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PREPARATION AND PROPERTIES OF CHIRAL FLUOROORGANIC COMPOUNDS

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I. INTRODUCTION

Selectively fluorinated chiral and non racemic molecules are commonly employed in analytical[1-4], biological[5-9], and medicinal[10-12] chemistry. Recently these compounds have become of interest also for the chemistry of polymers[13,14] and materials[15].

As an important area of research, several reviews and books have been published in recent years on fluoroorganic products. These reports deal either with the preparation of particular classes of compounds[16-27], or with the reactivity of some fluorinated agents[28-34], or with the applications of some fluorinated substances[8,9,19,24,35-38]. In no case has attention been focused specifically on chiral fluoroorganic compounds and these products will be the subject of the present review.

The asymmetric fluorination of complex and multifunctional chiral compounds by simple substitution for another functional group (e.g. in steroids and sugars) has been treated in several recent monographs. This report will be devoted to the complementary methodologies. The employment of chiral reagents on simple prochiral fluorinated substrates, the chemical or biochemical resolution of racemic mixtures of fluoroorganic molecules and the use of the so obtained chirons to prepare more complex substances will be described.

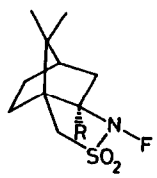
All the material presented in this monograph has been organized according to the synthetic method employed to prepare the chiral organofluorine substance. The reason for which the fluorine was introduced, the effects brought about by such an introduction, and selected applications of the chiral fluoroorganic compounds will be briefly discussed after the synthesis of the product.

Greater emphasis is given to more recent results.

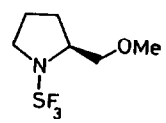
II. CHEMICAL METHODS

II.1. Chiral and non-chiral fluorinating reagents

The efforts to find new, mild, and selective fluorinating reagents led to the development of N-F compounds as substitutes for the potentially hazardous O-F ones. As a source of electrophilic fluorine, the two camphor derived N-fluoro sultams **1a,b** were prepared and used to synthetize α-fluorocarbonyl compounds from the corresponding metal enolates[39]. Medium to low enantioselectivites and yields were obtained. Complementarily, as a source of nucleophilic fluorine, the proline derived aminofluorosulfurane **2** was synthesized[40]. It performed enantioselective fluorodehydroxylation of racemic silylated alcohols *via* kinetic resolution, but the e.e.s were low.



	R
1a	H
b	CH_3



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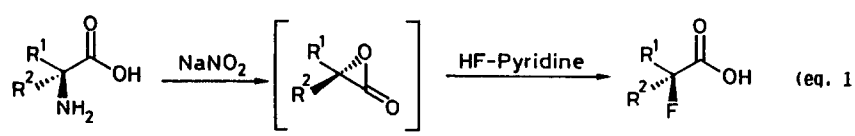
Fluorodehydroxylation of simple chiral secondary alcohols was performed with polymer-supported fluoride anions[41], potassium fluoride under phase-transfer conditions[42], or N,N-diethyl-hexafluoropropylamine[43,44] with high to medium stereospecificity with inversion of configuration (S_N2 process) being obtained.

Fluorodeamination of α-aminoacids with retention of configuration was realized by using HF-pyridine and sodium nitrite (eq.1). The stereochemical course was ascribed to the anchimeric assistance of the carboxylate group to give an intermediate α-lactone[45-48].



(eq. 1)

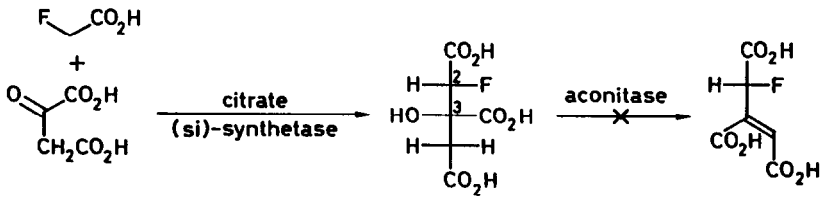
	R^1	R^2
3a	cyclohexyl-CH_2	H
b	H	CH_3
c	CH_3	H
d	D	H

The so obtained (S)-2-fluoro-2-cyclohexylpropionic acid (**3a**) was transformed into a 16-F-prostaglandin[49] and (R)- and (S)-2-fluoropropionyl fluorides were employed to establish the stereochemical course of halogen for halogen substitution in the gas phase (homolytic substitution $S_{HH}2$)[50-52].

Interestingly, some other α-fluorocarboxylic acids were used to establish the stereochemical course of plasmid coded fluoroacetate halidohydrolase. Fluoroacetate is produced by several higher plants[53-55], but it is a highly toxic substance. Various bacteria are resistant to fluoroacetate and a fluoroacetate specific halidohydrolase, H-1, catalysing the detoxification of fluoroacetate to glycolate was isolated from *Pseudomonas sp.*, strain A.

Incubation of (R)- and (S)-2-fluoropropionic acid (**3b,c**) and of (S)-[2-$^2H_1$]-fluoroacetic acid (**3d**) with this enzyme supports a direct displacement mechanism for the detoxification reaction as inversion of configuration was observed[56].

The toxicity of fluoroacetic acid (and other ω-fluorocarboxylic acids which can be transformed to it through catabolism) is due to the fact that the enzymes of the tricarboxylic acid cycle (citric acid cycle) utilize fluoroacetate. *In vivo* and *in vitro* citrate (*si*)-synthetase catalyses the stereosepecific abstraction of the *pro*-S proton from fluoroacetyl-CoA and the condensation of the so formed anion on the *si* face of oxaloacetate to give (2R,3R)-fluorocitric acid (**4**)[57-62] (Scheme 1). This stereoisomer, which is much more toxic than the other three possible ones, inhibits the citrate transport in mitocondria[61-65] and blocks the citric acid cycle by inhibiting the enzyme aconitase. In fact, some yeasts resistant to fluoroacetate overproduce aconitase. Probably, the -I effect of the fluorine atom plays a role in inhibiting the dehydration by aconitase on fluoro-citric acid **4** to give fluoro-aconitic acid **5**. The cycle is thus disrupted by the "lethal synthesis" of an antimetabolite. The implications for the rational design of enzyme inhibitors by fluorine introduction in a naturally occurring compound were exploited shortly after the molecular mechanism for fluoroacetate toxicity was elucidated.



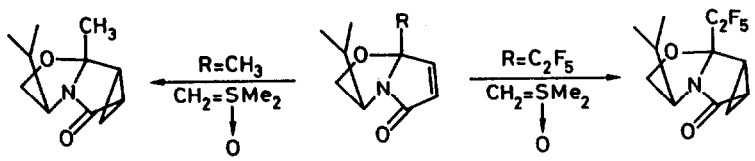
Scheme 1

II.2. Chiral substrates and reagents

Carbon-Carbon bond forming reactions When the approach of the chiral auxiliary is employed in order to generate a chiral centre in a molecule, a homochiral residue (chiral auxiliary) is bound to the substrate compound. A diastereoselective reaction is performed on the thus formed adduct, with the configuration of the chiral centre formed in the product being controlled by the stereocentres of the auxiliary agent. Finally, the auxiliary agent is removed. This approach has been employed successfully in the synthesis of several mono- and poly-fluorinated

compounds. The source of the fluoroorganic residue was either a fluoroalkyl halide (eq. 2,3,5) or a fluorocarbonyl compound (eq. 4,6-14).

The addition of pentafluoroethyl lithium to a N-valinol imide afforded the pentafluoroethyl chiral aminal **6a**[66]. The fluorinated chain was introduced to test if, according to the "Cieplack stereoelectronic effect", this highly electronegative residue induced the opposite stereoselection with respect to that observed for the unfluorinated analogue **6b**. However, the same stereoselectivities were observed (eq.2) thus casting some doubts on the generality of the "Cieplack" effect.



(eq. 2)

d.e. 97%

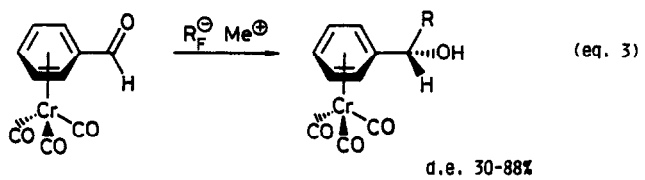
R

6a C_2F_5

b CH_3

d.e. 90%

The same pentafluoroethyllithium species[67-70] and some perfluorozinc derivatives[71] have been added with good diastereoselection to enantiomerically pure arene-chromium tricarbonyl aldehydes (eq.3). Some of the thus obtained complexed alcohols 7 proved to be good inducers of chirality in the Prelog-type asymmetric synthesis of α-hydroxy acids[67,71,72].

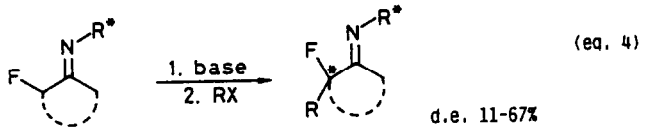


(eq. 3)

d.e. 30-88%

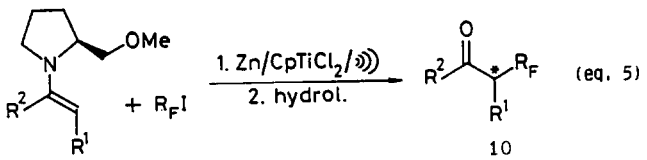
7

The lithium anions of α-fluoro imines **8**, obtained from racemic α-fluoroketones and chiral amines, were stereoselectively alkylated (eq.4) by using alkyl halides[73]. Similarly, a perfluoroalkyl chain was introduced α to a carbonyl group by resorting to chiral enamines derived from prolinol (eq.5)[74-76]. Treatment of **9** with a perfluoroalkyl iodide in the presence of Cp_2TiCl_2, Zn powder, and ultrasound afforded the corresponding α-perfluoroalkyl ketones **10**.



(eq. 4)

8



(eq. 5)

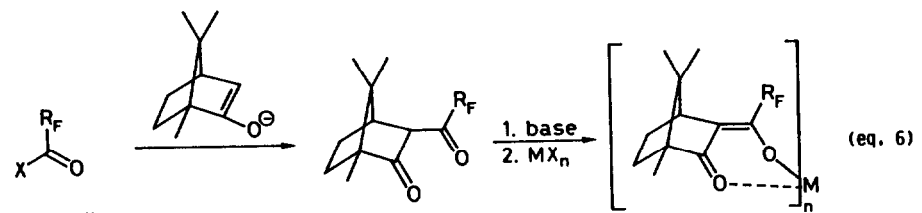
9

10

e.e. 54-76%

The introduction of a perfluoroacyl chain α to a carbonyl group produced fluorinated β-dicarbonyl compounds which are in general endowed with several interesting properties[24].

The commonly employed chiral shift-reagents **12b,c** belong to this class of products. They are obtained by treating the enolate of camphor with a perfluorocarboxylic ester or chloride **11a,b** to give the perfluoroalkyl β-diketones **12a** (eq. 6). These compounds are then treated with a lanthanide halide (or nitrate) in basic protic medium[77-79]. In non-polar solvents[80] the europium, praseodimium, and ytterbium trisdiketonates **12b,c** interact with donor sites of organic substrates and the diastereomeric adducts formed in the presence of non-homochiral substrates show in general different NMR spectra (^1H, ^{13}C, ^{19}F...). It becomes thus possible to determine the enantiomer ratios and sometimes the absolute configurations of analyzed compounds. The procedure is a routine one and it has been employed, for instance, on alcohols, amines, ethers, ketones, esters, sulphoxides.



(eq. 6)

	X
11a	OEt
b	Cl

12a

	R_F	M	n
12b	CF_3	Eu,Pr,Yb	3
c	n-C_3F_7	Eu,Pr,Yb	3
d	n-C_3F_7	Ag	1
e	n-C_3F_7	Ni	2

In the presence of both lanthanide and silver chiral shift-reagents, Pr-**12c** and **12d**, respectively, separation of resonances for enantiomeric olefin substrates was also observed[81] and the nickel(II) shift-reagent **12e** has been proposed as a stationary phase for gas chromatrographic resolution of racemic compounds[82].

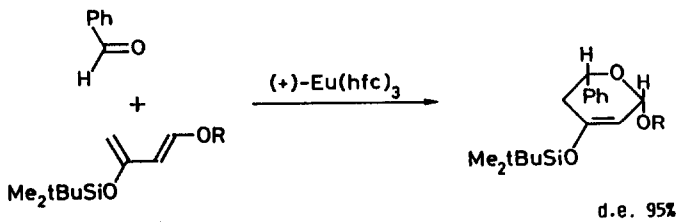
The presence of the perfluorinated chain in diketones **12a** increases their acidity with respect to corresponding unfluorinated compounds and this may contribute to their effectiveness.

Despite the fact that some other chiral shift-reagents have shown better resolving power[78], **12b,c** are those most commonly employed.

A more recent application of the lanthanide chiral shift-reagents is their use as chiral catalysts.

Eu-**12b,c** have been used as chiral Lewis acids for the asymmetric reduction of ketones with achiral NADH models[83], but low e.e.s were obtained.

Only medium enantiofacial selectivities were obtained when Eu-**12b** was used in cycloadditions of activated dienes with aldehydes, but the combination of chiral Eu-**12b** with chiral dienes exhibited striking interactivities (eq.7), resulting in diastereofacial excesses as high as 95%[84-89].

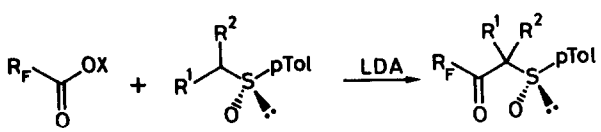


(eq. 7)

d.e. 95%

R = L-8-phenmenthyl

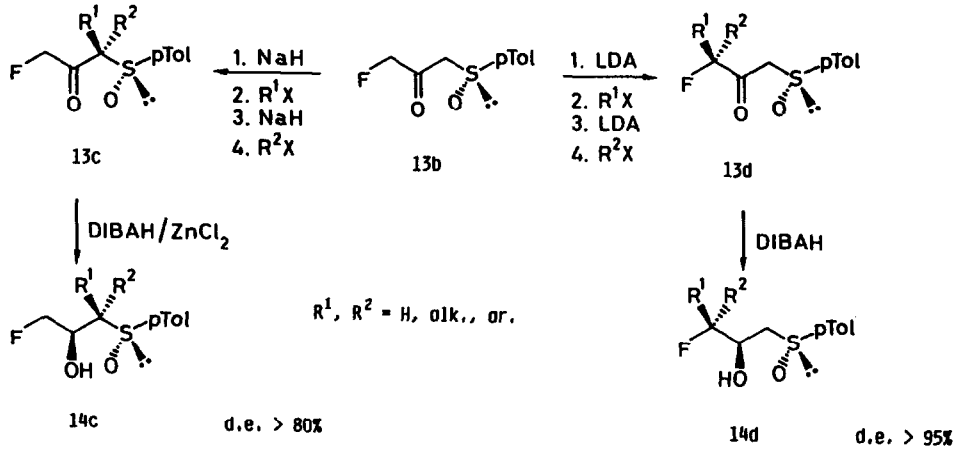
Mono- and poly-fluorocarboxylic esters or salts were used as the source of the fluoroorganic fragment in the synthesis of several homochiral 1-sulphinylalkyl-fluoroalkyl ketones **13** (eq.8)[90-95]. Alternatively, the mono-fluorinated sulphinyl ketones **13c** and **13d**, carrying alkyl residues on the sulphur- and fluorine-substituted carbons, respectively, were obtained through regioselective alkylation of the monosodium and the dilithium derivatives, respectively of the simplest form **13b** (Scheme 2). The carbonyl group of the monofluorinated compounds **13d** was reduced with high diastereoselection and the stereochemical course of the process was controlled by the configuration of the auxiliary sulphinyl group[96,97]. Under different reaction conditions a good diastereoselection could be obtained also in the reduction of the carbonyl group of fluoro-ketones **13c**[98].



(eq. 8)

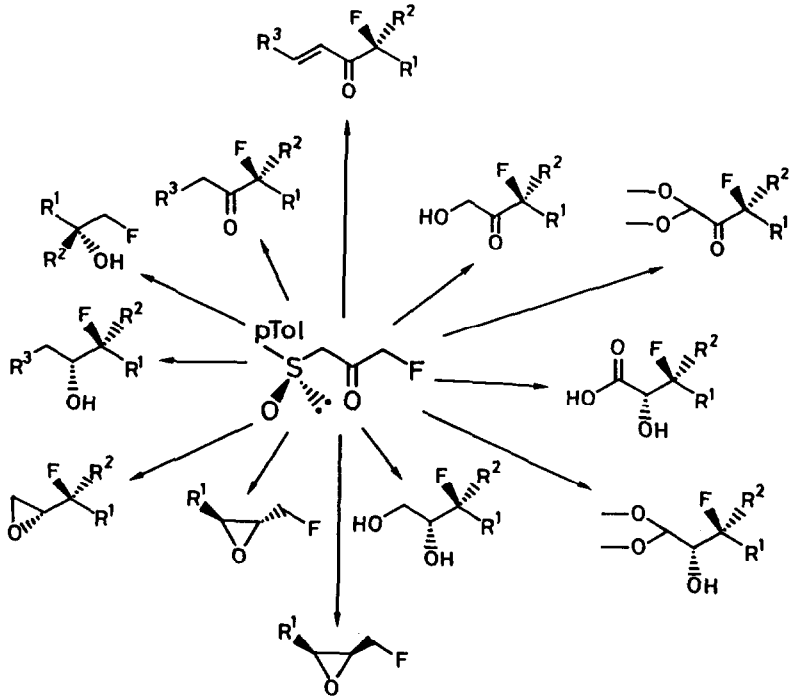
13a

R^1, R^2, = H, alk., ar.
X = Li, Na, alk.,
R_F = CH_2F, CHF_2, CF_2Cl, C_nF_{2n+1}, ...



Scheme 2

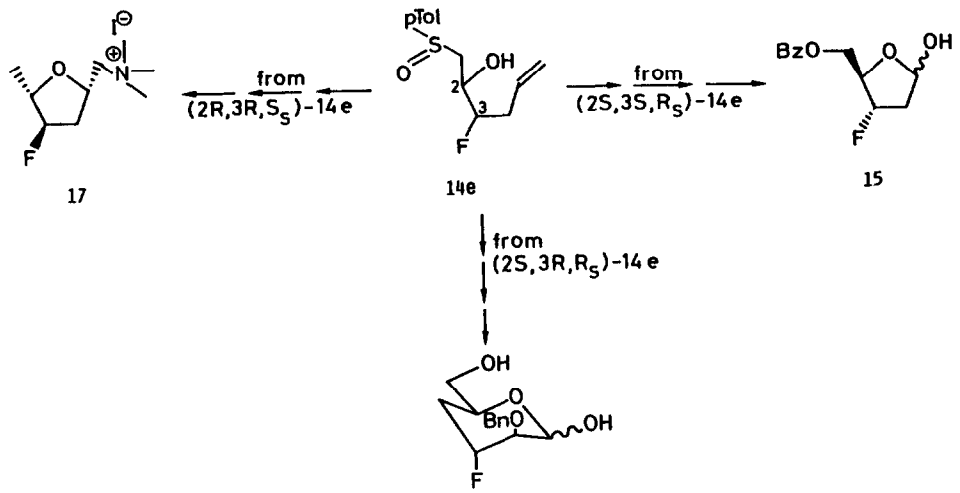
Different procedures for the removal of the auxiliary sulphinyl group from enantiomerically pure ketones **13** or alcohols **14** afforded several homochiral sulphur-free fluoroorganic compounds[99-102] (Scheme 3).



Scheme 3

The intramolecular attack of the oxygen of ketones **13** (in enolic form) or of alcohols **14** on a correctly positioned double bond present on side chains R^1or R^2 allowed several mono- and poly-fluorinated dihydropyrans, tetrahydropyrans, and tetrahydrofurans to be obtained in enantiomerically and diastereoisomerically pure form[103-105].

The homochiral fluoro-sulphinyl alcohols of type **14** were also used to prepare Mosher's acid[106,107] and some biologically interesting fluoroorganic compounds. Some acyclic nucleoside analogues were synthetized from **14d** ($R^1 = R^2 = H$ or $R^1 = H$, $R^2 = CH_3$)[108]. The dideoxy-monofluoro-ribofuranose **15**[109], the dideoxy-monofluoro-lyxopyranose **16**[110], the deoxy-fluoro-muscarine **17**[111], as well as other diastereoisomers of these sugars and alkaloids were synthetized in enantiomerically pure form (Scheme 4) starting from the homochiral fluoro-sulphinyl hexenol **14e** having the required absolute configurations. Nucleosides containing the furanose **15** proved to be highly active against HIV viruses[112,113] and different diastereoisomers of fluoromuscarine **17** showed activity similar to that of the parent, naturally occurring alkaloid[144].



17 14e 15

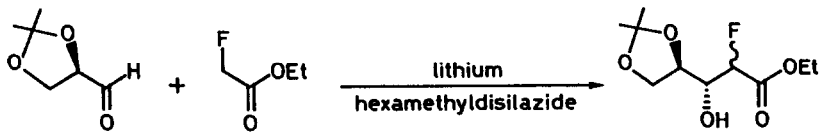
16

Scheme 4

In the cases described in eq. 6-8 the fluorocarbon framework of the chiral fluorinated products was afforded from fluorocarboxylic esters which worked as electrophiles in acylation reactions.

Some other cases will be considered below (eq. 9-14) in which the source of the fluorocarbon framework is still a fluorocarboxylic ester, but now the esters are used as nucleophilic species in Aldol-type reactions.

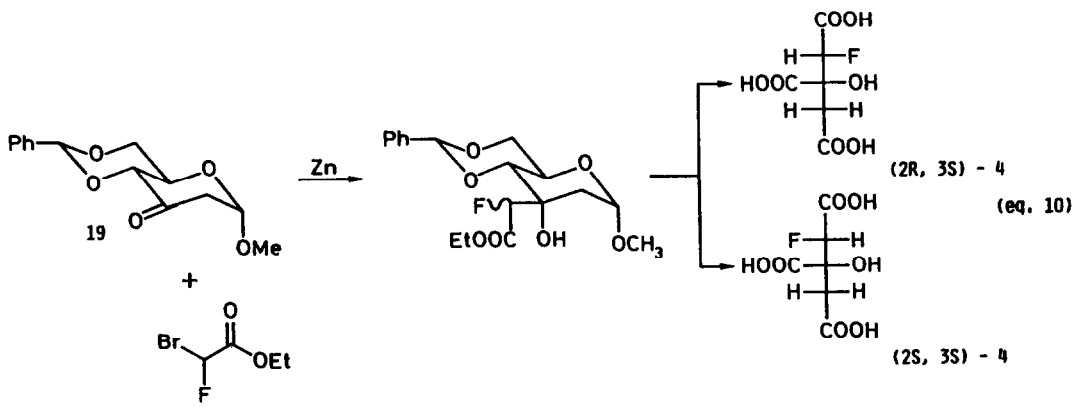
Ethyl fluoroacetate was transformed into its lithium enolate which added to D-2,3-0-isopropylidenglyceraldehyde acetonide **18a** (eq. 9) to give a nearly equimolar mixture of the two condensation products having the same configuration at the newly formed hydroxylated stereocentre, and opposite stereochemistries at the fluorinated carbons[115].



(eq. 9)

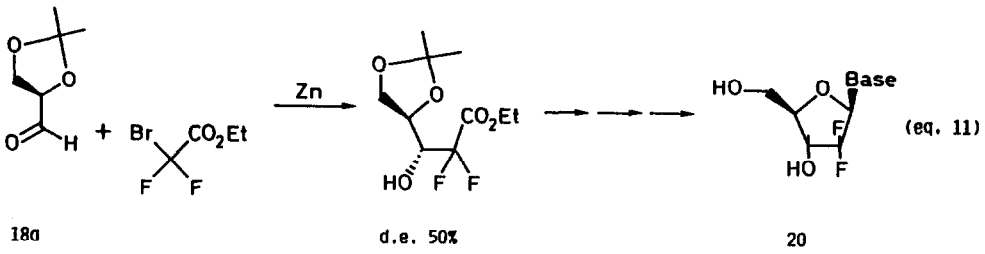
18a

Similarly, the Reformatsky reaction of ethyl bromofluoroacetate on the hexopyranoside-3-ulose **19** gave the two adducts deriving from the addition of the organozinc intermediate on the *re*-face of the ketone (eq. 10). The two isomers were isolated and separately elaborated to give (2S,3S)- and (2R,3S)-fluorocitric acid **4**[58].



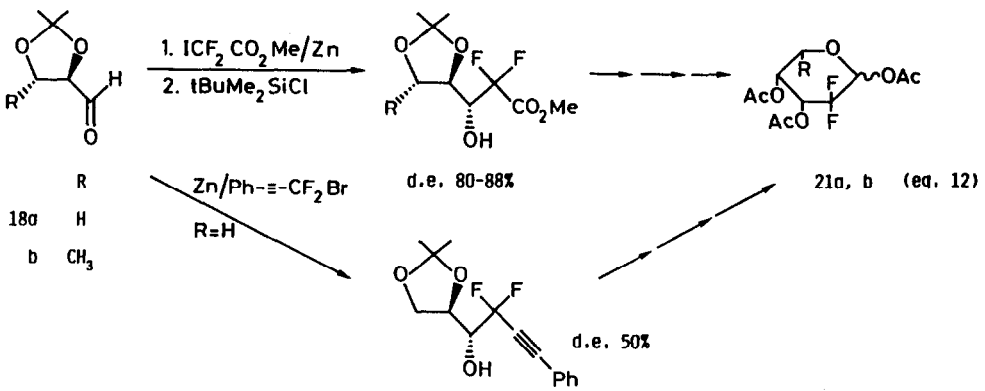
(eq. 10)

After the report of Fried[116] the Reformatsky reaction of ethyl bromodifluoroacetate on chiral aldehydes has become a frequently used methodology to prepare, in optically active form, the biologically interesting α,α-difluoro-β-hydroxyester moiety. Good chemical yields in the desired difluoro-hydroxy-esters were obtained by using glyceraldehyde acetonide **18a** as electrophilic species. The *anti* diastereoisomer formed preferentially[117] (eq. 11) and the stereochemical course of the reaction was rationalized according to Felkin's model. This isomer was transformed into 2-deoxy-2,2-difluoro-D-ribofuranosilnucleosides **20**.

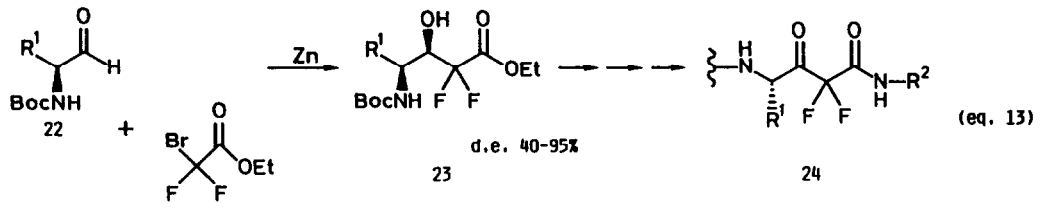


18a d.e. 50% 20

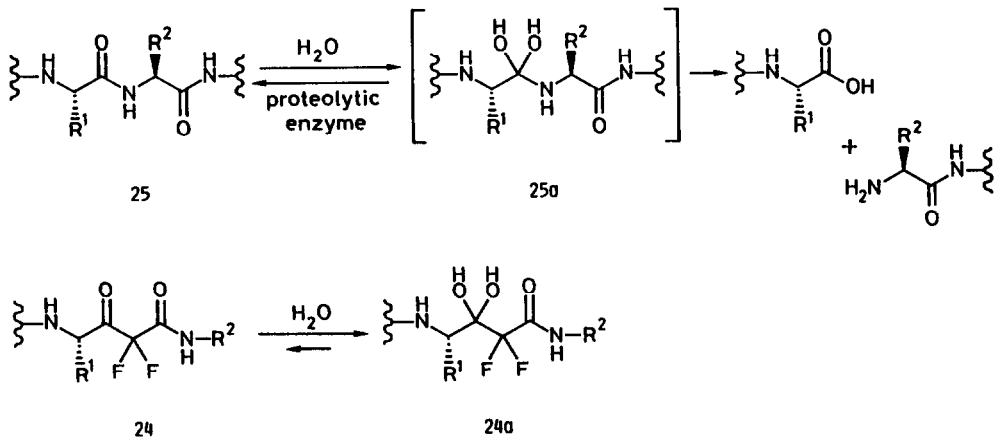
When methyliododifluoroacetate was used yields and diastereoselectivities were lower than those described above[118]. However, better results were obtained by transforming the organozinc intermediate into the corresponding trimethylsilyl ketene acetal[119]. In this way, starting from D-glyceraldehyde acetonide **18a** and 4-deoxy-L-threose acetonide **18b** the 2,2-difluoro-2-deoxy-D-ribopyranose **21a** and the 2,2-difluoro-2,6-dideoxy-L-galactopyranose **21b** were prepared effectively (eq. 12).



The pentose **21a** was synthesized also through the condensation of the zinc derivative of phenyl-bromodifluoromethylacetylene on **18a**, but the diastereoselection was lower[120]. When α-hydroxyaldehydes **18** were used in the Reformatsky reaction (eq. 11,12) the *anti* condensation products formed preferentially. In contrast, the formation of the *syn* compounds was favoured (eq. 13,14) when the α-aminoaldehydes **22** were used as electrophiles[121-123]. This stereochemical course was rationalized in terms of chelation of zinc halide by the amino-aldehyde.



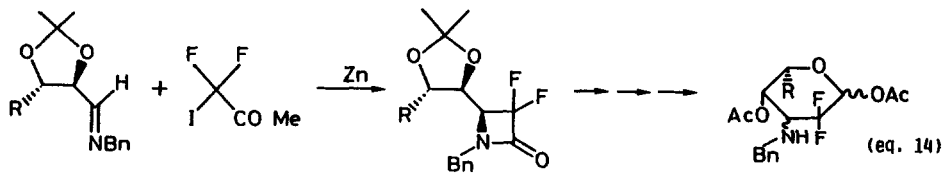
The α,α-difluoro-β-hydroxy-γ-amino esters **23** were thus obtained with medium to high diastereoselection and were transformed into the polypeptides **24** containing a difluoromethyleneketone moiety (eq. 13). These difluoropeptides proved to be effective inhibitors of several proteolytic enzymes. The general mechaism of enzymatic hydrolysis of the peptic bond is illustrated in Scheme 5.



Scheme 5

The rationale behind the use of the difluoropeptides **24** as inhibitors of proteolytic enzymes is that in cells the carbonyl group of **24** exists predominantly in the hydrated form **24a** as a consequence of the electron-withdrawing effect of fluorine atoms. The hydrated ketone **24a** is a structural mimic of the tetrahedral species **25a** formed during the enzymatic cleavage of the peptide substrate. Thus, in general, a compound containing a difluoroketone as a replacement for the enzymatically cleaved substrate amide bond might act as a "transition state analogue" inhibitor[124-125]. The nature of the R^1 and R^2 residues in **24** secure the target enzyme selectivity while the difluoromethylene ketone moiety causes enzyme inhibition.

Several hydrolytic enzymes have been inhibited effectively following this approach[122,123,126,127], for instance renin, a key-enzyme in some forms of hypertension[121,128-130].



R

26a H

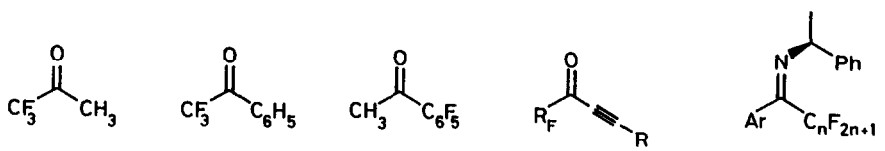
b CH_3

d.e. 51-62%

27 a,b

The Reformatsky reaction of methyl iododifluoroacetate on the benzylimines **26a,b** afforded α,α-difluoro-β-lactams which were elaborated to give the corresponding 2,2-difluoro-2,3-dideoxy-3-amino sugars **27a,b** (eq. 14). In this case too chelation between the imine and zinc halide was used to rationalize the preferential formation of *syn* lactams[131].

Oxido-Reduction reactions Several chiral alkyl-fluoroalkyl and aryl-fluoroalkyl secondary alcohols have been obtained through the asymmetric reduction of the corresponding ketones.



28a 28b 28c

R_F

28d CF_3

e CHF_2

f CH_2F

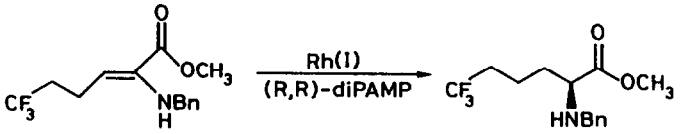
28e

1,1,1-Trifluoroacetone **28a** was reduced with chiral Grignard reagents[132] and α,α,α-trifluoroacetophenone **28b** was reduced with bornyloxyaluminium dichloride[133], and with various chiral dihydronicotinamides[134]. Some of these enzymatic models (NADH models) were shown to transfer enantioselectively a hydrogen atom to the fluorinated carbonyl and it has been suggested that the same reaction mechanism is operating *in vivo* during reductions performed by NADH dependent enzymes[135].

The methyl pentafluorophenyl ketone **28c** was reduced with a binaphtol-modified aluminium hydride reagent (BINAL-H) to give, with high enantiomeric excess, the corresponding alcohol which is a useful chiral derivatizing agent in gas chromatography and negative ion mass spectrometry[136].

The trifluoromethyl-alkynyl ketones **28d-f** were reduced with both BINAL-H and Alpine-borane[137]. For both reducing agents the enantioselectivity of the process was mainly determined by the nature of the R_F residue. The latter reagent gave higher e.e.s and it is interesting to observe that the former reducing agent gave preferentially the (R)-trifluoromethyl carbinol, but the (S)-difluoromethyl and (S)-fluoromethyl carbinols. This was ascribed to electronic repulsion between the trifluoromethyl group and the lone pair of binaphthoxyl oxygen of the reagent in a 6-centred cyclic transition state. This kind of reduction was employed in an asymmetric synthesis of an intermediate of 13,13-difluoroleukotriene B_4 [138].

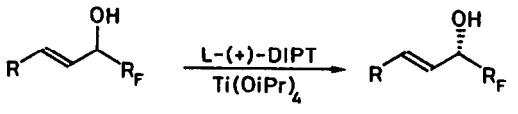
The acetate of methyl-trifluoromethyl carbinol was obtained with good e.e. through asymmetric hydrogenation of the enol-acetate of trifluoroacetone by using some rhodium(I) chiral phosphine complex catalysts[139]. The results obtained suggest that the presence of the electron withdrawing functionality (i.e. CF_3) gem to the acetoxy group, in addition to the olefin being able to chelate, increases e.e.s. The same reducing agent has recently been employed with good results in the synthesis of (S)-trifluoronorleucine methyl ester (eq. 15)[140].



(eq. 15)

e.e. 89%

The diastereoselective reduction of chiral perfluoroalkylaryl imines **28e** has been performed employing hydride reagents and the phenethyl auxiliary has been removed to prepare (S)-2,2,2-trifluoro-1-phenylethyl amine which was used as a chiral derivatizing agent[141].



(eq. 16)

e.e. 14-98

29 (S) - 29

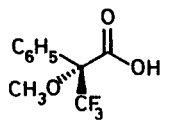
Finally, a single case of an oxidation reaction leading to a chiral fluoroorganic compound has been reported. The Sharpless epoxidation was used to kinetically resolve the fluoroalkyl-(E)-vinyl carbinols **29** (eq. 16). The kinetic preference in the asymmetric epoxidation of these fluoroalkyl substrates is the same as that of unfluorinated alcohols[142].

II.3 Chemical resolution

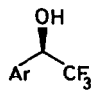
The formation and separation of diastereoisomeric derivatives of a racemic compound in order to resolve it into single pure enantiomers have been applied effectively to several fluoroorganic compounds.

Fluorocarboxylic acids were resolved through separation (via crystallization or chromatography) of esters[143-149], amides[150-155], or salts[13,148,156-162]. The same approach was employed for fluorinated alcohols[148, 163] and amines[164].

A particularly interesting case is the use of α-phenylethyl-amines for the resolution of α-methoxy-α-trifluoromethylphenylacetic acid **30** (Mosher's acid)[165,166]. This acid (whose absolute configuration has recently received a non-empirical confirmation)[167] is a chiral derivatizing agent[168-170] commonly employed to determine the enantiomeric excess and the absolute configuration of secondary and tertiary[171] alcohols and amines. The presence of the trifluoromethyl group contributes to the particular usefulness of **30** in the determination of optical purity as it allows the use of ^{19}F NMR[172]. Furthermore, it increases the volatility and solubility of ester and amide derivatives so that they can be analyzed and separated easily by GLC and HPLC.



(R) - 30



	R
(R)-31 a	phenyl
b	1-napthyl
c	9-anthryl

Another interesting example of resolution through formation of diastereoisomeric esters or salts is the obtainment of single enantiomers of trifluoromethyl carbinols **31a**[172-175], **31b**[176], and **31c**[177]. These alcohols are valuable chiral solvating agents commonly used in NMR spectroscopy[4]. In solution, alcohols **31** form diastereoisomeric solvates with several racemic substrates so that different signals can be obtained in the NMR spectra for the two enantiomers of the substrate. Particularly effective solvates may be formed with these alcohols as the strong electron withdrawing effect of the trifluoromethyl residue increases the ability of the hydroxyl proton to be involved in a hydrogen bond with a basic group of the substrate.

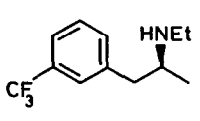
The optical purity and the absolute configuration of several chiral compounds have been determined in this way (e.g. amines[178,179] and phosphines[180], aminoacids[181], amino-oxides[182], oxaziridines[183,184], ethers[185], lactones[186-188], sulphoxides[189] and other sulphur derivatives)[190].

The phenyl- and 1-naphthyl-substituted alcohols **31a,b** have also been used as cosolvents in asymmetric synthesis. They were employed to prepare N-chloro-aziridines through asymmetric chlorination of the nitrogen atom of aziridines[191,192] and they were employed to synthetize oxaziridines both through oxidation of imines[193] and rearrangement of nitrones[194].

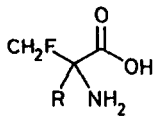
Other fluorinated compounds have been used as chiral derivatizing agents and chiral cosolvents (e.g. 1-pentafluorophenyl ethanol[136], α-methyl-α-methoxy-pentafluorophenylacetic acid[195,196], α-methoxy-α-trifluoromethyl-benzylisocyanate[197], α-fluorophenylacetic acid[48], [1-(9-anthryl-2,2,2-trifluoroethoxy]acetic acid[198], perfluoro-2-propoxypropionic acid[199], β-trifluoromethyl-β-methoxy-β-phenylethylamine[200], some trifluoromethylamines[156]), but they have found less wide application than those decribed above.

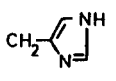
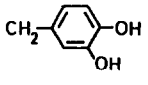
Another interesting approach to optical resolution is the preferential crystallization. A fundamental prerequisite for this kind of resolution is that the D,L form be a racemic mixture (conglomerate, i.e. an eutectic mixture of D and L crystals) and not a racemic compound.

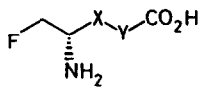
Fenfluramine **32** is a safe and effective anorectic drug. The activity is predominantly due to the (S)-(+)-enantiomer[201] which has been resolved through preferential crystallization of salts with a non-chiral acid[202,203].



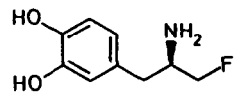
(S) - 32



	R
33a	D
b	H
c	
d	



	X - Y
35a	CH_2-CH_2
b	CH=CH



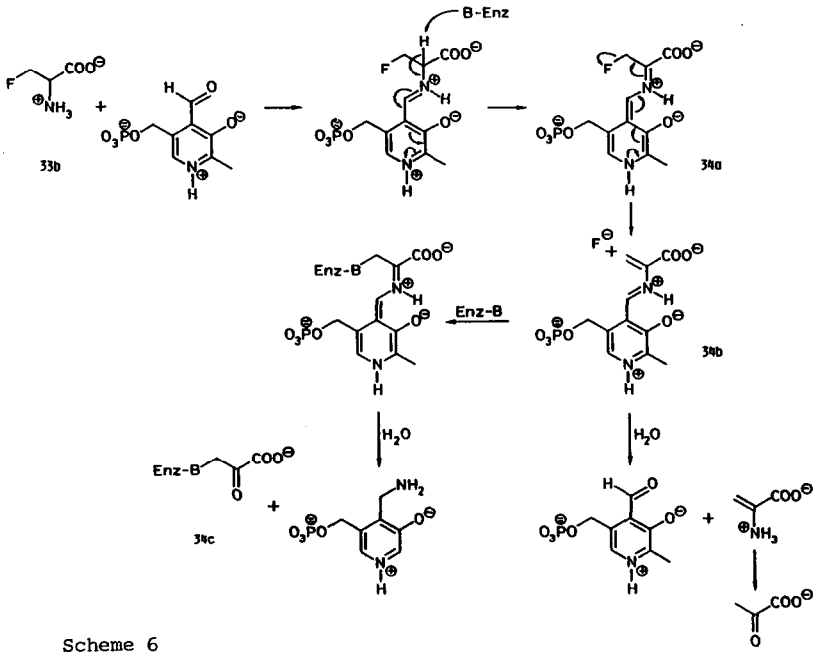
36

Similarly, a continuous resolution by preferential crystallization of the benzenesulfonate salt of 3-fluoro-D,L-alanine-2d **33a** afforded both the D and L enantiomers with an optical purity of 99% and recoveries of 93-99% of the theoretically obtainable pure isomer[158,204,205].

Interest in this fluoroaminoacid is due to the fact that, although both the enantiomers display a high degree of antibacterial activity, the D form is at least ten times less toxic than the L one[206].

The antibacterial activity of fluoro-deuterio-alanine **33a** is a consequence of the blockade of cell-wall biosynthesis. It works as an antimetabolite of D-alanine[207] which is a constituent of bacterial cell walls, but which does not play a role in human metabolism. Fluoroalanine **33b** was in fact found to be a mechanism-based irreversible inhibitor (suicide-substrate inactivator) of bacterial alanine racemase[208], the pyridoxal-phosphate dependent enzyme which provides bacteria for D-alanine by racemizing L-alanine. Subsequently, deuteriofluoroalanine **33a** was developed to enhance the *in vivo* stability of **33b** by exploitation of a $^2H/^1H$ isotope effect.

The proposed mechanism of enzyme inactivation (Scheme 6) clearly shows how fluorine plays a key-role in generating a highly selective and efficient inactivator. In general, the fluorine atom is not a good leaving group and so fluoroalanine **33b** can reach *in vivo* the active site of the target enzyme without being blocked (as occurs to indiscriminate alkylating species) by the numerous nucleophiles existing in cells.



Scheme 6

Fluoro-deuterio-alanine **33a** is very similar, from a steric and electronic point of view, to alanine, the natural enzyme substrate, and so the normal reaction sequence usually performed by alanine racemase is started on the fluorinated analogue. Abstraction of the α-proton of the aminoacid occurs to give the intermediate species

34a in which, formally, a negative charge is located β to the fluorine atom. Fluorine thus becomes a good leaving group just in the active site of the target enzyme. It exits as a fluoride ion producing the alkylating species **34b** which may evolve to give the inactivated enzyme **34c**.

The two enantiomers of β,β-difluoroalanine were shown to behave in a similar manner[209] and several other chiral fluoroaminoacids[210-212] (e.g. (S)-4-amino-5-fluoropentanoic acid[213-219] **35a** and (S,E)-4-amino-5-fluoro-2-pentenoic acid **35b**[220,221]) proved to be stereospecific and pharmacologically useful enzyme inhibitors.

α-Fluoromethylhystidine **33c** inhibits pyridoxal phosphate dependent decarboxylation of L-hystidine to hystamine, elevated levels of which are involved in allergy, gastric ulcers, and inflammation[222-224]. The activity resides in the (S) enantiomer as the (R) one is non-inhibitory. It is interesting to observe that α-chloromethylhystidine shows a good inhibitory activity against histidine decaboxylase *in vitro*. However, in contrast to its fluoro analogue, this compound is less stable in the presence of nucleophiles and, consequently, its *in vivo* activity as enzyme inhibitor is short-lived and low.

(R)-α-Fluoromethyldopa **33d** is inactive against dopa-decarboxylase, but the (S)-isomer is an effective mechanism-based inhibitor of that enzyme. A mechanism similar to the one reported in Scheme 6 for fluoroalanine has been proposed to rationalize the inactivation of dopa-decarboxylase by **33d**. (R)-Fluoromethyl-dopamine **36** inhibits irreversibly the same enzyme, and the (S)-enantiomer binds to the enzyme without causing inactivation[225,226].

Only the (-)-enantiomer of α-difluoromethyl ornithine is an irreversible inhibitor of mammalian ornithine decarboxylase, the enzyme which catalyzes the conversion of L-ornithine into putrescine, a polyamine implicated in rapid cell division including tumor growth[227,228].

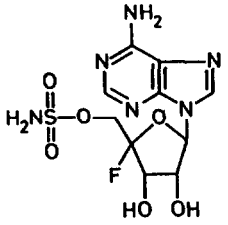
III. ENZYMATIC METHODS

III.1. Growing microorganisms

Fluorine is not an abundant element in the environment and in contrast to the other halogens the fluoride ion cannot be activated by enzymes *via* oxidation. These facts may in part account for the low number of fluoroorganic compounds isolated from living organisms. However, bacteria and higher plants are known to produce spontaneously fluorometabolites thus showing that organofluorine products are not xenobiotic substances[7]. Fluoroacetic acid, other saturated and unsaturated ω-fluorocarboxylic acids and fluoroacetone were isolated from plants growing in Africa, South America, Australia.

More interestingly, the normal metabolism of several plants leads to formation of fluorocitric acid starting from endogenous fluoroacetate. The biosynthesis, catalyzed by citrate (*si*)-synthase, is enantio- and diastereoselective, the (2R,3R)-fluorocitric acid **4** being formed with great preference over the other stereoisomers. The same enzyme accepts also fluorooxaloacetate as a substrate and in this case too the preferential formation of one of the four possible stereoisomers of fluorocitric acid was observed[60,61]. Also the catabolism of the two enantiomers of *erythro*-fluorocitric acid is different[57,59].

Two other chiral and naturally occurring compounds are nucleocidin **37**, a nucleoside carrying a fluorine atom in 4' position and endowed with anti-trypanosomal activity[229], and (-)-4-fluorothreonine **38** which showed antimicrobial activity[230].



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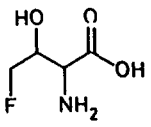
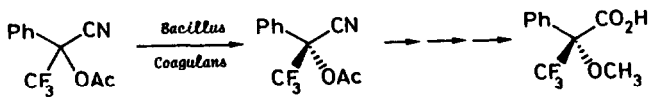


(-) - 38

Otherwise, partially fluorinated compounds can be metabolized by living organisms and when an organofluorine product is given to a living organism it often happens that chiral fluorinated metabolites (catabolites) can be isolated[231-233]. For instance, (+)-fluorosuccinic acid was obtained as a *Pseudomonal* metabolite of p-fluorophenylacetic acid[47] and (R)-α-fluoro-β-alanine is a product of the catabolism of 5-fluorouracil, a commonly employed antineoplastic agent[234,235]. The microbial oxidation of several fluorinated steroids was studied and definitively showed the ability of fluorine to disfavour *in vivo* oxidation at or adjacent to the fluorinated carbon[236,237].

However, an enantiospecific enzyme-catalysed Baeyer-Villiger oxidation of a racemic fluorinated ketone could be performed by using *Acinobacter* NCIB 987, and an intermediate for the synthesis of fluoro-carbocyclic nucleosides was thus prepared[238].

This methodology of using microbial transformations in order to obtain chiral fluorinated synthons from easily available prochiral substrates is becoming more and more frequently employed.



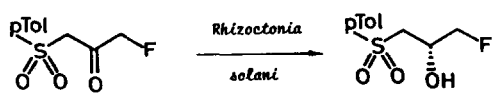
(±) - 39

(R) - 30

(eq. 17)

For instance, the commonly used Mosher's acid **30** was obtained through enantioselective microbial hydrolysis of cyanohydrin acetate racemic **39** (eq. 17)[239].

Despite the fact that α-fluoroketones are known to work as enzyme inhibitors[11], the reduction of some mono- and poly-fluorinated ketones was realized with high enantiomeric excess with growing cultures of several microorganisms (eq. 18)[240]. In some cases, both enantiomers could be obtained in high chemical and optical yields by using different microorganisms[241].

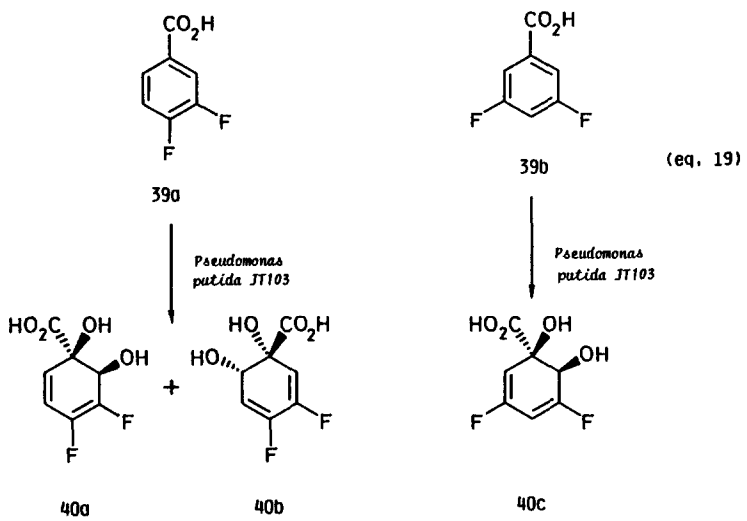


(eq. 18)

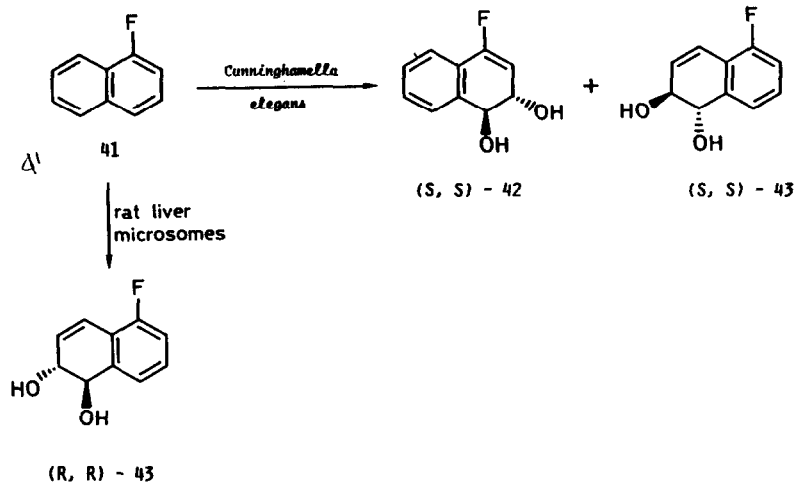
No single chemical process permits the direct and stereospecific oxidation of fluorinated benzenoid compounds to synthetically useful chiral substances. On the contrary, wild-type and mutant microbial strains have been used to biotransform some fluoroaromatic compounds to novel chiral fluorinated products[242,243].

The employment of microorganisms, which are defective in the enzymes for a well-defined oxygenative catabolic pathway, seems to be particularly promising as it has furnished in good yields chiral polyoxygenated fluoroorganic products starting from fluoroaromatic precursors[244-247,47].

For instance, *Pseudomonas putida* afforded 3-fluoro-3,5-cyclohexadien-1,2-*cis*-diol and its 6-methyl analogue with high enantiomeric excess starting from fluorobenzene and 4-fluorotoluene, respectively[248,249]. It is interesting to observe that the biotransformation of the other 4-halotoluenes gave racemic products whereas a mutant strain of the same microorganism[250] afforded an asymmetric oxidation of the difluorobenzoates **39a,b** to give the difluoro-dihydroxy-cyclohexadienes **40a-c** (eq. 19).



Also polynuclear fluoroaromatic compounds can be transformed effectively. *Cunninghamella elegans*[251] transformed 1-fluoronaphtalene **41** into *trans*-3,4-dihydro-3,4-dihydroxy-1-naphtalene **42** and *trans*-5,6-dihydro-5,6-dihydroxy-analogue **43**. The (S,S)-enantiomer of both compounds was formed preferentially, but (R,R)-**43** was the major antipode formed in the rat liver microsome oxidation of 1-fluoro-naphtalene (eq.20).

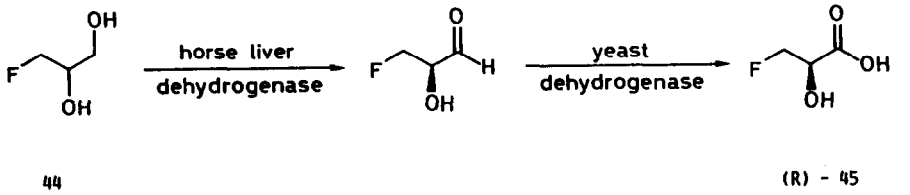


(eq. 20)

III.2. Oxido-reductases

Most enzymatic oxidoreductions reported in the literature for fluoroorganic compounds consist of transformations performed by the enzyme at non-fluorinated carbon(s) of a fluorinated substrate. Only one case of enzyme catalyzed formation of the carbon-fluorine bond has been described. In the presence of iodide and fluoride ion, horseradish peroxidase was shown to transform an alkene into an iodo-alkylfluoride[252], but the compound may not be expected to be produced in optically active form[253].

One single enantioselective oxidation of a fluorinated substrate has been reported (eq. 21). Horse liver alcohol dehydrogenase oxidized racemic 3-fluoro-1,2-propanediol **44** to the corresponding aldehyde which was further oxidized *in situ* into enantiomerically pure (R)-β-fluorolactic acid **45** by yeast aldehyde dehydrogenase[254,255].



(op. 21)

44

(R) - 45

The same enzymatic system was also used to reduce α-fluoroacetophenone into the corresponding fluorohydrin with nearly complete enantioselectivity. The formation of the fluorohydrin (instead of acetophenone) was considered as an indication that the reduction reaction of NADH-dependent alcohol dehydrogenases proceeded in general *via* hydride transfer[256].

(S)-β-Fluorolactate **45**, the enantiomer of the product of eq. 21, was obtained by reducing β-fluoropyruric acid with L-lactate dehydrogenase[257].

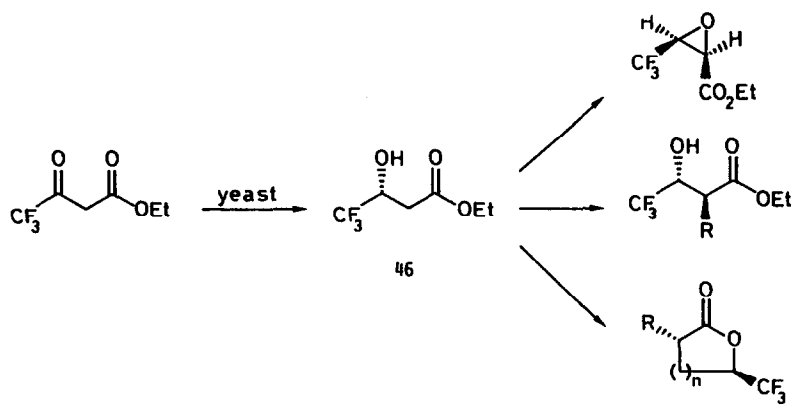
All other reductions of carbonyl[258-267] or olefin[260] double bonds have employed baker's yeast as the enzymatic system. Alkyl-perfluoroalkyl carbinols, aryl-perfluoroalkyl carbinols, allylic and homoallylic alcohols carrying a perfluoroalkyl chain were obtained in high chemical and optical yields through regio- and enantio-selective reduction of the corresponding ketones (eq. 22).

(eq. 22)

e.e. 82%

(R) - 31 b

Similarly, the carbonyl group of γ,γ,γ-trifluoroacetoacetate was reduced[261] to the corresponding (+)-R alcohol **46** which was elaborated to more complex compounds without loss of optical purity[262,268-271] (Scheme 7).



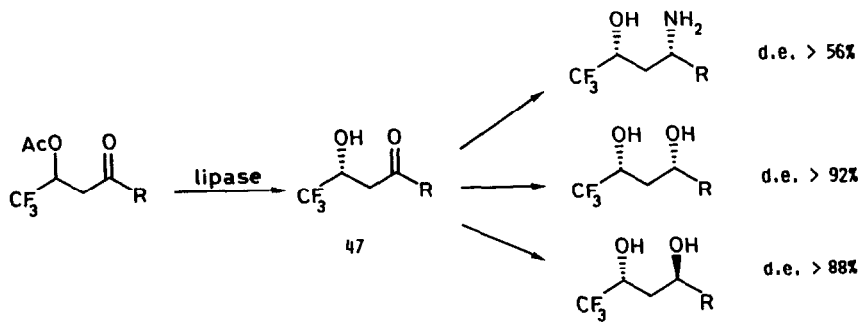
Scheme 7

Also some α-monofluorinated dialkylketones were reduced to the corresponding fluorohydrins with low diastereoselectivity, but medium to high enantioselectivity[240,272]. Interestingly, by changing the relative size of the two residues of the carbonyl carbon, the absolute configuration at the alcohol stereocentre of the products changed following Prelog's rule[273].

III.3. Esterases, lipases, and acylases

Several perfluoroalkyl substituted secondary alcohols have been obtained in optically active form through enzymatic hydrolyses of their esters, but until now no case of a resolution of perfluoroalkyl substituted tertiary alcohols has been described.

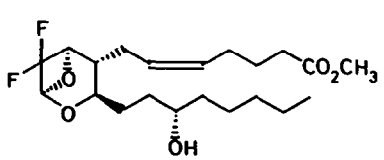
Trifluoromethyl carbinols carrying an alkyl, aryl, alkenyl, or alkynyl chain have been resolved by enantioselective hydrolyses usually employing lipases from *Candida cyclindracea* or *Pseudomonas sp*[264,274-277]. Some chiral trifluoromethyl 2-oxoalkyl-carbinols **47** thus obtained were further elaborated to give fluorinated 1,3-hydroxyamines and -diols with good diastereoselectivity (Scheme 8).



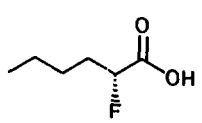
Scheme 8

Also alcohols having a pentafluoroethyl, 1,1-dichloro-2,2,2-trifluoroethyl[276], or chlorofluoromethyl[278] residue were resolved. For the last compounds, containing two adjacent carbon stereocentres, the fluorinated and the hydroxylated ones, mixtures of racemic *syn* and *anti* diastereoisomers were reacted and diastereo- and enantio-selective hydrolyses were observed. In some of the examined cases it was thus possible to produce α-fluoro-α-chloro alcohols enantiomerically and diastereomerically pure.

A fluorinated diol, used for the synthesis of 10,10-difluorotromboxane A_2 **48** was obtained by resolution of its diacetate with pig liver esterase[279]. The fluorotromboxane **48** was synthetized as the oxetane-acetal grouping present in natural tromboxanes suffers facile hydrolytic cleavage by a general acid catalyzed reaction. This lability seriously impedes the full realization of the therapeutic potential of the substance and it was thought that the strong electron withdrawing effect of fluorine in position 10 of the molecule could stabilize the adjacent acid-labile moiety of the thromboxane. Some interesting results were obtained in *in vitro* tests, but *in vivo* studies were less satisfactory[148].



48

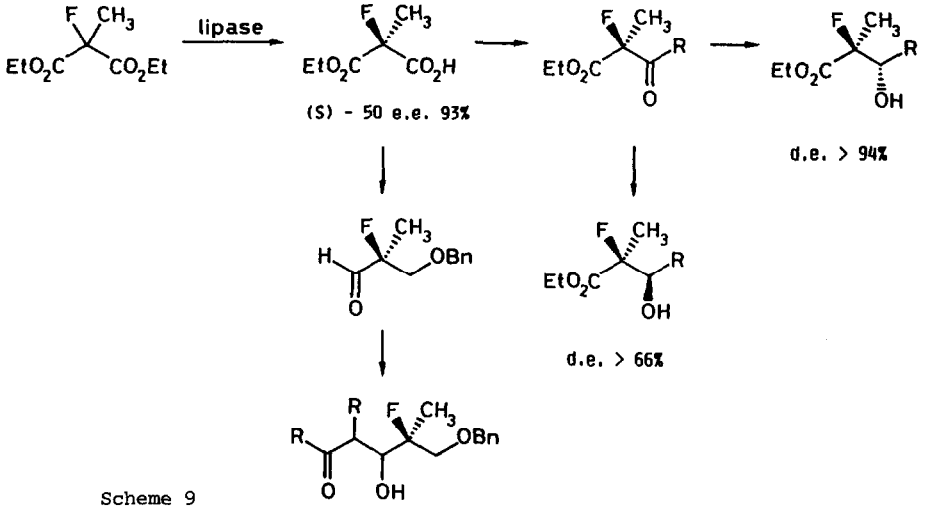


(R) - 49

In the enzymatic resolutions described above fluoroalcohols were obtained in optically active form through hydrolyses of their esters. Complementarily, fluorocarboxylic acids could be obtained in optically active form through enzymatic hydrolyses of their esters. Both the enantiomers of 2-fluorohexanoic acid **49** (an intermediate for the synthesis of antihypertensive prostaglandins and vasodilatator prostacyclins) were prepared through hydrolysis of the ethyl ester catalysed by bacterial lipase[280].

Similarly, some 2-fluoro-2-alkyl-malonic acid monoester were obtained in optically active form through partial resolution of the corresponding diethyl esters with lipase from *Candida cylindracea*[281-283].

Chemoselective elaborations of the acid and/or ester residues in thus obtained (S)-2-fluoro-2-methyl malonic acid monoethyl ester **50** allowed the preparation of several multifunctional compounds all containing the chiral fluorinated stereocentre present in the synthon **50** (Scheme 9)[284-289].

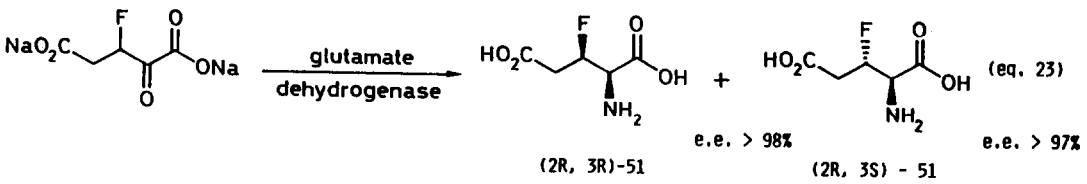


Scheme 9

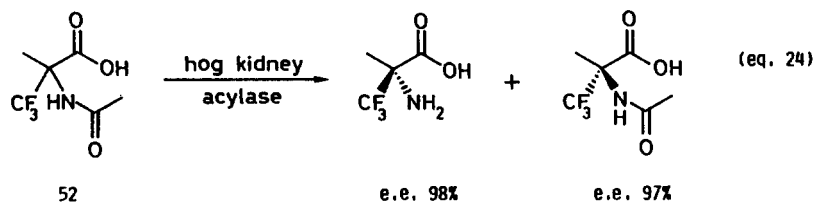
An enantioselective formation of carbon-heteroatom bond has also been described. Some α-trifluoromethyl-β-substituted propionic acids were formed with moderate enantiomeric excess through the asymmetric Michael addition of water, amines, and mercaptans to 2-trifluoromethylacrylic acid[290-292].

Chiral fluorinated aminoacids are endowed with interesting biological and pharmacological activities and several and different approaches for their enzyme catalyzed asymmetric synthesis have been described.

An elegant synthesis of enantiomerically pure (2R,3R) and (2R,3S)-3-fluoroglutamic acid[293] **51** was performed by using glutamate dehydrogenase[294] (eq. 23). The enzyme catalyzes the initial formation of an α-imino glutarate and then the reduction of the imine is performed. Undesired fluoride ion elimination does not occur as the employed enzyme is not a PLP-dependent transaminase.



Several[295] aminoacids carrying a trifluoromethyl or difluoromethyl residue were obtained by hydrolyzing the corresponding N-acetyl or N-trifluoroacetyl derivatives[296-299]. For instance[300], hog kidney acylase was used to hydrolyze the N-trifluoroacetyl derivative of α-trifluoromethyl alanine **52** and both the hydrolyzed product and the unreacted starting material, having opposite absolute configurations, were isolated with high optical purity (eg. 24).



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