Homochiral α-Fluoroketones from Racemic α-Fluorocarboxylic Esters and Enantiomerically Pure Sulphoxides

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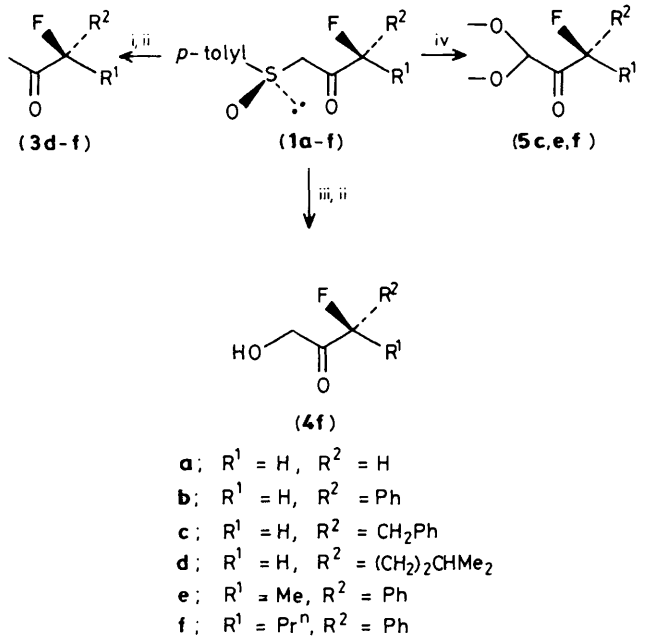
The α-fluoroalkyl ketones (**3**—**7**) carrying an alkyl, alkenyl, hydroxymethyl, or formyl residue were obtained in enantiomerically pure form by removing, by various methods, the auxiliary sulphinyl group from the α-fluoro α′-sulphinyl ketones (**1**) and (**2**) derived from chiral sulphoxides and commercially available α-fluorocarboxylic acids.

The fluoroalkyl sulphinyl ketones of type (**1**) and (**2**), key precursors in the syntheses of the α-fluoroalkyl ketones (**3**—**7**), were prepared either by acylation of the lithium derivative of (+)-(*R*)-alkyl *p*-tolyl sulphoxides by racemic α-fluorocarboxylic esters, or by a regioselective alkylation at the fluorinated, or sulphur-substituted, centre of preformed α-fluoro α′-sulphinyl ketones (*via* the α,α′-dilithium or α-monosodium derivative, respectively).[1] Compound (**1b**) (Scheme 1) was formed in quantitative yields by condensation of the α-lithium derivative of (+)-(*R*)-methyl *p*-tolyl sulphoxide with methyl α-fluorophenyl acetate. Similarly, (**2a**) was prepared from (+)-(*R*)-isopentyl sulphoxide and ethyl fluoroacetate.† Compounds (**1c** and **d**) and (**1e** and **f**), having a secondary and tertiary fluorinated carbon, were obtained in good yields and moderate diastereoselection,‡ from (**1a**) and (**1b**), respectively, by forming the corresponding α,α′-dilithium derivative with lithium di-isopropylamide [2 equiv. in tetrahydrofuran (THF); −78 °C], followed by addition of the appropriate alkyl halide. In all the cases examined the single diastereoisomers were obtained in pure form by flash chromatography or recrystallization, were fully characterized, and stored for several months without loss of optical purity. Finally, the compounds (**2b** and **c**), also carrying a substituent

† An equimolar mixture of the two epimers at the fluorinated (**1b**) or sulphur-substituted atom (**2a**) was obtained.

‡ The diastereoselectivity of the process depended on the substrate and on the alkylating agent employed and was not determined by the chirality of the carbon to be alkylated, but by that of the sulphinyl residue. For instance, the $(3S,R_S):(3R,R_S)$ ratio was 7:3 for (**1d**) prepared from (**1a**), and 2:8 for (**1e**) from (**1b**).



Scheme 1. *Reagents and conditions:* i, NaI–$(CF_3CO)_2O$–acetone, −40 °C; ii, Raney Ni, EtOH; iii, $(CF_3CO)_2O$–2,4,6-trimethylpyridine–CH_2Cl_2, −20 °C; iv, I_2, MeOH, heat.

Table 1. Yields and optical rotations of α-fluoroketone products (**3**—**7**).

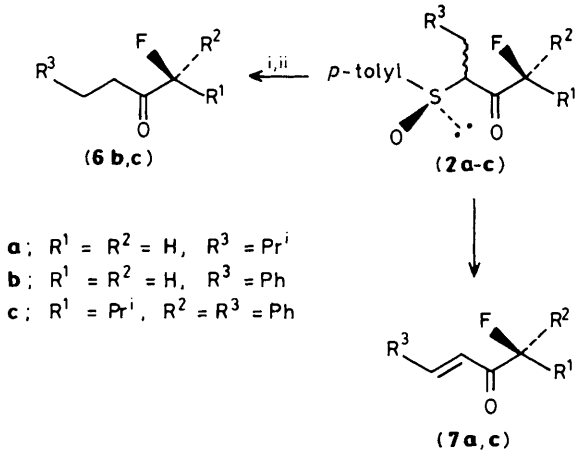
Product	R^1	R^2	Yield/%	$[\alpha]_D^{20}$/°(*c*, CHCl
(*S*)-(**3d**)	iso-C_5H_{11}	H	69	−87.6 (0.44)
(*S*)-(**3e**)	Ph	Me	73	−188 (0.8)
(*S*)-(**3f**)	Ph	Pr^n	71	−184 (1.1)
(*R*)-(**4f**)	Pr^n	Ph	44	+43.0 (0.45)
(*S*)-(**5c**)	CH_2Ph	H	86	+53.1 (1.1)[b]
(*S*)-(**5e**)	Ph	Me	88	−101 (1.1)
(*R*)-(**5f**)	Pr^n	Ph	89	+95.7 (1.1)
(**6b**)[c]	H	H	70	
(*R*)-(**6c**)[c]	Pr^n	Ph	73	+77.1 (1.1)
(**7a**)[d]	H	H	86	
(*S*)-(**7c**)[c]	Ph	Pr^n	88	+66.3 (0.8)

[a] With respect to (**1**) or (**2**). [b] Value obtained at 435 nm. [c] R^3 = Ph. [d] R^3 = Pr^i.

on the sulphinylated carbon, were prepared[2] in 45 and 72% yields§ by treating the monosodium anion (NaH–THF–dimethylformamide) of enantiomerically pure (**1a**) and (**1f**) respectively, with benzyl bromide.

The chiral sulphinyl group was removed from the single epimers of the key precursors (**1**) and (**2**) by various methods: deoxygenation[3] of the sulphoxide residues of (**1d**—**f**) (Scheme 1) and (**2b** and **c**) (Scheme 2) [NaI–$(CF_3CO)_2O$] followed by hydrogenolysis of the resulting α-fluoro α′-sulphenyl ketone (Raney Ni, EtOH, heat), to give the alkyl α-fluoroalkyl ketones (**3d**—**f**) and (**6b** and **c**) in good overall yields (see Table 1); heating (**2a** and **c**)[3] in toluene afforded the alkenyl α-fluoroalkyl ketones (**7a, c**) by elimination of *p*-toluenesulphenic acid (Scheme 2); and by Pummerer rearrangement

§ Although single epimers could be obtained in pure form by crystallization, compounds (**2**) were also reacted as a mixture of the diastereoisomers at the sulphur-substituted atom, since on removal of the auxiliary group that atom lost its chirality.



Scheme 2. *Reagents and conditions:* i, NaI–$(CF_3CO)_2O$–acetone, −40 °C; ii, Raney Ni, EtOH, heat; iii, toluene, heat.

which provided the fluoroalkyl ketones (**4f**) and (**5c, e** and **f**) in which the sulphinyl group is replaced by oxygenated functions. Treatment of the 3-fluoro-1-sulphinylhexanone (**1f**) with $(CF_3CO)_2O$–2,4,6-trimethylpyridine[4] produced an α′-trifluoroacetoxy-α′-sulphenylhexanone intermediate which, on hydrogenolysis (Raney Ni, EtOH, room temp.), gave the 1-hydroxy-3-fluoro-3-phenylhexan-2-one (**4f**) (Scheme 1). By boiling (**1c, e** and **f**) in methanol solution in the presence of iodine,[5] the protected β-keto-γ-fluoro aldehydes (**5c, e** and **f**) were isolated.

Starting from the key precursors (**1**) and (**2**) in enantiomerically and diastereoisomerically pure form, all the sulphur-free α-fluoroketones (**3**—**7**) were obtained in optically pure form and in good yields (see Table 1). No loss of chirality was observed at the chiral carbon atom during removal of the sulphinyl group,¶ even when the starting material had a secondary fluorinated centre.

To the best of our knowledge, the reactions described here represent the first general synthesis of acyclic and homochiral α-fluoroketones,[6] key intermediates in the chemistry of organofluorine compounds[7] and compounds of interest for their biological activity.[8]

Received, 28th September 1987; Com. 1406

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¶ In ^1H n.m.r. spectra (300 MHz) of (**3**—**7**) in the presence of $Eu(hfc)_3$, {tris[3-(heptafluoropropylhydroxymethylene)-camphorato] europium(III)} splitting of the signals as exhibited by racemic samples was not observed; the absolute configurations at the fluorinated centres were assigned by *X*-ray analysis and ^1H and ^{19}F n.m.r. spectroscopy of the sulphinyl fluorhydrins formed by diastereoselective reduction of the carbonyl group.