; N, 18.17.

5.13. Synthesis of the O-benzoyl-protected alcohol 19a

Following the same experimental procedure described for **9a**, **8a** (unresolvable mixture of two diastereoisomers—1.0 mmol, 176 mg) is reacted with DCC (1.1 mmol, 226 mg), DMAP (0.1 mmol, 12.2 mg), and PhCOOH (1.0 mmol, 122 mg) in CH_2Cl_2 (6 ml). The crude is purified by FC in *n*-hexane/ethyl acetate 4:1 giving **19a** as a resolvable mixture of two diastereoisomers in 94% overall yields: (2*S*/*R*,*S*/R_s)-2-[*O*-(benzoyl)]-1-(methylsulfinyl)-3, 3,3-trifluoropropan-2-ol (**19a**) (main reaction product), R_f=0.55; m.p.=86–87°C (isopropylether); 50% yield; ^1H NMR ($CDCl_3$), δ: 2.74 (s, 3H, CH_3), 3.16 (dd, 1H, CH_aS, J=13.14 and 8.89 Hz), 3.34 (dd, 1H, CH_bS, J=7.91 Hz), 5.97 (m, 1H, C*H*OH); ^{19}F NMR ($CDCl_3$), δ: −77.61 (d, 3F, CF_3, J=6.41 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 39.0 (s, CH_3), 52.2 (s, CH_2S), 65.3 (q, CHO, J=33.29 Hz), 123.2 (q, CF_3, J=281.13 Hz), 128.8 (s), 130.2 (s), 134.0 (s, ArC), 165.0 (s, CO); (2*R*/*S*,*S*/R_s)-**19a** (minor product), R_f=0.35; 44% yield; yellowish oil; ^1H NMR ($CDCl_3$), δ: 2.72 (s, 3H, CH_3), 3.19 (dd, 1H, CH_aS, J=9.66 and 3.86 Hz), 3.22 (d, 1H, CH_bS), 6.10 (m, 1H, C*H*OH); ^{19}F NMR ($CDCl_3$), δ: −77.79 (d, 3F, CF_3, J=6.41 Hz); ^{13}C NMR ($CDCl_3$), δ: (all dec) 39.5 (s, CH_3), 54.0 (s, CH_2S), 64.3 (q, CHO, J=35.13 Hz), 123.0 (q, CF_3, J=281.13 Hz), 128.8 (s), 130.2 (s), 134.0 (s, ArC), 164.0 (CO); IR(KBr) cm^{-1}: 1736.87 (C=O), 1284.89, 1179.21, 705.72; MS (*m*/*z*): 280; elemental analysis for $C_{11}H_{11}O_3F_3S$. Found (%): C, 47.88; H, 4.19; S, 10.77; F, 19.19. Calculated (%) C, 47.14; H, 3.98; S, 11.44; F, 20.34.

5.14. Reaction of reduction of the sulfinylic moiety into sulfenylic

Following the same methodology described for the compounds **11a** and **15a**, (2*S*/*R*,*S*/R_s)-**19a** (1.0 mmol, 280 mg) is reduced to sulfenylic derivative [$(CF_3CO)_2O$ (5.0 mmol, 706 μl), NaI (3.0 mmol, 447 mg), acetone (10 ml)]. After FC purification in *n*-hexane/ethyl ether 95:5, (2*S*/*R*)-2-[*O*-(benzoyl)]-1-(methylsulfenyl)-3,3,3-trifluoropropan-2-ol (**20a**) is isolated in 85% yield: R_f=0.40; m.p.=31°C (isopropylether); ^1H NMR ($CDCl_3$), δ: 2.74 (s, 3H, CH_3), 2.90 (dd, 1H, CH_aS, J=14.6 and 9.6 Hz), 2.99 (dd, 1H, CH_bS, J=3.4 Hz), 5.72 (ddq, 1H, CHO, J=9.6, 6.4 and 3.4 Hz), 7.4–7.7 and 8.05–8.15 (m, 5H, ArH); ^{19}F NMR ($CDCl_3$), δ: −77.62 (d, 3F, CF_3, J=6.4 Hz); ^{13}C NMR ($CDCl_3$) (all dec), δ: 16.0 (s, CH_3), 32.3 (s, CH_2), 68.5 (q, CCF_3, J=31.45 Hz), 123.4 (q, CF_3, J=282.98 Hz), 128.5 (s), 130.0 (s), 134.0 (s, ArC), 165.0 (s, CO); IR (KBr) cm^{-1}: 1733.61 (C=O), 1270.57, 1109.84, 1029.63, 711.75; MS (*m*/*z*): 264; elemental analysis for $C_{11}H_{11}O_2F_3N$. Found (%): C, 49.95; H, 4.24; F, 21.58. Calculated (%) C, 49.99; H, 4.20; F, 21.57.

5.15. Reaction of hydrogenolytic desulfenylation

As already described for **12a** and **16a**, the sulfide (2*S*/*R*)-**20a** (100 mg) is desulfenylated in ethanol (5 ml) with Raney-Ni (150 mg). After 4 h at reflux and after FC purification of the crude (petroleum ether/ethyl ether 95:5) (2*S*/*R*)-2-[*O*-(benzoyl)]-1,1,1-trifluoropropan-2-ol is obtained in 75% yield: R_f=0.35; ^1H NMR ($CDCl_3$), δ: 1.53 (d, 3H, CH_3, J=8.4 Hz), 5.53 (qq, 1H, CH, J=6.4 Hz), 7.3–7.6 and 8.0–8.1 (m, 5H, ArH); ^{19}F NMR ($CDCl_3$), δ: −79.81 (d, 3F, CF_3, J=6.4 Hz); elemental analysis for $C_{10}H_9O_2F_3$. Found (%): C, 55.09; H, 4.14; F, 26.18. Calculated (%) C, 55.05; H, 4.16; F, 26.12.

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