Homochiral Perfluoroalkyl-Group-Substituted Secondary Alcohols Through Stereoselective Reduction of Perfluoroalkyl 1-(*p*-Tolylsulfinyl)alkyl Ketones[1]

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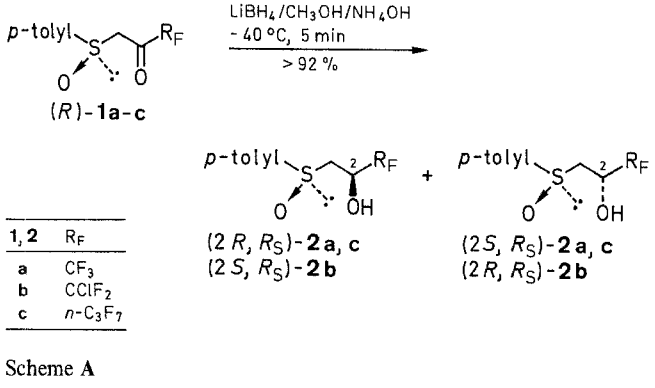
The reduction of some enantiomerically pure perfluoroalkyl α-(*p*-tolylsulfinyl) ketones was performed. Alcohols containing perfluoroalkyl and *p*-tolylsulfinyl groups were obtained with high diastereoselection when a phenyl residue was present on the sulfinylated carbon and with lower diastereoselection in the other cases. Removal of the chiral sulfinyl group from single diastereoisomers gave secondary alcohols containing a perfluoroalkyl group in enantiomerically pure form.

We are engaged in the exploitation of α-fluoro α′-sulfinyl ketones for the synthesis of sulfur-free fluorinated compounds in enantiomerically pure form. In our approach, fluorocarboxylic acids or esters[4] are the source of the fluoroorganic frameworks and optically pure alkyl *p*-tolyl sulfoxides provide the chiral auxiliary group for the diastereoselective reactions to be performed on the α-fluoro-ketone moiety. The final removal of the sulfinyl residue allowed to obtain α-monofluoro ketones and α-monofluoro alcohols[5] in enantiomerically pure form. Here we describe how homochiral perfluoroalkyl secondary alcohols have been prepared through a diastereoselective reduction of enantiomerically pure perfluoroalkyl 1-sulfinylalkyl ketones followed by the removal of the auxiliary group through a two-step procedure.

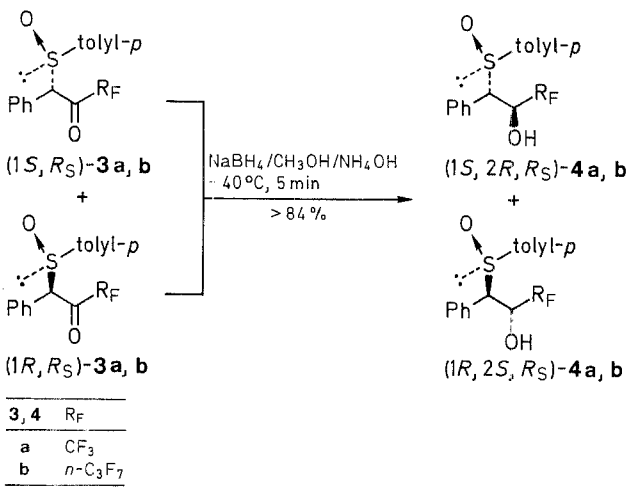
The starting perfluoroalkyl 1-*p*-tolylsulfinylalkyl ketones **1a–c**, **3a, b** were prepared[4] by acylation of the lithium derivative of (+)-(*R*)-methyl 4-methylphenylsulfoxide and of (+)-(*R*)-benzyl 4-methylphenylsulfoxide with the esters or the lithium salts of trifluoroacetic, chlorodifluoroacetic, and heptafluorobutyric acids.

Stereospecific transformations of β-keto sulfoxides to the corresponding secondary alcohols by hydride reagents have been reported and it was already shown how, depending on the substitution pattern and on reaction condition adopted, the chirality of the alcohol is determined by the chirality of the sulfinyl group or by that of the α-substituted carbon.[6]

The reduction of the carbonyl group of the trifluoromethyl ketone **1a** was performed with several different borohydride species (lithium, sodium, potassium, or tetrabutylammonium borohydride in methanol/aqueous ammonia; sodium or tetrabutylammonium cyanoborohydride in methanol/acetic acid with, or without, zinc chloride).[7] In all cases it occurred cleanly and the sulfinyl alcohol **2a** with the $2R,R_S$ configuration formed preferentially ($2R,R_S$:$2S,R_S$ isomer ratio, < 70:30) (Scheme **A**, Table 1, see below for the assignment of the absolute configurations). The best results were obtained when lithium borohydride was employed in methanol/aqueous ammonia solution. The yields and the diastereoselection observed in the reduction of the chlorodifluoromethyl and heptafluoropropyl ketones **1b** and **1c** were similar to those observed for **1a**. On the contrary, the reduction of carbonyl substrates **3a, b** in which a phenyl residue was present on the sulfinyl substituted carbon, occurred with a much higher diastereoselection (> 95%). When a mixture[8] of ($1S,R_S$)-**3a** and its $1R,R_S$-isomer was reacted with sodium borohydride in methanol/aqueous ammonia solution, we isolated exclusively the alcohols **4a** having the $1S,2R,R_S$ and $1R,2S,R_S$ absolute configurations (diastereoisomer ratio,



Scheme A



Scheme B

66:34).[9] Correspondingly, a mixture of epimers at the carbon stereocenter of **3b** afforded (1*S*,2*R*,R_S)-**4b** and (1*R*,2*S*,R_S)-**4b** in a 70:30 ratio (Scheme **B**).

Table 1. Perfluoroalkyl-Substituted *p*-Tolylsulfinylalkyl Alcohols **2** and **4** Prepared

Product	Yield (%)[a] (2*S*,R_S): (2*R*,R_S)	R_f[b] (solvent)	mp (°C) (solvent)	Molecular Formula[c] or Lit. $[\alpha]_D^{20}$	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{19}F-NMR ($CDCl_3/C_6F_6$) δ, *J*(Hz)
(2*R*,R_S)-**2a**	92 (30:70)	0.25 (A)	109–110 (*n*-hexane/EtOAc)	+199.1° (1.00)[7]	+196° (1.0)	2.48 (s, 3H, CH_3); 3.08, 3.17 (m, 1H each, CH_2); 4.52 (m, 1H, CH); 7.4, 7.6 (m, 4H_{arom})	−80.6 ($^3J_{H,F}$ = 6.4)
(2*S*,R_S)-**2a**		0.36 (A)	113–114 (*n*-hexane/EtOAc)	+257.6° (1.00)[7]	+260° (1.1)	2.48 (s, 3H, CH_3); 2.99, 3.07 (m, 1H each, CH_2); 4.57 (m, 1H, CH); 7.4, 7.6 (m, 4H_{arom})	−80.0 ($^3J_{H,F}$ = 6.6)
(2*S*,R_S)-**2b**	92 (68:32)	0.29 (A)	112–113 (*n*-hexane/EtOAc)	$C_{10}H_{11}ClF_2O_2S$ (268.7)	+186° (0.8)	2.49 (s, 3H, CH_3); 3.11, 3.17 (m, 1H each, CH_2); 4.59 (m, 1H, CH); 7.4, 7.6 (m, 4H_{arom})	−64.5, −67.0 ($^3J_{H,F}$ = 7.3)
(2*R*,R_S)-**2b**		0.38 (A)	113–114 (*n*-pentane)	$C_{10}H_{11}ClF_2O_2S$ (268.7)	+257° (1.0)	2.49 (s, 3H, CH_3); 3.06 (d, 2H, $^2J_{H,H}$ = 7.0, CH_2); 4.60 (m, 1H, CH); 7.4, 7.6 (m, 4H_{arom})	−64.5, −66.0 ($^3J_{H,F}$ = 7.3)
(2*R*,R_S)-**2c**	94 (30:70)	0.33 (A)	129–130 (*n*-hexane/EtOAc)	$C_{12}H_{11}F_7O_2S$ (352.3)	+154° (1.0)	2.41 (s, 3H, CH_3); 3.24 (m, 2H, CH_2); 4.35 (m, 1H, CH); 7.48, 7.69 (m, 4H_{arom})[d]	−82.0 (dd, 3F, *J* = 8.0, 11.3); −126.8 (m, 2F, CF_2CF_3); −121.3, −128.5 (m, 2F, CF_2CH)
(2*S*,R_S)-**2c**		0.40 (A)	115–116 (*n*-pentane)	$C_{12}H_{11}F_7O_2S$ (352.3)	+201° (0.9)	2.42 (s, 3H, CH_3); 2.86, 3.17 (m, 1H each, CH_2); 4.59 (m, 1H, CH); 7.43, 7.66 (m, 4H_{arom})[d]	−82.0 (dd, 3F, *J* = 8.6, 11.0); −126.8 (m, 2F, CF_2CF_3); −121.3, −126.9 (m, 2F, *J* = 17.7, CF_2CH)
(1*S*,2*R*,R_S)-**4a**	86 (34:66)	0.24 (B)	137–138 (*n*-hexane/EtOAc)	$C_{16}H_{15}F_3O_2S$ (328.3)	+241° (1.2)	2.39 (s, 3H, CH_3); 3.81 (d, 1H, *J* = 4.0, CHS); 4.98 (m, 1H, CHOH); 7.0–7.4 (m, 9H_{arom})	−76.9 ($^3J_{H,F}$ = 6.3)
(1*R*,2*S*,R_S)-**4a**		0.34 (B)	164–165 (*n*-pentane/*i*-Pr_2O)	$C_{16}H_{15}F_3O_2S$ (328.3)	−6.95° (3.3)	2.39 (s, 3H, CH_3); 3.91 (d, 1H, ^3J = 2.5, CHS); 5.20 (m, 1H, CHOH); 7.1–7.4 (m, 9H_{arom})	−75.9 ($^3J_{H,F}$ = 7.4)
(1*S*,2*R*,R_S)-**4b**	84 (30:70)	0.30 (B)	142–143 (*n*-hexane/EtOAc)	$C_{18}H_{15}F_7O_2S$ (428.4)	+232° (1.0)	2.39 (s, 3H, CH_3); 3.87 (dd, 1H, *J* = 4.5, 2.0, CHS); 4.99 (m, 1H, CHOH); 7.1–7.4 (m, 9H_{arom})	−81.8 (dd, 3F, *J* = 8.8, 11.0, CF_3); −119.2, −126.0 (m, 2F, CF_2CH); −127.0 (dd, 2F, CF_2CF_3)
(1*R*,2*S*,R_S)-**4b**		0.38 (B)	152–153 (*n*-pentane/*i*-Pr_2O)	$C_{18}H_{15}F_7O_2S$ (428.4)	−6.39° (3.5)[e]	2.37 (s, 3H, CH_3); 3.93 (br t, 1H, *J* = 2.9, CHS); 5.38 (m, 1H, CHOH); 7.0–7.3 (m, 9H_{arom})	−81.8 (t, 3F, *J* = 9.5, CF_3); −119.5, −124.0 (m, 2F, CF_2CH); −127.0 (br s, 3H, CF_2CF_3)

[a] Reported values refer to the two diastereoisomers obtained from the reduction of **1a–c** and **3a, b** (Schemes **A** and **B**).

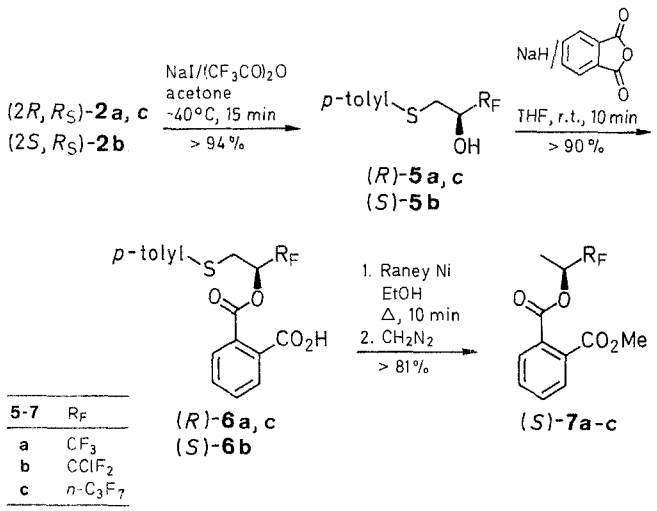
[b] Values obtained on TLC silica gel 60 F_{254} (Merck); eluting mixtures: A: *n*-hexane/EtOAc/AcOH (35:20:0.5); B: *n*-hexane/EtOAc (7:3).

[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.25, S ±0.28.

[d] Spectrum registered in DMSO-d_6.

[e] Value obtained at λ = 365 nm.

Single diastereoisomers of all the fluorinated β-hydroxysulfoxides **2a–c** and **4a, b** could be obtained in pure form through chromatography or crystallization and full characterization of the products is reported in Table 1.



Scheme **C**

The removal of the auxiliary sulfinyl group was accomplished in a way similar to that already employed for monofluoro alcohols.[5] The *p*-tolylthio alcohols (*R*)-**5a**, (*S*)-**5b**, and (*R*)-**5c** were isolated in nearly quantitative yields (Scheme **C**) by deoxygenation, with sodium iodide and trifluoroacetic anhydride,[10] of the sulfur atom of (2*R*,R_S)-**2a**, (2*S*,R_S)-**2b**, and (2*R*,R_S)-**2c**, respectively (Table 2). Treatment of the sodium alcoholates of **5a–c** with phthalic anhydride afforded the hydrogen phthalates **6a–c**. Hydrogenolysis of these products with Raney-nickel in ethanol solution[11] and successive methylation with diazomethane gave the easy to handle methyl phthalates **7a–c** of 1,1,1-trifluoro-2-propanol, 1-chloro-1,1-difluoro-2-propanol, and 3,3,4,4,5,5,5-heptafluoro-2-pentanol, all having the *S*-absolute configuration (Table 3).

Similarly, the (1*S*,2*R*,R_S)-sulfinyl alcohols **3a, b** were deoxygenated to the (1*S*,2*R*)-sulfide derivatives **8a, b**, which upon hydrogenolysis with Raney-nickel gave (*S*)-3,3,3-trifluoro-1-phenyl-2-propanol (**9a**) and (*S*)-3,3,3,4,4,5,5-heptafluoro-1-phenyl-2-pentanol (**9b**). Starting from (2*S*,R_S)-**2c** and from (1*R*,2*S*,R_S)-**3a, b** the procedure described above afforded the final compounds (−)-(*R*)-**7c** (75% overall yield), (+)-(*R*)-**9a** (83% overall yield), and (+)-(*R*)-**9b** (81% overall yield) (Scheme **D**).

Table 2. *p*-Tolylthio-Substituted Alcohols **5a–c**, **8a, b** Prepared

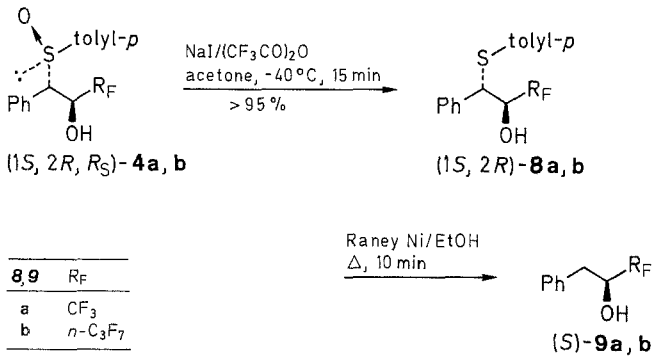
Product	Solvent for Chromatography	Yield (%)	Molecular Formula[a]	$[\alpha]_D^{20}$ (1.0, $CHCl_3$)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
(*R*)-**5a**	*n*-hexane/EtOAc (95 : 5)	94	$C_{10}H_{11}F_3OS$ (236.3)	−78.9°	2.35 (s, 3H, CH_3); 2.96 (dd, 1H, $^2J_{H,H}$ = 14.6, $^3J_{H,H}$ = 10.5, CHS); 3.25 (dd, 1H, $^3J_{H,H}$ = 3, CHS); 3.93 (m, 1H, CHO); 7.15, 7.33 (m, 4H_{arom})
(*S*)-**5b**	*n*-hexane/ether (9 : 1)	95	$C_{10}H_{11}ClF_2OS$ (252.7)	−84.6°	2.35 (s, 3H, CH_3); 2.96 (dd, 1H, $^2J_{H,H}$ = 14.3, $^3J_{H,H}$ = 10.3, CHS); 3.32 (dd, 1H, $^3J_{H,H}$ = 3.3, $^4J_{H,F}$ = 0.6, CHS); 3.97 (m, 1H, CHO); 7.18, 7.35 (m, 4H_{arom})
(*R*)-**5c**	*n*-hexane/ether (4 : 1)	95	$C_{12}H_{11}F_7OS$ (336.3)	−65.1°[b]	2.38 (s, 3H, CH_3); 2.93 (dt, 1H, CHS); 3.32 (m, 1H, CHS); 4.08 (m, 1H, CHO); 7.27, 7.39 (m, 4H_{arom})
(1*S*,2*R*)-**8a**	*n*-hexane/EtOAc (4 : 1)	98	$C_{16}H_{15}F_3OS$ (312.3)	+206°[c]	2.33 (s, 3H, CH_3); 4.26 (m, 1H, $^3J_{H,F}$ = 6.8, CHO); 4.46 (d, 1H, $^3J_{H,H}$ = 3.4, CHS); 7.0–7.5 (m, 9H_{arom})
(1*S*,2*R*)-**8b**	*n*-hexane/ether (9 : 1)	96	$C_{18}H_{15}F_7OS$ (412.4)	+136°[d]	2.33 (s, 3H, CH_3); 4.46 (m, 1H, $^3J_{H,F}$ = 22, CHO); 4.57 (t, 1H, $^3J_{H,H}$ = $^4J_{H,F}$ = 2.5, CHS); 7.0–7.5 (m, 9H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.28, H ±0.27, S ±0.38.
[b] (*S*)-**5c**; $[\alpha]_D^{20}$ +65.9 (*c* = 1.1, $CHCl_3$).
[c] (1*R*,2*S*)-**8a**; $[\alpha]_D^{20}$ −214° (*c* = 1.0, $CHCl_3$).
[d] (1*R*,2*S*)-**8b**; $[\alpha]_D^{20}$ −131° (*c* = 1.1, $CHCl_3$).

Table 3. Compounds **7** and **9** Prepared

Product	Yield (%) (from **2**, **4**)	Molecular Formula[a] or Lit. $[\alpha]_D$	$[\alpha]_D^{20}$, λ(nm) (*c*, solvent)	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)	^{19}F-NMR ($CDCl_3/C_6F_6$) δ, *J*(Hz)
(*S*)-**7a**	71	$C_{12}H_{11}F_3O_4$ (276.2)	+10.7° (365) (3.0, $CHCl_3$)	1.54 (d, 3H, $^3J_{H,H}$ = 6.7, CH_3); 3.91 (s, 3H, CO_2CH_3); 5.53 (m, 1H, CH); 7.6–7.8 (m, 4H_{arom})	−79.4 (d, $J_{F,H}$ = 6.5)
(*S*)-**7b**	70	$C_{12}H_{11}ClF_2O_4$ (292.7)	+4.5° (365) (4.6, $CHCl_3$)	1.56 (d, 3H, $^3J_{H,H}$ = 6.5, CH_3); 3.92 (s, 3H, CO_2CH_3); 5.59 (m, 1H, CH); 7.6–7.8 (m, 4H_{arom})	−65.2 (t, *J* = 7.5)
(*S*)-**7c**	72	$C_{14}H_{11}F_7O_4$ (376.2)	+44.7° (365) (2.8, $CHCl_3$)	1.58 (br d, 3H, $^3J_{H,H}$ = 8.0, CH_3); 3.91 (s, 3H, CO_2CH_3); 5.71 (m, 1H, CH); 7.6–7.8 (m, 4H_{arom})	−81.9 (t, 3F, *J* = 10, CF_3); −121.7, −126.0 (m, 2F, CF_2CH); −126.9 (bd, 2F, CF_2CF_3)
(*S*)-**9a**[b]	81	−47.4° (1.76, CH_3OH)[19]	−47.9° (589) (1.4, CH_3OH)	2.84 (dd, 1H, $^2J_{H,H}$ = 14.5, $^3J_{H,H}$ = 10.0, CHPh); 3.07 (dd, 1H, $^3J_{H,H}$ = 3.2, CHPh); 4.14 (m, 1H, CHOH); 7.3 (m, 5H_{arom})	−80.7 (d, $J_{F,H}$ = 7.0)
(*S*)-**9b**	75	$C_{11}H_9F_7O$ (290.2)	−28.1° (589) (2.0, CH_3OH)	2.88 (dd, 1H, $^2J_{H,H}$ = 14.8, $^3J_{H,H}$ = 11.0, CHPh); 3.14 (dt, 1H, $^3J_{H,H}$ = 2.5, CHPh); 4.33 (m, 1H, CHOH); 7.4 (m, 5H_{arom})	−82.0 (m, 3F, CF_3); −122.0, −128.8 (m, 2F, CF_2CH); −126.9 (dd, 2F, CF_2, CF_3)

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.29.
[b] Different NMR spectra were reported for the compound in Ref. 19.



(1S, 2R, R_S)-**4a, b** (1S, 2R)-**8a, b** (S)-**9a, b**

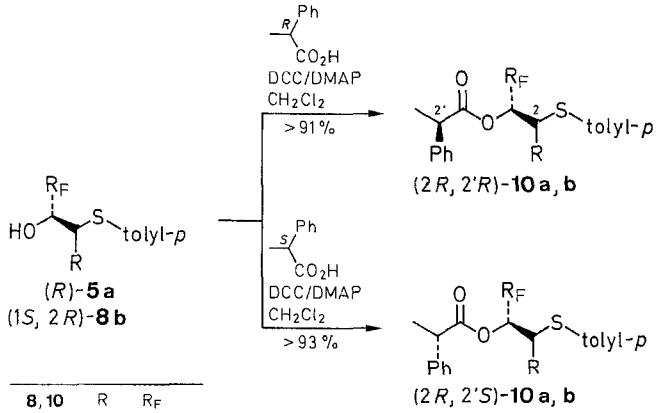
8,9	R_F
a	CF_3
b	n-C_3F_7

Scheme **D**

The method here described allowed therefore to prepare both enantiomers of perfluoroalkyl secondary alcohols **7c** and **9a, b** starting from the precursors **1c, 3a, b** having the same *R*-absolute configuration at the sulfinyl auxiliary group.

The absolute configuration at the alcoholic center of the trifluoropropanol (−)-**5a** and of the heptafluoropentanol (+)-**8b** were assigned through the esters **10a, b** obtained from the (*S*)- and (*R*)-2-phenylpropionic acid, a chiral derivatizing agent, which has been employed for the assignment of the absolute configuration of secondary alcohols,[3,12,13] amines,[13,14] and thiols,[15] through liquid chromatography[14] or ^{1}H-NMR spectroscopy.[3,12,13,15] In the present case, the chemical shift differences between externally diastereotopic protons observed in the ^{1}H-NMR spectra of the esters **10** can be rationalized according to the preferred conformations of these products reported in Scheme **E**. The hydrogens on the sulfinylated carbons of the esters **10a, b** obtained from the (*R*)-2-phenylpropionic acid were at higher fields (as a consequence of the shielding effect that the phenyl ring of the 2-phenylpropionic acid exerts on the facing protons of the alcohol) than the corresponding hydrogens of the esters prepared from the (*S*)-2-phenylpropionic acid thus proving the *R*- absolute configuration of the alcoholic center.[16]

The configurations of the alcoholic center of all the chlorodifluoromethyl compounds **2b, 5b–7b**, heptafluoropropyl derivatives **2c, 5c–7c, 3b, 4b, 8b, 9b** and trifluoromethyl compounds **3a, 4a, 8a, 9a** were assigned for similarities of the optical rotations and of the physical and spectral data with those of **2a, 5a–7a** and **4b, 8b, 9b**. The two sulfinyl propanols **4a**, obtained through the reduction of **3a** had the same relative stereochemistry at the two carbon stereocenters as, on deoxygenation of their sulfur atom, they afforded enantiomeric sulfide derivatives **8a**.

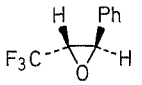


(R)-**5a** (1S, 2R)-**8b** (2R, 2'R)-**10a, b** (2R, 2'S)-**10a, b**

8,10	R	R_F
a	H	CF_3
b	Ph	n-C_3F_7

Scheme **E**

This relative stereochemistry was shown to be *anti* as the S_N2 displacement of the *p*-tolylthio residue by action of the adjacent hydroxyl group afforded a *trans*-1-trifluoromethyl-2-phenyl oxirane **11** ($^3J_{H,H}$ = 1.8 Hz).[18] Similarly the deoxygenation of the two diastereoisomeric heptafluoropropyl-containing sulfinyl alcohols **4b** gave enantiomeric sulfides **8b** to which the *anti* relative stereochemistry was assigned by analogy with **8a**.



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As perfluoroalkyl 1-sulfinylalkyl ketones of type **1** are easily obtained[4] in one step from perfluorocarboxylic esters, which are a very convenient source of fluoroorganic molecules, and from enantiomerically pure alkyl *p*-tolyl sulfoxides, which are easily available compounds, the described synthetic sequence seems to be of quite general applicability for the preparation of perfluoroalkyl secondary alcohols. The access to enantiomerically pure compounds depends on the separation of the diastereoisomeric sulfinyl alcohols **2** and **4**, which could be realized easily on gram scale through flash chromatography and/or crystallization. The procedure here described complements the few methods reported in the literature to prepare chiral and non-racemic perfluoroalkyl-containing alcohols.[19–24]

^{1}H-NMR spectra were obtained on a Bruker CPX-300 or a Varian EM 390 spectrometer using TMS as internal standard and $CDCl_3$ as solvent unless otherwise stated. ^{19}F-NMR spectra were recorded on a Bruker WP 80 SY instrument (75.39 MHz): δ_F values upfield from $CFCl_3$, and C_6F_6 was used as internal standard (−162.9). $[\alpha]_D$ values were obtained on a Jasco DIP-181. Melting points are uncorrected and were obtained on a capillary apparatus. Flash chromatographies were performed with silica gel 60 (63–200 μm) Merck and TLC were run on silica gel 60 F_{254} plates (Merck). Commercially available reagent grade solvents were employed without purification. Borohydrides, trifluoroacetic anhydride, and Raney-nickel were purchased from Fluka; NaI, NaH, and phthalic anhydride were obtained from Carlo Erba.

Perfluoroalkyl-Substituted α-(*p*-Tolylsulfinyl) Alcohols 2a–c, 4a, b; Typical Procedure:

A cooled solution (−40 °C) of $LiBH_4$ (11 mmol) in methanolic aqueous ammonia (32%) (9:1, 20 mL) is added dropwise into a solution of perfluoroalkyl 1-sulfinylalkyl ketone **1** (10 mmol) dissolved in the same solvent mixture (10 mL) under argon at −40 °C. After stirring for 5 min, dil. HCl is added until pH 2 is reached, CH_3OH is removed under reduced pressure and the residue is extracted with ether (3 × 100 mL). The organic layers are combined and dried (Na_2SO_4). Evaporation under reduced pressure of the solvent and flash chromatography of the raw product with the eluting system reported in Table 1 gives the pure diastereoisomers **2, 4**. Yields, physical, and spectral data are reported in Table 1. An analytical sample is obtained by crystallization.

When lithium, or sodium, or potassium, or tetrabutylammonium borohydride in CH_3OH/NH_4OH, or when sodium or tetrabutylammonium cyanoborohydride in CH_3OH/AcOH are used as reducing agents only slight variations in the chemical yields and in the diastereoselectivity of the process are obtained. In the reduction of **1a** the addition of a chelating metal ($ZnCl_2$) before the reducing agent ($NaBH_3CN$ in CH_3OH/AcOH) slightly lowered the diastereoselection (2*R*,R_S:2*S*,R_S = 6:4).

Perfluoroalkyl-Substituted α-(*p*-Tolylthio) Alcohols 5a–c, 8a–b; Typical Procedure:

A solution of trifluoroacetic anhydride (4.95 mL, 35 mmol) in acetone (10 mL) is added under argon into a cooled solution of diastereoisomerically pure perfluoroalkyl-substituted α-(*p*-tolylsulfinyl alcohol **2** and **4** (5 mmol) and of NaI (3.00 g, 20.0 mmol). Stirring is continued at −40 °C for 15 min, then sat. aq. Na_2SO_3 solution (35 mL) is added. The resultant light yellow mixture is treated with sat. aq. $NaHCO_3$ solution until evolution of CO_2 has ceased. Acetone is evaporated *in*

vacuo and the residual aqueous phase is extracted with ether (3 × 80 mL). The collected organic extracts are dried with (Na_2SO_4), and evaporated. The residue is purified by flash chromatography (Table 2).

2-(*p*-Tolylthio)ethyl Hydrogen Phthalates 6a–c; General Procedure:
A solution of the perfluoroalkyl substituted α-(*p*-tolylthio) alcohol **5** (5 mmol) in dry ether (5 mL) is added dropwise under argon at 0 °C to an oil-free suspension of NaH (0.17 g, 7.0 mmol) in dry ether (5 mL). After 15 min a solution of phthalic anhydride (0.89 g, 6.0 mmol) in dry ether (10 mL) is added dropwise and stirring is continued for 20 min at room temperature. A sat. aq. solution of NH_4Cl (5 mL) is added at −10 °C, followed by the addition of 1 N HCl until pH 3 is reached. The aqueous layer is extracted with EtOAc (3 × 50 mL), the collected organic phase dried (Na_2SO_4), and the solvent removed under reduced pressure. Flash chromatography of the residue affords the hydrogen phthalate **6** in yields > 92% and in pure form.

(R)-1-2,2,2-Trifluoro-1-(p-tolylthiomethyl)ethyl Hydrogen Phthalate **(6a)**: eluting system for flash chromatography: toluene/EtOAc/CH_3OH (20:80:10); $[\alpha]_D^{20}$ −80° (*c* = 1.2, $CHCl_3$).

$C_{18}H_{15}F_3O_4S$ (384.4) calc. C 56.24 H 3.93 S 8.34; found 56.01 4.20 8.07

^{1}H-NMR ($CDCl_3$): δ = 2.41 (s, 3 H, CH_3); 3.27 (m, 2 H, CH_2S); 5.60 (m, 1 H, CH); 7.0–8.0 (m, 9 H_{arom}).

(S)-2-Chloro-2,2-difluoro-1-(p-tolylthiomethyl)ethyl Hydrogen Phthalate **(6b)**: eluting system for flash chromatography: cyclohexane/EtOAc/AcOH) (35:15:0.5); $[\alpha]_D^{20}$ −145° (*c* = 1.1, $CHCl_3$).

$C_{18}H_{15}ClF_2O_4S$ (400.8) calc. C 53.93 H 3.77 S 8.00; found 53.70 3.90 7.83

^{1}H-NMR ($CDCl_3$): δ = 2.34 (s, 3 H, CH_3); 3.15–3.50 (m, 2 H, CH_2); 5.70 (m, 1 H, CH); 7.0–8.0 (m, 9 H_{arom}).

(R)-2,2,3,3,4,4,4-Heptafluoro-1-(p-tolylthiomethyl)butyl Hydrogen Phthalate **(6c)**: eluting system for flash chromatography: cyclohexane/EtOAc/AcOH (45:10:0.5); $[\alpha]_D^{20}$ −57.6° (*c* = 1.0, $CHCl_3$). [(*S*)-**6c**; $[\alpha]_D^{20}$ +58.8° (*c* = 1.1, $CHCl_3$).

$C_{20}H_{15}F_7O_4S$ (484.4) calc. C 49.59 H 3.12 S 6.62; found 49.33 2.94 6.86

^{1}H-NMR ($CDCl_3$): δ = 2.10 (s, 3 H, CH_3); 3.25 (m, 2 H, CH_2); 5.77 (m, 1 H, CH); 6.8–7.7 (m, 8 H_{arom}).

Methyl Phthalates 7 of Perfluoroalkyl-Substituted Secondary Alcohols; Typical Procedure:
The *p*-tolylthio-substituted alkyl hydrogen phthalate **6** (3.5 mmol) is heated at reflux in EtOH (15 mL) under an H_2 atmosphere in the presence of Raney-Ni (W-2, 0.6 g) for 5 min. The Ni is removed by filtration and washed with EtOH (3 × 3 mL). The solution is evaporated under reduced pressure, the oil is dissolved in ether (5 mL) and treated with a 0.3 N etheral solution of diazomethane (2.0 mL). After stirring for 5 min at room temperature, a drop of AcOH is added, the solvent is removed under reduced pressure, and the residue is flash chromatographed to afford the methyl phthalate **7** of the sulfur-free alcohol in yields > 79%. Physical and spectral data are reported in Table 3.

α-Perfluoroalkylphenethyl Alcohols 9; General Procedure:
The *p*-tolylthio-substituted compound **8** (5 mmol) is boiled in the presence of Raney-Ni (W-2, 1.0 g) for 5 min in EtOH (25 mL) under an H_2 atmosphere. The Ni is removed by filtration and washed with EtOH (3 × 5 mL). Evaporation of the solvent under reduced pressure and flash chromatography affords the alcohol **9** in yields > 82%. Physical and spectral data are reported in Table 3.

Esters 10a, b from (+)-(*S*)-2-Phenylpropionic Acid, or its (−)-(R)-Enantiomer, and from the *p*-Tolylthio-Substituted Alcohols 5a and 8b; General Procedure:
4-Dimethylaminopyridine (2.5 mg, 0.02 mmol) is added to a dichloromethane solution (1.0 mL) containing the alcohol **5a** or **8b** (0.2 mmol), the (+)-(*S*)-2-phenylpropionic acid (33 mg, 0.22 mmol) and dicyclohexylcarbodiimide (50 mg, 0.24 mmol). After 4 h at room temperature the dicyclohexyl urea is removed by filtration, washed with *n*-hexane (3 × 1 mL), and the combined filtrate is washed with 1 N HCl (1 mL), sat. aq. $NaHCO_3$ solution (1 mL), and brine (1 mL). The organic phase is dried (Na_2SO_4), and the solvent is removed to afford the ester (2′*S*)-**10** in nearly pure form. Flash chromatography with *n*-hexane/ether gives an analytically pure sample in 91% yields.

Similarly, when the (−)-(*R*)-2-phenylpropionic acid is employed, the ester (2′*R*)-**10** is obtained.

(2*R*,2′*S*)-**10a**:

$C_{19}H_{19}F_3O_2S$ (368.4) calc. C 61.94 H 5.20; found 62.08 5.38

^{1}H-NMR ($CDCl_3$): δ = 1.53 (d, 3 H, *J* = 7.5Hz, CH_3); 2.34 (s, 3 H, Ar-CH_3); 3.05 (dd, 1 H, CHS); 3.17 (dd, 1 H, CHS); 3.67 (q, 1 H, CHCO); 5.36 (m, 1 H, CHO); 7.1–7.4 (m, 9 H_{arom}).

(2*R*,2′*R*)-**10a**:

$C_{19}H_{19}F_3O_2S$ (368.4) calc. C 61.94 H 5.20; found 62.13 5.36

^{1}H-NMR ($CDCl_3$): δ = 1.53 (d, 3 H, *J* = 7.5 Hz, CH_3); 2.31 (s, 3 H, Ar-CH_3); 2.94 (dd, 1 H, *J* = 11 Hz, CHS); 3.15 (dd, 1 H, *J* = 3.0 Hz, CHS); 3.80 (q, 1 H, CHCO); 5.34 (m, 1 H, CHO); 7.0–7.4 (m, 9 H_{arom}).

(1*S*,2*R*,2′*S*)-**10b**:

$C_{27}H_{23}F_7O_2S$ (544.52) calc. C 59.55 H 4.26; found 59.17 3.99

^{1}H-NMR ($CDCl_3$): δ = 1.59 (d, 3 H, *J* = 7.5 Hz, CH_3); 2.32 (s, 3 H, Ar-CH_3); 3.88 (q, 1 H, CHCO); 4.47 (dd, 1 H, 1 H, CHS); 5.89 (m, 1 H, CHO); 6.8–7.4 (m, 14 H_{arom}).

(1*S*,2*R*,2′*R*)-**10b**:

$C_{27}H_{23}F_7O_2S$ (544.52) calc. C 59.55 H 4.26; found 59.23 4.03

^{1}H-NMR ($CDCl_3$): δ = 1.57 (d, 3 H, *J* = 7.0 Hz, CH_3); 2.32 (s, 3 H, Ar-CH_3); 3.80 (q, 1 H, CHCO); 4.41 (t, 1 H, *J* = 3.5 Hz, CHS); 5.91 (m, 1 H, CHO); 6.8–7.5 (m, 14 H_{arom}).

(1*R,2*S**)-1-Phenyl-3,3,3-trifluoro-1,2-epoxypropane (11):**
To a solution of **8a** (4.0 g, 12.80 mmol) in CH_2Cl_2/CH_3NO_2 (1:1, 50 mL), trimethyloxonium tetrafluoroborate (2.85 g, 19.25 mmol) is added in one portion under argon at −5 °C. Stirring is maintained for 10 min after reaching room temperature (20 min). Solvent is removed under reduced pressure at 20 °C, the crude sulfonium salt is dissolved in DMF (120 mL), and NaH (55% mineral oil dispersion, 1.12 mg, 25.6 mmol) is added at −45 °C. The temperature is left to raise at 10 °C (50 min), stirring is continued for 10 min, then a sat. aq. solution of NH_4Cl (100 mL) and water (100 mL) are added at −20 °C. The reaction products are extracted with ether (3 × 20 mL), the organic layers are collected, dried (Na_2SO_4), and the solvent is removed. The residue is distilled on a Büchi Kugelrohr apparatus (80 °C/67 mbar) to give **11** as a pure oil.

$C_9H_7F_3$ (188.2) calc. C 57.45 H 3.75; found 57.79 4.03

^{1}H-NMR ($CDCl_3$): δ = 3.50 (dq, 1 H, $^3J_{H,H}$ = 21.8 Hz, $^3J_{H,F}$ = 5.3 Hz, $CHCF_3$); 4.12 (d, 1 H, CHPh); 7.2–7.5 (m, 5 H_{arom}).

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(1) Homochiral fluoroorganic compounds, 9; for parts 8 and 7 see references 2 and 3, respectively.
(2) Bernardi, R., Bravo, P., Cardillo, R., Ghiringhelli, D., Resnati, G. *J. Chem. Soc. Perkin Trans. 1*, (M), **1988**, 1701; (S), **1988**, 216.
(3) Bravo, P., Ganazzoli, F., Resnati, G., De Munari, S., Albinati, A. *J. Chem. Res.*, (*M*), **1988**, 1701; (*S*), **1988**, 216.

(4) Bravo, P., Piovosi, E., Resnati, G. *Synthesis* **1986**, 579.
Bravo, P., Piovosi, E., Resnati, G., De Munari, S. *Gazz. Chim. Ital.* **1988**, *118*, 115.
(5) Bravo, P., Resnati, G. *J. Chem. Soc. Chem. Commun.* **1988**, 218.
Bravo, P., Resnati, G. *Tetrahedron Lett.* **1987**, *28*, 4865.
(6) Posner, J.H., in: *The Chemistry of Sulfones and of Sulfoxides*, Patai, S., Rappoport, Z., Stirling, C. (eds.), Wiley, New York, 1988, p. 823.
Unsubstituted β-keto sulfoxides: Solladie, G., Frechou, C., Demailly, G. *Tetrahedron Lett.* **1986**, *27*, 2867.
α-Substituted β-ketosulfoxides: Ogura, K., Fujita, M., Inaba, T., Takahashi, K., Iida, H. *Tetrahedron Lett.* **1983**, *24*, 503.
Guanti, G., Narisano, E., Pero, F., Banfi, L., Scolastico, C. *J. Chem. Soc. Perkin Trans. 1* **1984**, 189.
(7) The sodium borohydride reduction of (*R*)-**1a** has already been described: Yamazaki, T., Ishikawa, N., Iwatsubo, H., Kitazume, T. *J. Chem. Soc. Chem. Commun.* **1987**, 1340.
(8) A mixture of diastereoisomers of anhydrous ketone and of hydrated form was used. Under the basic and protic reaction conditions here adopted in the reduction, 1-sulfinylalkyl ketones undergo rapid diastereoisomer equilibration through enolization.[6]
(9) The configuration of the isolated alcohols show the chirality at the sulfur stereocenter has no influence of the steric course of the reduction of these 1-phenyl-1-arylsulfinylalkyl ketones as the process seems to be controlled by the chirality at the carbon stereocenter. Different explanations have been suggested for this type of behavior.[6]
(10) Drabowicz, J., Oae, S. *Synthesis* **1974**, 107.
(11) Bravo, P., Resnati, G., Viani, F., Arnone, A. *Tetrahedron* **1987**, *43*, 4635.
Tsuchihashi, G., Iruchijma, S., Ishibashi, M. *Tetrahedron Lett.* **1972**, 4605.
(12) Raban, M., Mislow, K. *Tetrahedron Lett. 1965*, 4249.
(13) Helmchen, G. *Tetrahedron Lett.* **1974**, 1527.
(14) Helmchen, G., Volter, H., Schuhle, W. *Tetrahedron Lett.* **1977**, 1417.
Helmchen, G., Nill, G., Flockerzi, D., Schuhle, W., Youssef, M.S.K. *Angew. Chem.* **1979**, *91*, 64; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 62.
(15) Helmchen, G., Schmierer, R. *Angew. Chem.* **1976**, *88*, 770; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 703.
(16) The configuration assignment of (−)-**3a**, based on ^{1}H-NMR analysis of the esters obtained from the (*R*)- and (*S*)-2-phenylpropionic acids, was firmly established by the following chemical correlation. Compound (−)-**5a** was esterified with (*R*)- and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) following the procedure similar to the preparation of esters **10a, b**.
*(S)-MTPA ester of (R)-***5a**:
^{1}H-NMR ($CDCl_3$): δ = 2.34 (s, 3H, CH_3); 2.99 (dd, 1H, $^2J_{H,H}$ = 14 Hz, $^3H_{H,H}$ = 10 Hz, CHS); 3.25 (dd, 1H, $^3J_{H,H}$ = 2 Hz, CHS); 3.62 (q, 3H, *J* = 1.5 Hz, OCH_3); 5.51 (m, 1H, CHO); 7.1–7.6 (m, 9 H_{arom}).
*(R)-MTPA ester of (R)-***5a**:
^{1}H-NMR ($CDCl_3$): δ = 3.35 (s, 3H, CH_3); 3.07 (dd, 1H, $^2J_{H,H}$ = 14 Hz, $^3J_{H,H}$ = 11 Hz, CHS); 3.28 (dd, 1H, $^3J_{H,H}$ = 2.5 Hz, CHS); 5.50 (m, 1H, CHO); 7.1–7.7 (m, 9 H_{arom}).
Removal of the *p*-tolylthio residue (with Raney-Ni, similar to the preparation of **9**) from the esters thus obtained gave the two diastereoisomeric MTPA-esters of 1,1,1-trifluoro-2-propanol, whose ^{1}H-NMR chemical shifts were those reported by Mosher[17] for the same compounds. Both the (2*R*,R_S)-1-(4-methylphenyl)sulfinyl-3,3,3-trifluoropropan-2-ol **(3a)** and its (2*S*,R_S)-isomer have been recently described;[7] however in that paper the absolute configurations of these products have been mistyped (personal communication by Prof. T. Kitazume).
(17) Dale, J.A., Dull, D.L., Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.
(18) Durst, T., Viau, R., Van Den Elzen, R., Nguyen, C.H. *J. Chem. Soc., Chem. Commun.* **1971**, 1334.
Farnum, D.G., Veysoglu, T., Cardè, A.M., Cardè, R.T. *Tetrahedron Lett.* **1977**, 4009.
(19) Tain Lin, J., Yamazaki, T., Kitazume, T. *J. Org. Chem.* **1987**, *52*, 3211.
(20) Bucciarelli, M., Forni, A., Moretti, I., Torre, G. *Synthesis* **1983**, 897.
(21) Seebach, D., Renaud, P., Bernd Schweizer, W., Zuger, M.F., Brienne, M.J. *Helv. Chim. Acta* **1984**, *67*, 1843.
(22) Hanzawa, Y., Kawagoe, K., Ito, M., Kobayashi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1633.
(23) Koenig, K.E., Bachman, G.L., Vineyard, B.D. *J. Org. Chem.* **1980**, *45*, 2362.
(24) Solladie-Cavallo, A., Suffert, J. *Synthesis* **1985**, 659.