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Synthesis of Chiral and Bioactive Fluoroorganic Compounds

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1.- INTRODUCTION

A few higher plants and bacteria are the only living organisms which are able to metabolise inorganic fluoride.[1] Naturally occurring organofluorine compounds are extremely rare.[2-4] Only ten such products have been reported, six of them being ω-fluorocarboxylic acids isolated from *Dychapetalum toxicarium*.[5,6] Fluoroorganic derivatives can therefore be considered as practically xenobiotic substances.

Despite this fact, the selective introduction of a fluorine atom or a fluorinated residue into a biologically active molecule is emerging as an extremely effective tool for modifying its physicochemical properties and

consequently its physiological behaviour. The rationale for these modifications lies in the peculiarities of this halogen.

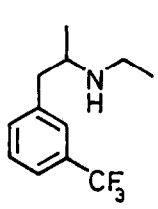
The fluorine atom is the second smallest substituent after hydrogen as measured by van der Waals radius (1.35 A versus 1.20 A). The substitution of fluorine for hydrogen results in minimal change of the steric requirements of the molecule. Sometimes this allows fluorinated analogues to follow the metabolic pathway of the parent hydrogen compounds (often via enzyme receptors where stringent steric requirements are imposed) leading finally to their incorporation into the organism.[7] The carbon-fluorine bond length is 1.39 A and the carbon-oxygen bond length is 1.43 A. Fluorine can function as a hydrogen bond acceptor and it becomes easy to understand why the replacement of hydroxyl by fluorine often allows biological properties to be retained. Fluorine is the most electronegative element and it alters the electron density, basicity, and acidity of neighbouring groups. The chemical and enzymatic reactivity of surrounding functionalities is affected and the conformation of the whole molecule may be changed due to dipole interactions.

In conjugated systems, tautomeric effects are brought about. In an aromatic nucleus, a fluorine substituent releases electrons through the mesomeric effect and an increased electron density in the *ortho* and *para* positions results. While a methyl group weakly increases the electron density in the *ortho* and *para* positions, a trifluoromethyl residue causes a strong opposite effect in the same positions. The trifluoromethyl group has been suggested to have physical properties intermediate between those of a methyl and a carbomethoxy group.[8]

The carbon-fluorine bond is at least 14 Kcal/mole stronger than the carbon-hydrogen bond and as a consequence, the introduction of fluorine makes the substrate relatively resistant to metabolic transformations and this property has been exploited in attempts to protract the action of a drug by blocking the sites involved in oxidative degradation.[9-11]

Finally, the trifluoromethyl group is highly lipophilic (it has a π constant greater than methyl and ethyl: $\pi_{CH_3} = 0.50$, $\pi_{C_2H_5} = 1.00$, $\pi_{CF_3} = 1.07$). This property may contribute to the absorption, transport, and delivery of an agent to its biological target, which is a preliminary process to its activity. The effective concentration of the drug in the target tissue can thus be increased by improving the ability of the molecule to penetrate lipid bilayers.

Any biological activity of a molecule originates from a recognition process that the living organism performs on the active compounds. This recognition consists in the interaction of the small molecule (drug) with a large, usually proteinaceous counterpart (receptor site, pharmacophore). A cascade of events amplifies the original molecular interaction into a macroscopic phenomenon, viz. the biological activity. Different factors such as steric hindrance, electronegativity, dipole interactions, lipophilicity... all contribute to the process of molecular recognition. We have briefly discussed the effects of fluorine on these parameters, but as far as molecular recognition is concerned they have to be considered and understood in three dimensions.[12,13] This has long been recognised where diastereoisomers are concerned, but only in recent years have the scientific community and the drug regulatory authorities fully recognised the relevance of chirality to biological activity and molecular recognition.[14-15] This is despite the fact that some fundamental observations have been made as early as 1956.[16] In FDA guidelines enantiomers may be considered as impurities and data on safety and efficacy have to be produced for each stereoisomer.[17,18]



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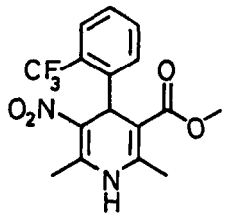

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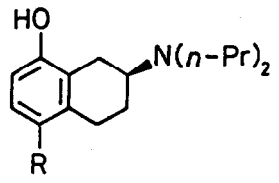
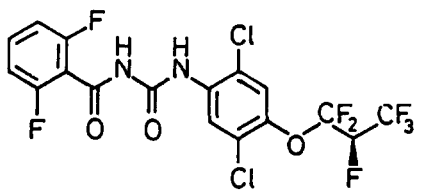


	R
3a	H
3b	F



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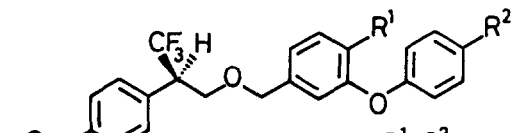
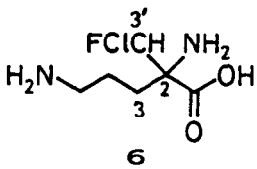


	R^1	R^2
5a	H	H
b	F	H
c	H	Br



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For agrochemicals the non-useful stereoisomer may interact with the ecological system and can be considered as an environmental pollutant.[19-21]

For many years it was considered that the racemic form should have, in the worst case, half of the activity of the more active enantiomer. It has been shown[22] that this approach can lead to sophisticated nonsense in pharmacokinetics and clinical pharmacology. It is now commonly accepted that there are differences in the uptake and transportation for two enantiomers. Two antipodes can also have different affinities and/or intrinsic activities at the receptor sites, which result in the differential responses. Chirality can have a significant effect on the dosage form used and the presence of one enantiomer may affect the metabolism of the other, leading to changes in pharmacokinetics. Side-effects and toxicity can also vary for the two antipodes.

For instance, *rac*-fenfluramine **1** was originally marketed as an amphetamine analogue devoid of stimulant effect, for use as an anorectic agent. Its (*S*)-(+)-enantiomer has the same configuration as (+)-amphetamine and (+)-methylamphetamine,[23] both of which are stimulant anorectic agents. (+)-Fenfluramine is the active isomer[24-27] and the side effects of the racemic drug are due to the (-)-enantiomer. As a result, (+)-fenfluramine has been marketed as a "turning point for your overweight patients". Another example can be drawn from the field of 1,4-dihydropyridine calcium channel antagonists. The (*S*)-enantiomer of Bay K 8644 (**2**) is an activator and the (*R*)-enantiomer an antagonist of L-type Ca^{++} channels.[28,29]

It can be observed that in these two reported examples both the pharmacological activity and the relevance of chirality to this activity is not induced by the presence of the trifluoromethyl group. Both properties are somehow characteristic of the structural class of the two drugs and the trifluoromethyl groups only determine the specific pharmacological profiles of the compounds. However, it has to be remembered that it is the *lack of side-effects* and *low toxicity* that determines the success of many drugs.

UH-301 (**3b**) is an example in which the effect of fluorine introduction is just on the enantioselectivity of the molecular recognition process. Racemic 8-hydroxy-2-di-*n*-propylaminotetralin **3a** (8-O4-DPAT) behaves *in vivo* as a potent agonist at the serotonin receptor subtype 5-HT_{1A}. In contrast, the 5-fluoro analogue **3b** as a racemate appeared to have no serotonergic activity.[30,31] (*R*)-**3b** Is an agonist at the 5-HT_{1A} receptor and the (*S*)-enantiomer binds to this receptor, but it lacks efficacy and so antagonises the effect of the (*R*)-enantiomer.

In all the three examples discussed here and in several other cases the fluorine residue is far away from the stereogenic centre. The importance of the stereochemical aspect of the fluorinated residue also holds when the halogen is located on the chiral atom. The first two examples will be drawn from the field of crop protection. The benzoylurea **4** has a good environmental behaviour and the (+)-isomer is 2.2 times more active than the (-)-enantiomer against *Heliothis virescens L-1*.[32] For the new pyrethroids **5** the (*R*)-enantiomer is more active than the (*S*).[33,34] A third example is drawn from the field of pharmacologically interesting compounds. (α)-(Chlorofluoromethyl)ornithines (**6**) are effective time-dependent irreversible inhibitors of ornithine decarboxylase, a key enzyme in the biosynthesis of polyamines. The (2*R*,3'*S*)-isomer is the most efficient of the four diastereoisomers, being, in terms of apparent dissociation constant, nearly one order of magnitude more potent than the (2*S*,3'*R*)-enantiomer and more than one order of magnitude more potent than the (2*R*,3'*R*)-isomer, which is the epimer at the fluorinated stereocentre.[35]

The above considerations form the subject of the present report. Various reviews and books have appeared in recent years on fluorination methods[36] and on applications of organofluorine compounds.[37] Some of them have dealt with bioactive molecules.[38] However, in no case has specific attention been devoted to the relevance of chirality to the synthesis of selectively fluorinated bioactive products. In the present review all the material presented has been organised according to the synthetic procedure employed to prepare the chiral fluorinated substances, with greater emphasis being given to more recent results. Methods for the introduction of a fluorine atom or a fluorinated residue on a complex polyfunctional substrate are presented, focussing mainly on the stereochemical aspects. Particular attention is devoted to the synthesis of fluorinated bioactive molecules either starting from a proper fluorinated chiron or employing a biotransformation process, or using a chiral reagent, or catalyst.

2.- NUCLEOPHILIC FLUORINATION

2.1.- Covalent Sources of Nucleophilic Fluorine

Dialkylaminotrifluorosulfuranes have become the most commonly employed sources of nucleophilic fluorine. Diethylaminosulfur trifluoride (DAST), or its methyl and morpholino analogues, are the reagents of choice for the laboratory substitution of fluorine for hydroxyl. The reaction involves the nucleophilic

$$R^1-OH + R^2_2NSF_3 \xrightarrow{-HF} R^1-OSF_2NR^2_2 \xrightarrow{F^-} R^1-F + FSONR^2_2 + F^- \quad (1)$$

7

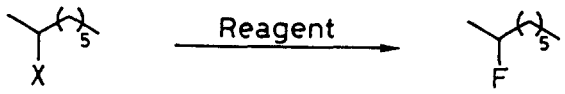
displacement of fluorine on sulfur by the oxygen of the hydroxyl group to give hydrogen fluoride and an alkoxydiethylaminosulfur difluoride intermediate 7 (eq. 1). A good leaving group is thus generated at the alcohol carbon atom and intermolecular attack of fluoride ion at this site leads to the desired alkyl fluoride.

Spectroscopic[39,40] and chemical evidence[41,42] has been reported for the formation of intermediate species of type 7. The evolution of these species is mechanistically dependent on the structural type. S_N1 reactions occur with substrates that form carbonium ions easily. The stereochemical course and the carbocation-type rearrangements accompaning the fluorination reaction in some cases can be rationalised by assuming the formation of ions or ion-pairs.[43-45]

With most substrates, however, an S_N2 process is preferred and hydroxyl replacement by fluorine is often claimed to occur with complete inversion of configuration. (*S*)-2-Octanol **8a** gives (*R*)-2-fluorooctane **9** of 97.6% optical purity[46] (Scheme 1) and a similar inversion of chirality was observed with (*R*)-1-decyn-3-ol,[47] (*S*)-dimethyl 2-hydroxysuccinate[48,49] and several natural products.[50-58] On the other hand, complete retention of configuration is observed in many reactions, and the participation of a neighbouring group can account for this result. As a classical example, 3β-hydroxy-Δ^5-steroids **10a** give the corresponding 3β-fluoro derivatives **11a**, while 3α-fluoro compounds **11b** are obtained when the starting steroids **10b** have no double bonds (Scheme 2).

Several other examples of neighbouring group participation have been observed, for instance with vitamins D[59] and other steroids,[42] sugars[60-63] and nucleosides,[64-69] prostaglandins[70,71] and prostacyclins,[72] and α-amino-β-hydroxycarboxylic acids.[73] The group involved in this participation can be

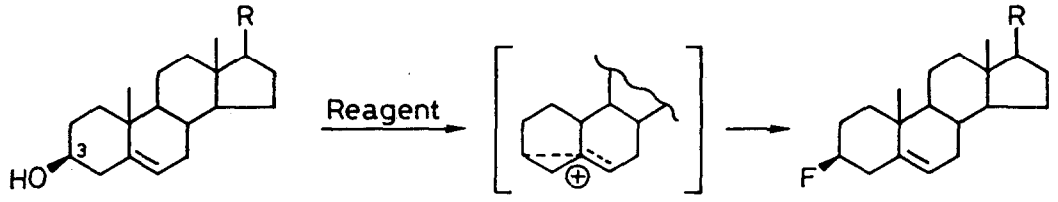
Scheme 1



8a-c 9

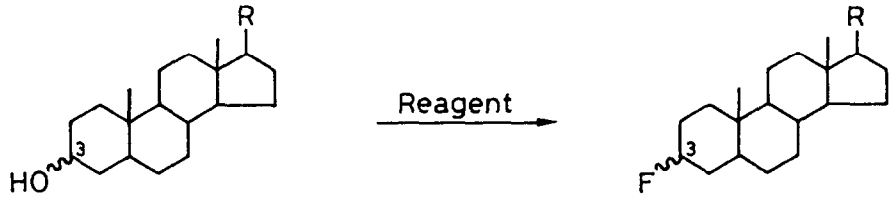
Starting Compound	X	Reagent	Absolute Configurations 8	9	Yield %	Optical Purity %
8a	OH	DAST	S	R	48	97.6
8a	OH	FAR	S	R	78	88
8b	$OSiMe_3$	$C_6H_5PF_4$	S	R	58	67.6
8c	OTs	$(n\text{-}Bu)_4F$	R	S	57	>99
8c	OTs	$(n\text{-}Bu)_3PFCH_3$	R	S	40	100
8c	OTs	KF	R	S	50	90.7

Scheme 2



10a 11a

Entry	R	Reagent	Yield %
1a	C_8H_{17}	DAST	95
2a	O	DAST	82
3a	$COCH_3$	DAST	81
4a	C_8H_{17}	FAR	90
5a	O	FAR	90-96
6a	$COCH_3$	HF	12



10b 11b

Entry	C-3	R	Reagent	C-3	Yield %
1b	3β	C_8H_{17}	DAST	3α	43
2b	3α	O	DAST	3β	14
3b	3β	O	DAST	3α	47
4b	3β	O	FAR	3α	42
5b	3β-,5α,6α-epoxy	O	FAR	3α	20
6b	3β-,5β,6β-epoxy	O	FAR	3α	40-50
7b	3β-,$\Delta^{5(10)}$	OAc	FAR	3β-,$\Delta^{5(10)}$	90

a carbon-carbon double bond[44,74] or a heteroatom (oxygen,[66] sulfur,[60] nitrogen,[61,62,75] chlorine[39]) and the migration of this group can also occur. For instance, when the altropyranose **12** is treated with DAST it affords the 2-deoxy-2-fluoro derivative **13a** with retention of configuration along with the rearranged

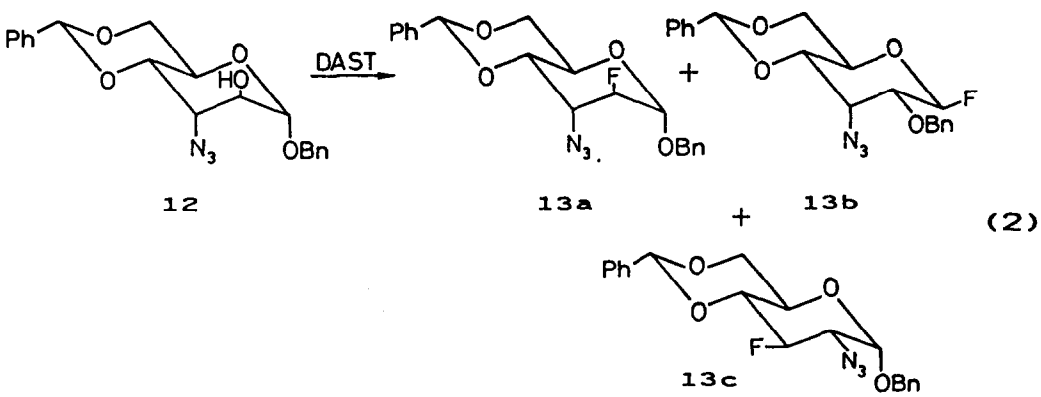
products **13b,c** (eq. 2) in which inversion of configuration has occurred at C-1, C-2 and C-2, C-3, respectively, as a consequence of the particiption of the neighbouring benzyloxy and azido groups.[61,76-78]

In polycylic systems such as gibberellin derivatives[79] the stereochemical course of the reaction may be determined by the strain of the ring system. The aptitude of a neighbouring group to participate in the replacement of an hydroxyl by fluorine can be prevented (eq. 3) by suitably diminishing the electron density of the group.[65,68]

DAST has been used for the transformation of aldehydes and ketones into corresponding geminal difluoromethyl and difluoromethylene products. This reaction usually requires higher temperatures and longer reaction times than those needed for the fluorination of alcohols. Conditions required to perform the transformations are nevertheless sufficiently mild for use in natural product analogue synthesis (sugars,[80,81] nucleosides,[82-84] inositol derivatives,[85-87] steroids[88-93]). The transformation of a carbonyl group into a difluoromethylene unit can also be performed by using sulfur tetrafluoride[94,95] and iodine fluoride.[96]

When DAST is reacted with sulfoxides having at least one α-hydrogen atom, it affords α-fluorosulfides, probably through a Pummerer-type rearrangement. In this way a fluorine atom has been introduced at C-5' of several nucleosides[97-99] and the reaction has been employed for the synthesis of two 4',5'-unsaturated 5'-fluoroadenosine nucleosides (eq. 4) which are potent mechanism-based inhibitors of *S*-adenosyl-L-homocysteine hydrolase.[84]

The free anomeric hydroxyl of various furanose and pyranose sugars can be replaced using DAST,[100-102] and similarly, in the presence of N-bromosuccinimide, phenylthioglycosides are converted into glycosyl fluorides[103,104] (eq. 5). Most functional groups found in carbohydrates are unaffected and retention of configuration has sometimes been observed. When 2-hydroxypyranoses are treated with DAST a sulfur, nitrogen, or oxygen residue present on C-1 migrates stereospecifically to C-2 with inversion of configuration (eq. 6) and fluoride ion enters at C-1.[60]



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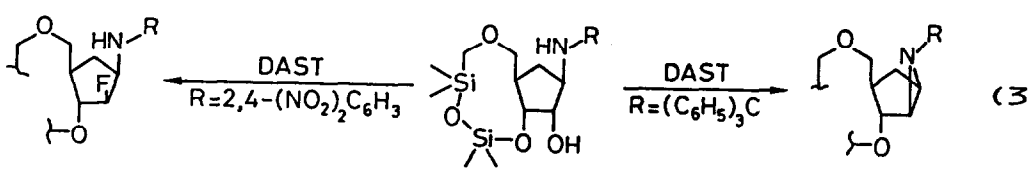

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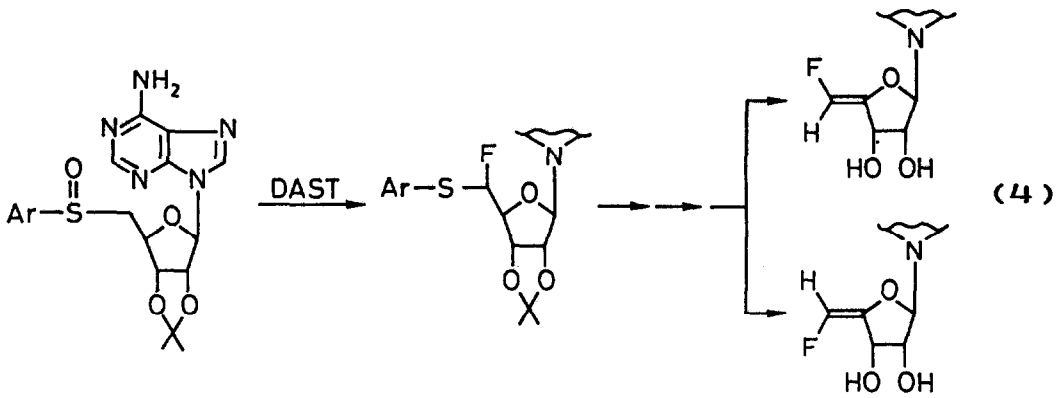

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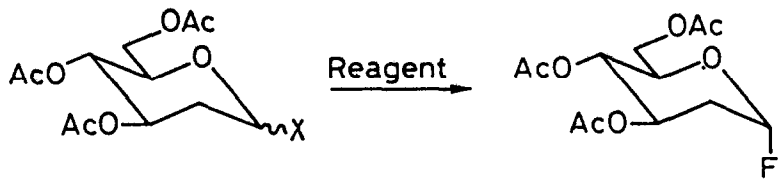


(5)

X	Reagent	Yield %
α-C_6H_5S	DAST/NBS	70
β-OAc	HF anhydrous	77

Glycosyl fluorides are also obtained from the corresponding thioglycosides by using hypervalent iodine fluorides.[105, 106] Inversion of configuration at the anomeric centre occurs on substrates in which the group on C-2 does not take part in the reaction. Another interesting transformation performed by this reagent is the opening of the cephalosporin ring system with the formation of β-fluoro-β-lactam products (eq. 7). As in the phenylthioglycosides, the fluorine replaces the sulfur with inversion of configuration.[107]

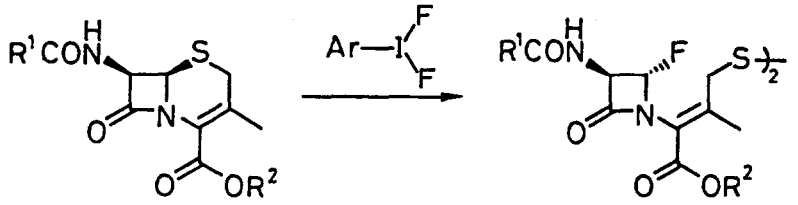
The chiral sulfurane **14a** has been prepared and used for the enantioselective fluorodehydroxylation of racemic substrates. The alkyl fluorides obtained in this way, however, were of low optical purity.[108]

Sulfur tetrafluoride, the starting material for the preparation of DAST and other aminofluorosulfuranes, has a reactivity similar to that of these more recent reagents, but the problems of toxicity and high pressure associated with its use have prevented its extensive exploitation on laboratory scale. A mechanism similar to that described above for DAST (eq. 1) has been suggested with a fluoride ion displacing an *in situ* generated good leaving group through an S_Ni, S_N1, or S_N2 pathway.[109] The stability of the intermediate possible carbocations is of fundamental importance for the stereochemical course of the reaction. In some cases fluorodehydroxylation reactions occurring with selective retention and inversion of configuration may take place selectively on superficially similar products. In (+)-dimethyl tartrate, the first hydroxyl is replaced with inversion and the second with retention of configuration.[110-113]

Indications of S_N1-type displacement[109] come from the isolation of the same 2:1 mixture of

(6)

X= OMe, OAc, SPh, N_3



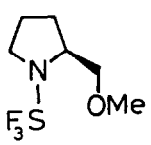
(7)

fluorodeoxyephedrines **16**, starting from either ephedrine **15a** or pseudo ephedrine **15b** (eq. 8). Indications for S_N2 processes are the preferential inversion observed starting from L-threonine **17a**, L-allo threonine **17b** (eq. 9), and L-threonine ethyl ester.[114]

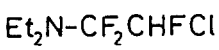
Several α-fluoromethyl-α-amino acids and α-fluoromethyl amines have been synthesised through fluorodehydroxylation of the corresponding hydroxymethyl precursors.[113,114] These products are efficient and selective mechanism-based irreversible inhibitors of various pyridoxal-phosphate dependent enzymes (e.g. (*S*)-3-fluoroalanine-2-d (**18a**),[115] (*S*)-α-fluoromethylhistidine (**18b**),[116-119] (*S*)-α-fluoromethyl hystamine (**19b**),[113] (*S*)-α-fluoromethyldopa (**18c**), (*R*)-α-fluoromethyldopamine (**19c**),[120] (*S*)-4-amino-5-fluoropentanoic acid,[121-127] (*S,E*)-4-amino-5-fluoropent-2-enoic acid,[128,129] (-)-α-difluoromethyl-ornithine,[130-133] (2*R*,3'*S*)-α-chlorofluoromethylornithine (**6**)[35]).

Sulfur tetrafluoride has also been used for the transformation of carboxylic residues into trifluoromethyl groups on steroid substrates[134] and elsewhere.

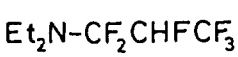
α,α-Difluoromethyl substituted amines (commonly known as FARs, the acronym for Fluoroalkyl Amine Reagents) are used for the substitution of fluorine for hydroxyl. The two most commonly used are



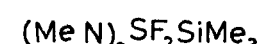
14a



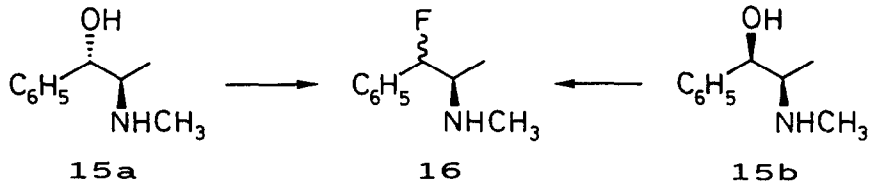
14b



14c



14d



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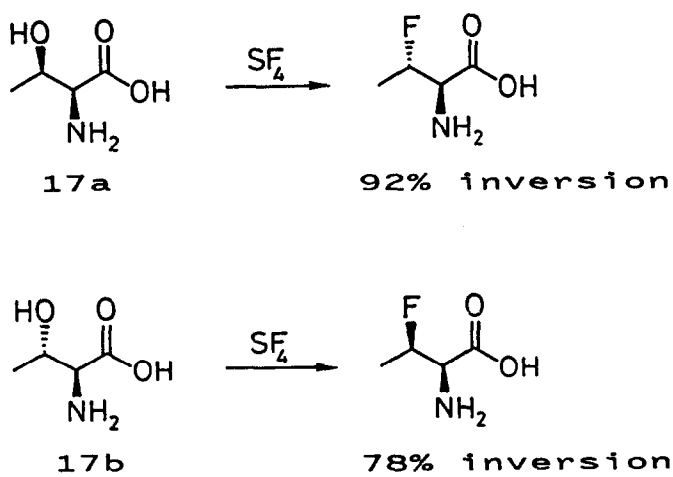
Yarovenko's reagent (*N,N*-diethyl-2-chloro-1,1,2-trifluoroethylamine, **14b**) and Ishikawa's reagent (*N,N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine, **14c**) both of which are commercially available.

For the fluorodehydroxylation reaction a mechanism has been suggested in which the oxygen of the hydroxyl replaces one of the fluorines adjacent to the nitrogen. A good leaving group is thus formed and a fluoride ion displaces it. An S_N1 or an S_N2 mechanism is operative depending on substrate and reaction conditions. The product distribution obtained can, in some cases,[74,135-142] be rationalised by assuming the intermediate formation of a carbonium ion on which the fluoride enters. Evidence for the S_N2-type mechanism is provided by the observation that when **14c** is used, (*R*)-1-phenylethanol affords (*S*)-1-fluoroethylbenzene[143] and ethyl (*R*)-mandelate gives ethyl (*S*)-2-fluoro-2-phenylacetate.[144-146] A similar inversion of configuration has been given by (+)-*n*-octyl mandelate on reaction with **14b**.[147]

Some other examples are reported in Scheme 2 (entries 4a,5a,4b-7b). Akin to DAST, the retention of configuration observed starting from 3β-hydroxy-$\Delta^{5(6)}$- and 3β-hydroxy-$\Delta^{5(10)}$-steroids can be attributed to the participation of the neighbouring double bond. Anchimeric assistance occurrs also in the reaction of ephedrine analogues. Ishikawa's reagent proved useful also for the preparation of glycosyl fluorides from the corresponding sugars.[105]



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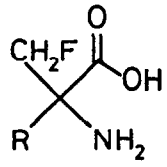
2.2.- Ionic Sources of Nucleophilic Fluorine

Many different sources of fluoride ion have been used to substitute fluorine for halogens, tosylates, or mesylates.



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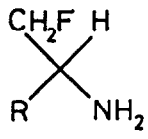

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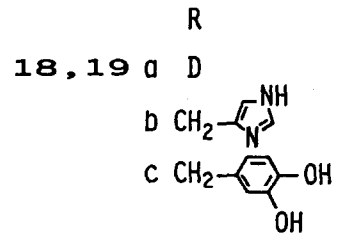
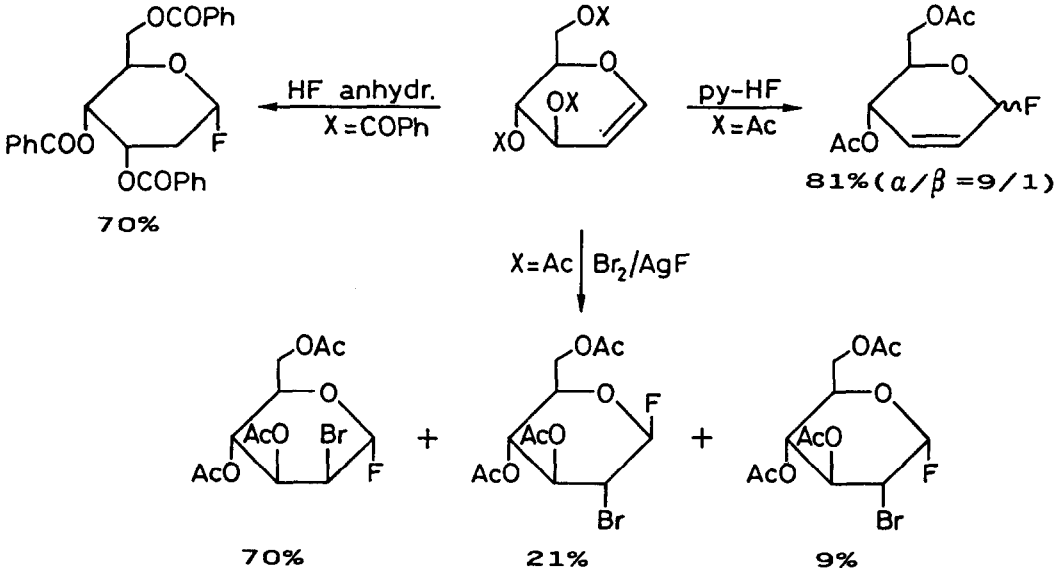


Tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F, **14d**) is a recently developed, readily soluble, highly nucleophilic source of unsolvated fluoride ion. It displaces mesylates with inversion of configuration on furanoses and pyranoses,[148] opens an epoxide ring on inositol derivatives[149] with *trans* stereochemistry, and affords glycosyl fluorides from the corresponding bromides.[150]

Tetrabutylammonium fluoride has been reported to open epoxide rings,[151] to substitute for triflate residues,[152-155] and to perform the direct substitution of fluorine for hydroxyl when a triflamide residue is present at the α position.[156] The polymer-supported version of the reagent is a clean source of "naked" fluoride for S_N2 reactions.[157] Various [^{18}F] labelled oestrogens[158-160] have been successfully prepared using [^{18}F]-tetrabutylammonium fluoride. The employment of tetrabutylphosphonium bifluoride (*n*-$Bu_4PF{\cdot}HF$) on 3β-mesyloxysteroids led to higher substitution vs. elimination ratios than those given by tetrabutylammonium fluoride,[161] and tetrabutylammonium dihydrogentrifluoride can also be used for the

Scheme 3

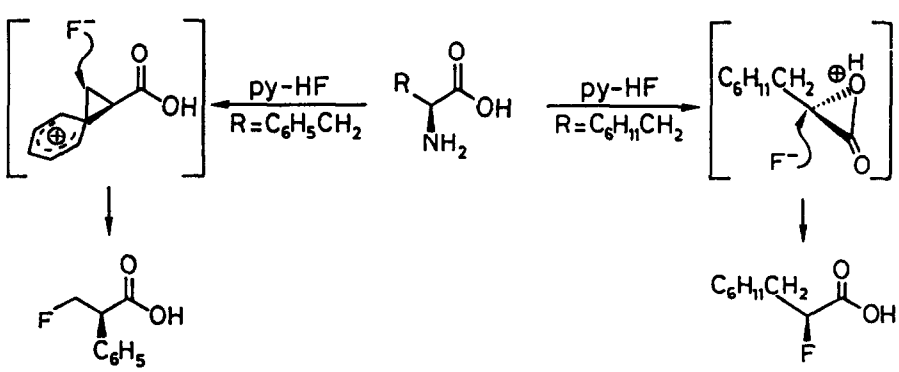


same reaction.[162,163] Alkali metal fluorides (such as caesium fluoride, sodium fluoride, but mainly potassium fluoride) and other metal fluorides (such as mercury(II) fluoride, titanium(IV) fluoride, lead(IV) fluoride, silver(I) fluoride sometimes in the presence of calcium(II) fluoride) are the classical sources of fluoride ion. Fluorination normally occurs via an S_N2 mechanism with inversion of configuration.[164-169] Retention of configuration is sometimes observed, in steroid substrates due to steric factors[170] and in carbohydrates due to neighbouring group participation.[171]

Silver fluoride[172-175] and silver tetrafluoroborate have also been used to transform, with varying stereochemical results, glycosyl chlorides and bromides into glycosyl fluorides. Potassium fluoride has been employed under phase transfer conditions for the stereospecific substitution of mesylates,[176] and potassium hydrogen difluoride allows the *trans* opening of epoxides.[177,178] The use of crown ethers[179] or other donor solvents such as glycols and glymes[180] has allowed the employment of milder conditions and the selective substitution of one out of various leaving groups.[181]

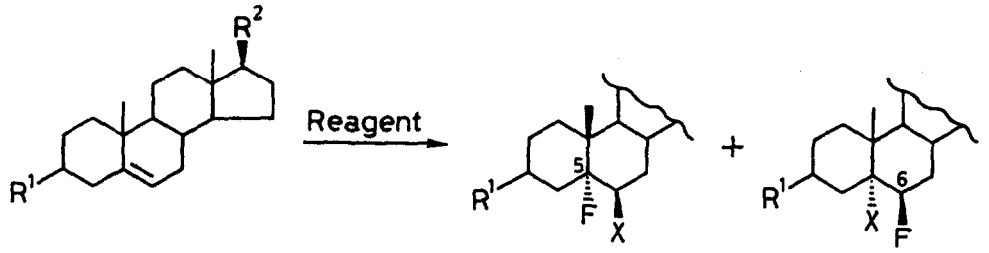
Hydrogen fluoride is a cheap fluorinating agent, but due to its corrosive nature, low boiling point, and high toxicity it is now used in the laboratory only when more convenient reagents can not be employed. Anhydrous hydrogen fluoride is a powerful Lewis acid. Polar basic solvents (diethyl ether, tetrahydrofuran, dioxan) and, more effectively, weak bases (potassium fluoride,[182-185] diisopropylamine,[186] triethylamine,[187-190] and, most popular, pyridine) have been used to tame this characteristic.

Hydrogen fluoride reacts effectively and stereoselectively with several functional groups of natural products. A *trans* addition to the carbon-carbon double bond of numerous steroids has been performed, the halogen entering at the site which can better accommodate a positive charge.[191-194] When an apparent *cis* addition has been observed it might come from a normal *trans* addition followed by epimerization.[194] Anhydrous hydrogen fluoride adds cleanly to benzoylated glycals[195] to afford 2-deoxy-α-glycosyl fluorides (Scheme 3). When pyridinium polyhydrogen fluoride (py-HF) is used, the Ferrier rearranged products can be isolated in good yields.[196,197] Glycosyl fluorides can also be obtained through direct replacement of the anomeric hydroxyl group with hydrogen fluoride.[198-200] Inversion of configuration usually occurs and when retention is observed it may be due to an isomerization reaction of the initially formed product[201] or to the participation of a *trans* substituent present on C-2, which leads to double inversion.[202] The employment of py-HF allows higher yields to be obtained.[203,204]



(10)

Scheme 4



Entry	R^2	R^1	Reagents	X	Yield % (5-F/6-F ratio)
1	OH	OH	dimethyldibromo-hydantoin/py-HF	Br	61 (mixture)
2	OAc	C_8H_{17}	IF	I	65 (pure 5-F)
3	OAc	C_8H_{17}	BrF	Br	70 (1/3.7)
4	H	C_8H_{17}	bis(sym-collidine) iodonium(I)tetrafluoroborate	I	65 (pure 5-F)
5	OAc	C_8H_{17}	bis(pyridine)iodonium(I) tetrafluoroborate	I	58 (pure 5-F)
6	OAc	$COCH_3$	N-iodosuccinimide HF	I	70 (pure 5-F)
7	OH	OAc	N-iodosuccinimide HF	I	68 (pure 5-F)

The *trans* opening of an epoxide by HF has been used extensively on steroids[205-210] and sugars.[182] Once again, when *cis* fluorohydrins are isolated they probably come from epimerization of the initially formed *trans*-fluorohydrin.[211] Boron trifluoride has often been used as a co-reactant in order to increase the availability of protons. Py-HF reacts to give a clean *trans* opening of oxirane rings present on acid sensitive substrates such as shikimic acid precursors.[212,213] The same reagent has been used to open azirine rings to give α-fluoroketones and in this way pregnenolone has been transformed into its 17α-fluoro derivative.[214]

The reaction of α-amino acids with excess of sodium nitrite in py-HF affords α-fluorocarboxylic acids with retention of configuration[48,215,216] (eq. 10). In some cases β-fluorocarboxylic acids are formed through a stereospecific rearrangement occurring with retention of configuration at the α-carbon.[217-219] Lowering the hydrogen fluoride content of the py-HF reduces the extent of this rearrangement reaction.

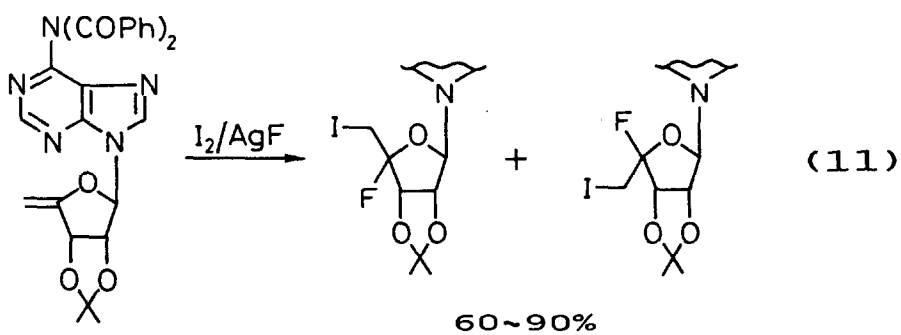
The fluoro-dediazoniation reaction has been extensively used for the fluorination of aromatic rings. Irradiation of the diazonium tetrafluoroborate of 2-amino-L-histidine has afforded 2-fluoro-L-histidine and the same sequence has been used in a synthesis of 4-fluoro-L-histidine.[220,221] The thermal decomposition

of a diazonium hexafluorophosphate salt has been employed in the synthesis of a 2-fluoromorphine analogue.[222]

Iodine-, bromine-, and chlorine-fluoride are too reactive to be widely used with polyfunctional hydrocarbon substrates. However, the net addition of X-F molecules (X=I, Br, Cl) to the carbon-carbon double bond of a steroid or sugar has frequently been performed by generating the reactants *in situ* from a source of positive halogen in the presence of fluoride ions. *N*-Halosuccinimides have been the most frequently employed sources of positive halogens, but other sources have also been adopted (e.g. *N*-bromoacetamide). The fluoride ions usually come from anhydrous hydrogen fluoride, but silver(I) fluoride or py-HF have also been successfully employed (Scheme 4). Bis(sym-collidine)iodonium(I) tetrafluoroborate[223] and bis(pyridine)iodonium(I) tetrafluoroborate[224] have been proposed as milder substitutes of above described reactant mixtures. The *trans* addition of the two halogens of X-F molecule is usually preferred[225] and Markovnikoff products form with good selectivity. This stereochemical course can be rationalised by considering that the reaction occurs through an ionic process analogous to the electrophilic addition of halogens to olefins. In this respect, the exclusive formation of glycosyl fluorides (glucosyl, mannosyl,[226-230] arabinosyl,[231] galactosyl[232] fluorides) starting from the corresponding glycals is due to the fact that the positive charge of the intermediate halonium ion is stabilised on C-1 by the anomeric oxygen (Scheme 3). Nucleocidin is a naturally occurring 4'-fluoronucleoside.[233, 234] This compound and several other 4-fluoronucleosides[235] have been prepared through iodofluorination of the appropriate 5-deoxy-pent-4-enofuranosyl intermediate (eq. 11).

On steroid substrates good yields of addition products of iodine- and bromine-fluoride were also obtained by using interhalogens prepared by the direct action of elemental fluorine.[236] The formation of *anti*-Markovnikoff addition products is often observed (Scheme 4).[237-240] The steric requirements of the whole molecule of the steroid seem to prevail on the electronic factors and they can frequently account for the regio- and stereo-selectivity of the attack of the fluoride anion on the intermediate halonium ion.

The electrophilic *anti*-1,2-addition of the elements of methanesulfenyl fluoride on 2-cholestene has been realised by treatment with dimethyl(methylthio)sulfonium tetrafluoroborate and triethylamine trishydrofluoride.[241] The isolated product is probably formed through the attack of fluoride on an intermediate episulfonium ion so that the stereochemical considerations described above hold also for this type of reaction.

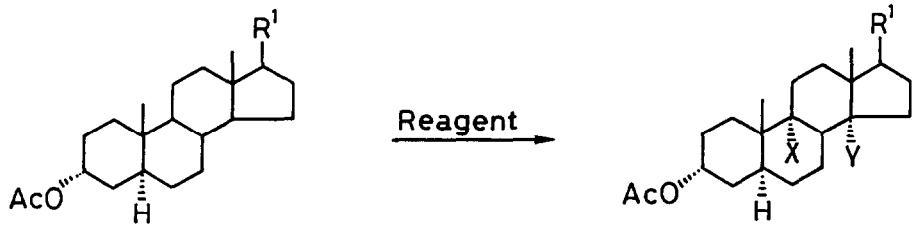


(11)

3.- ELECTROPHILIC FLUORINATION

The electron affinity of the fluorine atom is very high and in this respect F_2 can be considered as an electrophilic reagent.[242] Despite its high reactivity, fluorine diluted with nitrogen has been employed effectively for fluorination of various bioactive substrates through quite different types of reactions.

Scheme 5



Entry	R^1	Reagent	X	Y	Yield %
1	H	F_2/N_2	F	H	35
			H	F	30
2	α-OH;β-$COCH_3$	F_2/N_2	F	H	60
3	β-OAc	CF_3OF	F	H	70

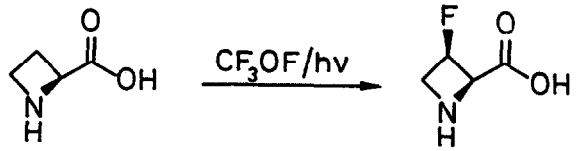
It has been added to the C_{16}-C_{17} double bond of some pregn-16-en-20-one steroids and to the C_6-C_7 double bond of an androsta-1,4,6-triene-3,17-dione.[243,244] Exclusive *cis* addition of the two fluorine atoms from the α side has been observed, but moderate to low yields have been obtained. The direct fluorination of particularly electron rich aromatic rings such as that of L-dopa has been performed.[245]

In other studies, fluorine has been employed for the replacement of tertiary hydrogens on sp^3 carbons of several steroids (Scheme 5, entries 1,2).[246] The hydrogen which is bound to the carbon through an orbital with the highest p contribution is substituted preferentially.[247,248] Since this contribution is diminished by the presence of an oxygen functionality on a nearby carbon, the presence of oxygenated functions on the steroid can direct the selective substitution to any of the tertiary C-5, -9, -14, -17, or -25 positions. Retention of configuration is observed in all cases.

Fluorine has also been shown to replace a thiol residue. L-cysteine has afforded L-3-fluoroalanine in 33% yield along with minor amounts of L-3,3-difluoroalanine.[249]

3.1.- RO-F Reagents

Fluoroxy compounds (hypofluorites, R_fO-F) are much more tractable and selective fluorinating agents than is elemental fluorine. They were the first result of research aimed at taming this aggressive halogen. Fluoroxy-trifluoromethane (CF_3OF) is one of the oldest, most stable, and best studied of this class of reagent and other perfluoroalkyl hypofluorites show a similar behaviour to that of the simplest member.[250-252]



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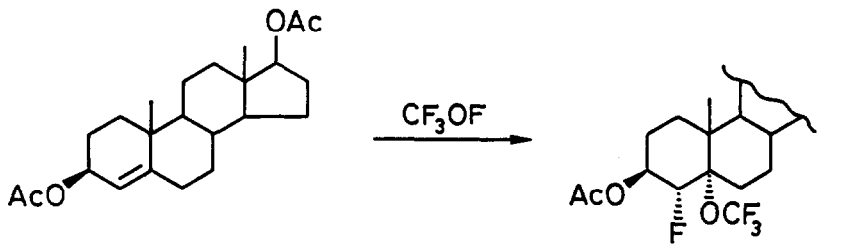
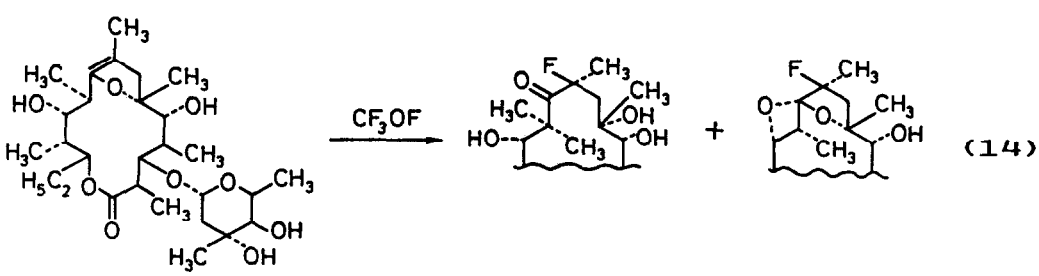


(13)

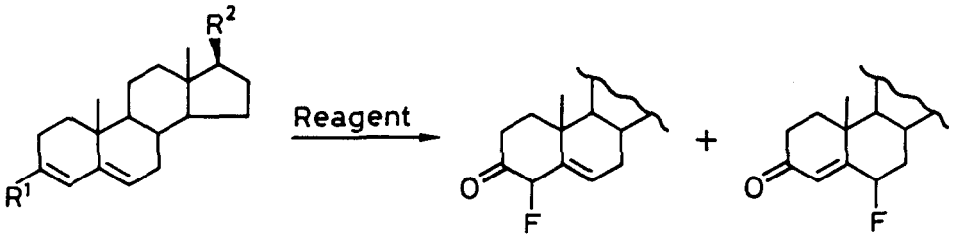
Fluoroxy-trifluoromethane is still sufficiently reactive to effect the fluorination of tertiary saturated carbons (Scheme 5, entry 3). In the presence of radical inhibitors and in $CFCl_3/CHCl_3$ solvent mixture it replaces the hydrogen at C-9 and C-15 of some steroids with retention of configuration.[246] Selective fluorination of primary and secondary saturated carbons has been obtained through a light-induced, liquid phase reaction. *Cis*-3-fluoro-L-azetidine-2-carboxylic acid was isolated in 53% yield (eq. 12) when the amino acid has been photofluorinated in liquid hydrogen fluoride.[253-255]

Trifluoromethyl hypofluorite gives addition products with several types of carbon-carbon double bonds .[256] For example, with olefinic double bonds *cis*-Markovnikoff addition to the less hindered face of the olefin is observed.[257] The reaction proceeds via attack of fluorine on the more nucleophilic terminus of the olefin to afford an intimate ion pair which rapidly combines with the counterion (CF_3O^- or F^-). When the substrate is an allylic alcohol or acetate (eq. 13) no internal nucleophilic participation occurs. The involvement of a bridged cation in these reactions can therefore be excluded. When the olefinic bond is an enol acetate,[250,258-264] enol ether, [251,265-267] or enamine system,[268] α-fluoroketones are major reaction products, and by-products coming from the addition of CF_3OF or F_2 across the double bond are isolated in some cases.[252] There is some evidence that the α-fluoroketones are not the hydrolysis products of initially formed addition compounds. Steroids,[250,260,261,265] triterpenoids,[259] and sugars[251,268-272] have been fluorinated in this way and sometimes yields have been very high. With the dienol acetate formed from 3-keto-Δ^4-steroids fluorination occurs exclusively at the terminal position of the unsaturated system, but the stereoselectivity of the process is low (Scheme 6, entries 1, 2). The corresponding dienamines react



(14)

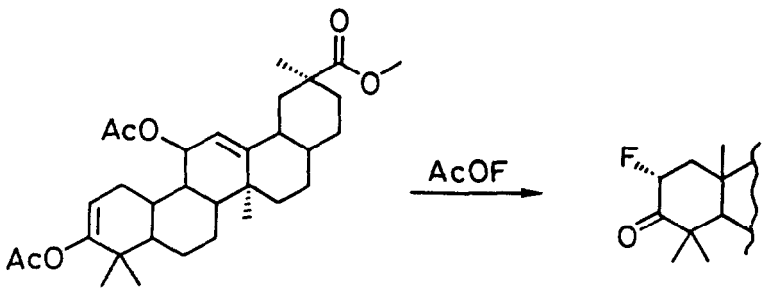
Scheme 6



Entry	R^1	R^2	Reagent	Yield % (4α/4β ratio)	Yield % (6α/6β ratio)
1	OAc	OAc	CF_3OF	-	58(1/0.6)
2	OAc	OAc	C_2F_5OF	-	70(1/1.6)
3	OEt	OH	22a	27	26(1/1.5)
4	OAc	OAc	22a	-	72(1/2)
5	OAc	OAc	22b	-	55(1/8.5)
6	OAc	OAc	22c	-	52(1/7)
7	$OSiMe_3$	OAc	22a	15	36(1/1.7)
8	$OSiMe_3$	OAc	22d	4	68(1/4)
9	OAc	OAc	23	-	95(4/6)
10	N⬡	OH	$FClO_3$	55(>95/<5)	-
11	N⬡	C_7H_{15}	$C_6H_5IF_2$	-	18(<5/>95)
12	OEt	C_7H_{15}	$C_6H_5IF_2$	-	14(<5/>95)
13	$O\text{-}C_6F_4\text{-}pCF_3$	C_7H_{15}	$C_6H_5IF_2$	-	11(<5/>95)

largely at the intermediate site of the conjugated diene system, while dienol silyl ethers give both regioisomeric products.[252]

Particularly interesting is the fluorination of 3-*O*-mycarosyl-8,2-anhydroerithronolide B with trifluoromethyl hypofluorite,[266,267] which affords the (8*S*)-fluoroerithronolide B and its 6,9;9,11-spiroketal in 5 and 58% yield, respectively (eq. 14).



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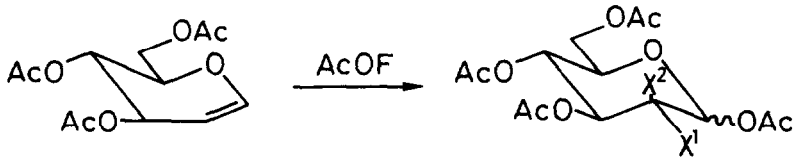


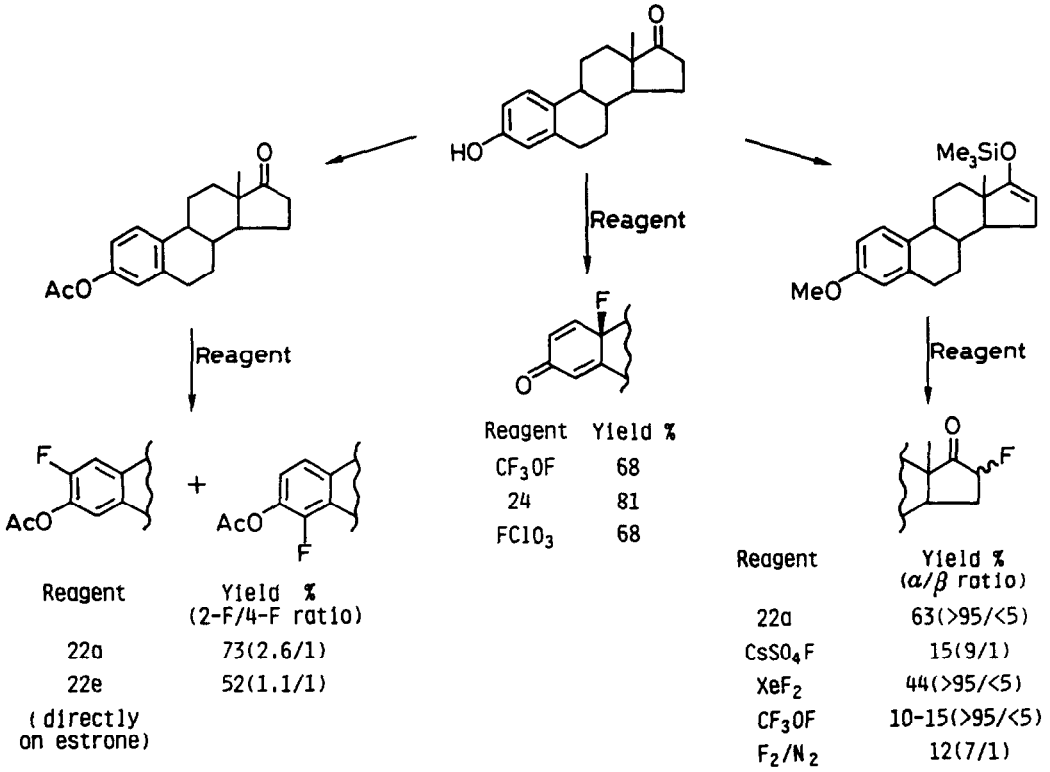
(16)

X^1	X^2	ratio
F	H	7
H	F	1

Trifluoromethyl hypofluorite also fluorinates phenolic rings. The electrophilic nature of the process is shown by the entrance of the fluorine *ortho* and *para* to the oxygen atom.[273] On some oestrogens[274] *para* fluorination occurred exclusively to give 10β-fluoro-3-oxo-1,4-oestradienes (Scheme 7). The same *ipso* fluorination reaction occurred with tyrosine derivatives (Scheme 8). A single product has been isolated, but its stereochemistry has not been established.[275]

Acetyl hypofluorite is a milder fluorinating reagent than trifluoromethyl hypofluorite. It reacts with activated and deactivated olefins (i.e. enol acetates, enol ethers, and α,β-enones), to afford *cis*-Markovnikoff addition products preferentially. On steroid substrates[276,277] fluorine and acetoxy residues enter from the less hindered face of the double bond with complete regio- and stereo-selectivity.

Scheme 7

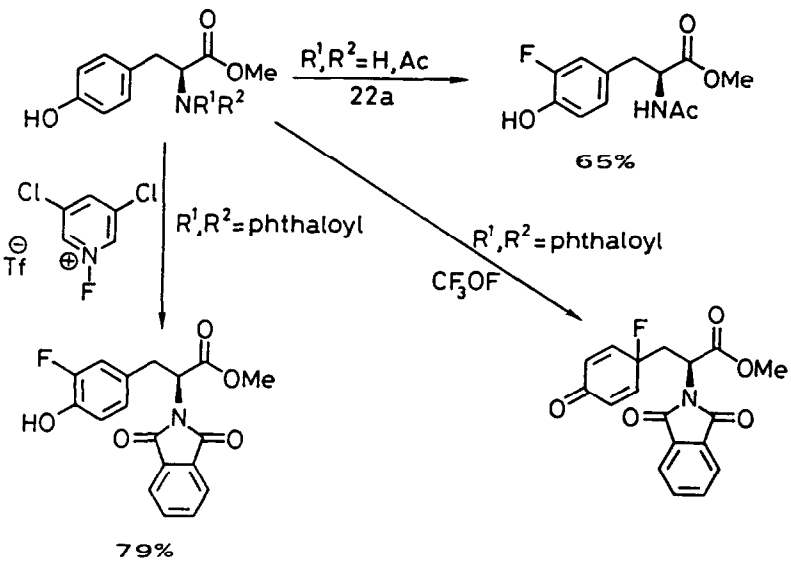


Reagent	Yield % (2-F/4-F ratio)
22a	73(2.6/1)
22e	52(1.1/1)
(directly on estrone)	

Reagent	Yield %
CF_3OF	68
24	81
$FClO_3$	68

Reagent	Yield % (α/β ratio)
22a	63(>95/<5)
$CsSO_4F$	15(9/1)
XeF_2	44(>95/<5)
CF_3OF	10-15(>95/<5)
F_2/N_2	12(7/1)

Scheme 8

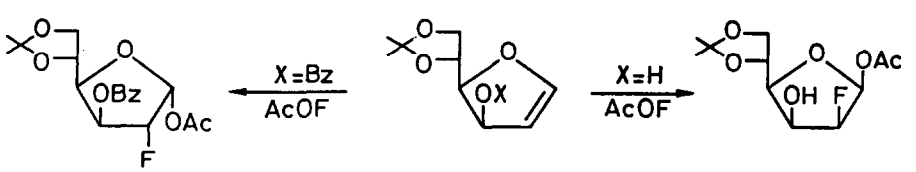


In some cases the initially formed α-fluoro-β-acetoxy ketone spontaneously eliminates acetic acid to give α-fluoro-α,β-enone products. The carbon-carbon double bond of an enol acetate is more electron rich than that of an olefin so it can be fluorinated selectively (eq. 15). The α-fluorination of a ketone can thus be performed without attacking a double bond present in a molecule.[277] The direct fluorination of a lithium enolate can also be realised and this reaction was employed in the synthesis of 12-fluoro-forskolin.[278]

Various 2-deoxy-2-fluorosugars have been obtained by addition of acetyl hypofluorite to protected hexose and pentose glycals (eqs. 16,17).[279-282] For instance, 3,4,6-tri-*O*-acetylglucal has afforded a mixture of gluco- and manno-2-deoxy-2-fluoro derivatives in 7:1 ratio.

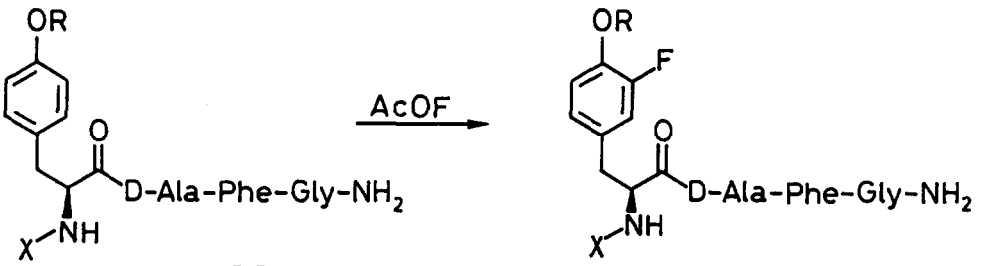
The direct fluorination of an activated aromatic ring can be performed in good yields and high selectivity. The *N*-terminal tetrapeptide amide Tyr-D-Ala-Phe-Gly-NH_2 **20a**, a μ-specific opiate agent, has two aromatic rings. That of tyrosine is the more activated to electrophilic substitution and can be selectively fluorinated.[283] Protection of the phenol and amine residues (Scheme 9, entries 2 and 3) is not necessary, as good yields are also obtained starting from the parent peptide (entry 1).

Fluorodemercuration and fluorodestannylation reactions (i.e. replacement of chloromercurio and trimethyltin residues, respectively) have been used to fluorinate aromatic rings. For instance, (-)-6-fluorometharaminol,[284] a norepinephrine analogue, and 6-fluoro-L-dopa[285] have been prepared in this



(17)

Scheme 9



20

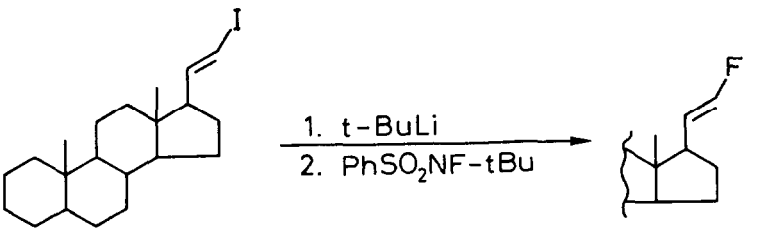
Entry		R	X	Yield %
1	20a	H	H	50
2	20b	Bz	BOC	65
3	20c	H	BOC	50

way. In both cases [^{19}F]- and [^{18}F]-AcOF have been used. [^{18}F]-AcOF has also been employed to prepare fluorinated sugars,[286-289] steroids,[290] and other products.

3.2.- R_2N-F Reagents

The continuing search for stable, safe, and effective agents for electrophilic fluorination has focussed on compounds containing an N-F moiety. These products are, in general, much less aggressive than those containing an O-F functionality, and can therefore be considered as second generation reagents in fluorine-taming research.

The N-F bond is in general poorly reactive. In order to have a good electrophilic fluorinating reagent it is necessary to decrease the electron density at the nitrogen atom. This has been realised by introducing electron withdrawing groups on the nitrogen[291,292] or including this atom in a pyridine ring.[293] Stable and safe, but reactive and non hygroscopic, reagents have thus been obtained.



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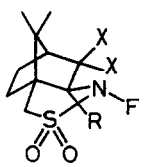
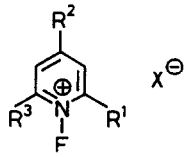
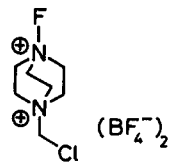
80%



	R	X
21a	H	H
b	CH_3	H
c	H	Cl



	R^1	R^2	R^3	X^-
22a	H	H	H	OTf
b	H	H	H	$OSO_2nC_4F_9$
c	CH_2OMe	H	CH_2OMe	OTf
d	SO_3^-	CH_3	H	-
e	CH_3	CH_3	CH_3	OTf



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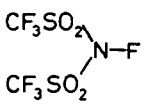

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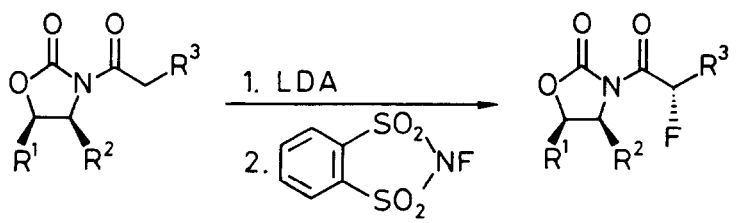
N-t-Butyl-*N*-fluorobenzenesulfonamide[294] has been used to prepare alkenyl fluorides via lithiation of the corresponding iodides (eq. 18). The reaction occurred without loss of stereochemistry at the double bond. The α-mono- and α,α-difluorination of serine-derived phosphonates was performed in moderate yields by using *N*-fluorobis(benzenesulfon)imide.[295]

One of the main applications of N-F reagents has been the preparation of α-fluorocarbonyl compounds by fluorination of the suitable enol derivatives. The two camphor derived *N*-fluoro compounds **21a, b** have been employed for the enantioselective fluorination of lithium or sodium enolates of esters and ketones.[296] Chemical and optical yields were generally low. Better results have been obtained using the dichloro-camphor reagent **21c**.[297]

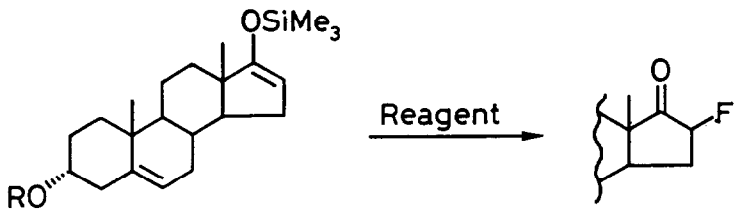
Medium to high enantioselectivity has been obtained when chirality was not in the reagent, but in the substrate,[298,299] for instance when 1-fluoro-2,4,6-trimethylpyridinium triflate has been reacted with the lithium enolates of 8-phenylmenthol esters of α-alkylmalonates to give corresponding α-fluoro-α-alkylmalonates.[300] A more effective approach has been based on the use of the Evans' oxazolidone chiral auxiliary (eq. 19). Specifically, the lithium imide enolates of **25a,b** have been fluorinated[301] cleanly (80-



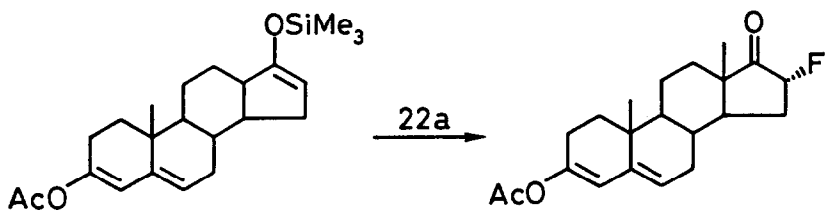
(19)

	R^1	R^2	R^3
25a	Ph	Me	Alk, Ar
b	H	i-Pr	Alk

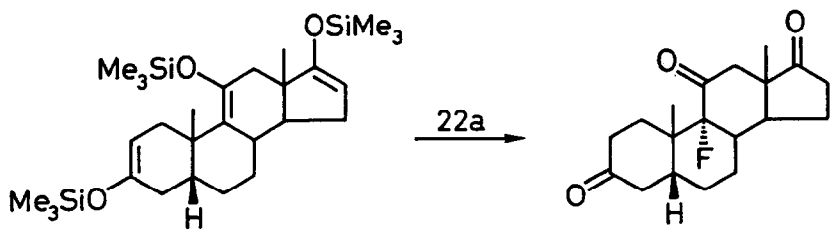
Scheme 10



Reagent	R	Yield % (α/β ratio)
22a	$SiMe_3$	43 (>95/<5)
23	$SiMe_3$	70 (94/6)
XeF_2	Ac	69 (9/1)



54%



51%

88%) and with good to excellent diastereoselectivities (86-97%) by using *N*-fluoro-*o*-benzenedisulfonimide. Some racemization problems have been found in the removal of the chiral auxiliary.

Metal enolates have not been the most commonly employed substrates for electrophilic fluorination. Enol esters,[293] silyl enol ethers,[292,302-304], enol acetates,[292] and enamines[293] have generally been preferred. In Scheme 6 several examples are given of the synthesis of the pharmacologically important 6α-fluoro-4-androsten-17β-ol-3-one. It is evident that the regioselectivity of 6β-fluorination increases with the bulkiness of the *N*-fluoro pyridinium salt used (entries 3-8). Enamines of 3-keto-Δ^4-steroids are fluorinated selectively at C-4, but double bond migration leads to the isolation of 4-fluoro-4-androsten-17β-ol-3-ones in

moderate yields.

The examples reported in Schemes 7 and 10 show that it is possible to achieve not only stereo- and regio-, but also site-selective fluorinations. A silyl enol ether is fluorinated preferentially to an olefinic carbon-carbon double bond, a dienol acetate moiety, and an aromatic ring. An even more challenging possibility is to fluorinate selectively a trialkylated silyl enol ether, leaving unaffected the two dialkylated silyl enol ethers present in the substrate molecule.

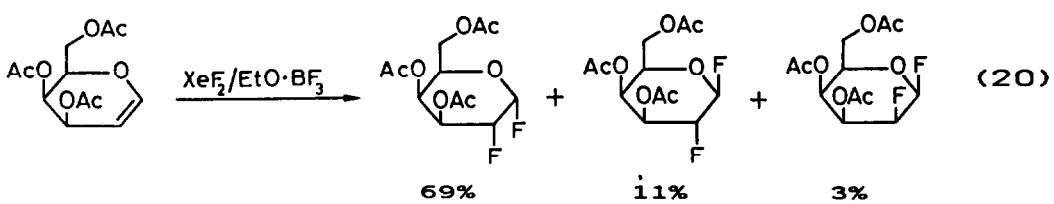
Activated aromatic rings have been fluorinated at the more nucleophilic positions. Tyrosine and various oestrogens have been fluorinated selectively *ortho* to the hydroxyl group (Scheme 8) by using 1-fluoropyridinium salts.[293,305,306] *N*-Fluorobistrifluoromethylsulfonimide[291] (**24**) selectively *p*-fluorinated oestrogens in acetic acid to give 10β-fluoro-3-oxo-1,4-oestradienes in high yields.

3.3.- Other Electrophilic Fluorinating Agents

Some of the reactions described above have also been performed using "classical" sources of electrophilic fluorine. These reagents, however, have found less wide application as a consequence of the problems that are sometimes found in their handling.

Perchloryl fluoride reacts with enol,[307] enolate[308], enol ether,[309] enol acetate,[310] enamine[311,312] and enamide[313] systems present in steroid molecules (Scheme 6, entry 10). Fluorine was thus inserted in the 2α, 4, 6α or 6β, 16α, and 21 positions. Difluoromethyl- and trifluoromethyl-steroids have been obtained by direct fluorination of the sodium enolate of corresponding fluoromethylene and difluoromethylene enolate precursors. The lithium or potassium anions of mono- and di-phosphonates were also fluorinated.[314,315] In this way, for instance, it has been possible to prepare difluoromethanediphosphonic acid, a useful phosphonate analogue of the pyrophosphoric unit (see section 4.2).

When reacted with phenolic substrates, perchloryl fluoride affords preferentially[316] or exclusively[317,318] products of fluorination in the *para* position. Several 10β-fluoro steroids have been prepared (Scheme 7) starting from the corresponding 1,3,5(10)-oestratrien-3-ols. On the other hand, using caesium fluoroxysulfate the same substrates afford products of substitution at the two *ortho* positions.[319] A similar selectivity is shown by xenon difluoride with L-dopa derivatives.[320] Both of these electrophilic fluorinating agents have also been employed for the α-fluorination of keto functionality present in steroids, polypeptides, and sugars. As usual, the carbonyl group was transformed into an enol ether,[321-323] silyl enol ether,[324,325] or enol acetate,[326] and fluorination of these intermediates afforded the desired α-fluorocarbonyl products. Iodoarene difluorides behave in a similar manner,[325,327] but yields are lower (Scheme 6, entries 11-13).



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In the presence of $BF_3 \cdot Et_2O$ xenon difluoride reacts by *cis* addition of fluorine to the enol ether group of some acetylated glycals to give the corresponding 1,2-dideoxy-1,2-difluorosugars.[328] The double bond of the enol ether is attacked predominantly from the less hindered side (eq. 20).

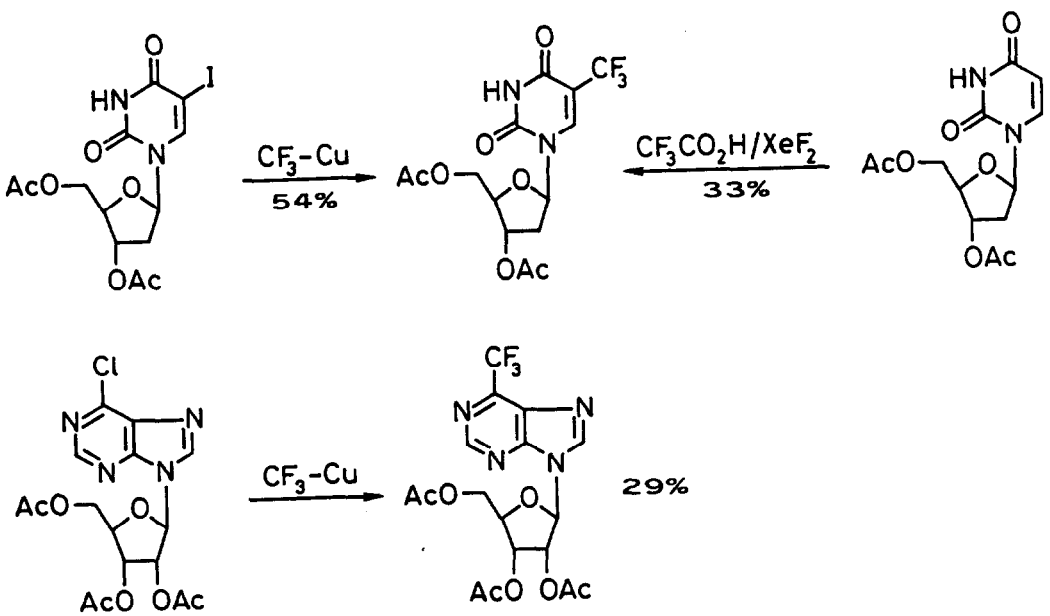
4.- CARBON-CARBON BOND FORMING PROCESSES

4.1.- Perfluoroalkyl Substituted Compounds

When the presence of a perfluorinated residue (usually a trifluoromethyl group) is required in a bioactive target molecule, either the total asymmetric synthesis from a perfluoroalkyl substituted precursor or the fluoroalkylation reaction of a convenient intermediate may be employed. If the latter approach is used, chirality is always present in the substrate molecule and a perfluoroalkylated organometallic derivative (prepared from a perfluoroalkyl halide) is often employed as the nucleophilic species in the carbon-carbon bond forming reaction.

The trifluoromethyl-copper complex formed by treatment of trifluoromethyl iodide with copper powder in a polar solvent replaces iodo, bromo, or chloro substituents in pyrimidine and purine nucleosides to afford the corresponding trifluoromethyl nucleosides in moderate to good yields (Scheme 11). The mild reaction conditions leave unaffected the sugar moiety, the hydroxyl groups of which are usually, but not always, protected.[329,330] Similar reactions have also been performed with the pentafluoroethyl iodide copper complex.[331]

Scheme 11



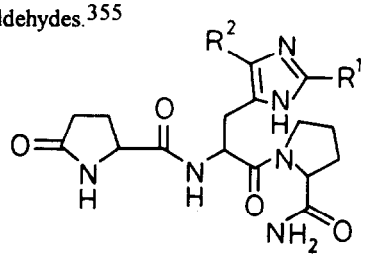
A perfluoroalkyl chain has also been introduced at C-5 of uridine systems by replacing an hydrogen atom on that site. By treatment of perfluorocarboxylic acids with xenon difluoride an intermediate trifluoromethyl radical is generated and it is intercepted by the base to afford the desired product.[332] Yields are lower than those produced by the perfluoroalkyl copper method.

Trifluoromethyl radicals generated by ultraviolet irradiation of trifluoromethyl iodide in pyridine solution preferentially substituted the α-hydrogen of some linearly conjugated dienone steroids.[333,334] Under similar reaction conditions, addition of trifluoromethyl iodide to unconjugated steroid olefins is preferred over hydrogen substitution.[335] The imidazole ring of histidine has also been photochemically trifluoromethylated to a mixture of C-2 and C-4 substitution products.[336-340] Methanol is used as solvent in this case and triethylamine as base. The same reaction has been performed on the tripeptide Glp-His-Pro-NH_2 (TRH, **25a**) and the two isomeric products 2- and 4(5)-CF_3-Im-TRH (**25b** and **25c**) were isolated in pure form.[341] Ultraviolet irradiation was also employed in the selective trifluoromethylation of the mercapto group of unprotected amino acids with trifluoromethyl iodide in liquid ammonia.[342]

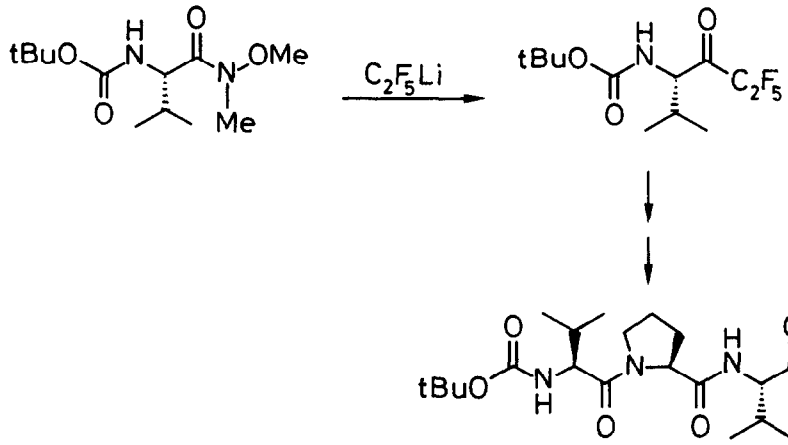
A new and efficient nucleophilic trifluoromethylating reagent is trifluoromethyltrimethylsilane. In this compound, the bond between the pseudohalogen trifluoromethyl and the trimethylsilyl group is polarised, with the trifluoromethyl group bearing substantial negative charge. Under fluoride ion catalysis clean addition of the trifluoromethyl group to carbonyl residues occurs at room temperature. This reaction has been performed on steroid ketones[343,344] with complete diastereoselection, while when sugar aldehydes have been used as substrates[345] a 1:1 mixture of the two trifluoromethyl products has been formed.

Perfluoroalkyllithiums have been added to the carbonyl group of optically pure arene-chromium tricarbonyl complexes to give the corresponding secondary or tertiary alcohols with high diastereoselectivity.[346-348] With boron trifluoride etherate the same organometallic species adds also to chiral imines with moderate to high diastereoselectivity.[349] 1,1-Dichloro-2,2,2-trifluoroethyllithium has been used to prepare (*S*)-2-hydroxy-4,4,4-trifluorobutyric acid,[350,351] and *in situ* formed pentafluoroethyllithium has been added to a peptidic *N,O*-dimethylhydroxamic acid to give a pentafluoroethyl ketone, which was further elaborated to the peptide analogue **26**, a potent inhibitor of human neutrophil elastase (eq. 21).[352]

Perfluoroalkylzinc compounds have been added to arene-chromium aldehydes.[353] Longer perfluorinated chains can be introduced by using these more stable organometallic derivatives, but the diastereoselectivity of the process is lower than that found when corresponding lithium organometallic derivatives were used. In the presence of catalytic Cp_2TiCl_2 and with ultrasound promotion, some perfluoroalkylzinc species add to an enamines derived from (*S*)-*O*-methylprolinol. The diastereoselectivity of the process is moderate and the absolute configuration of prevailing product was not established.[354] The employment of these milder reaction conditions allows the condensation of trifluoroethylzinc iodide with peptidic aldehydes.[355]



	R^1	R^2
25 a	H	H
b	CF_3	H
c	H	CF_3



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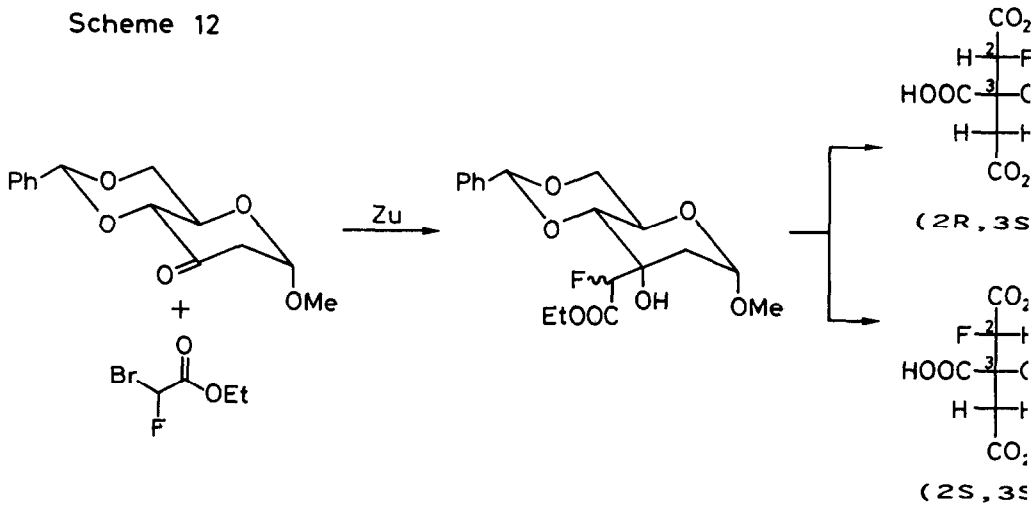
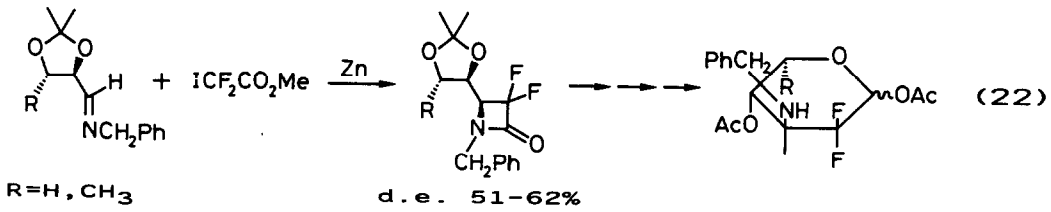
4.2.- Difluoromethylene Substituted Compounds

The Reformatsky reaction of fluorine-containing α-haloesters with carbonyl compounds has been use widely for the preparation of selectively fluorinated products. Methyl 2,2-dichloro-3,3,3-trifluoropropionat has been reacted with a protected serine aldehyde to give the corresponding α-trifluoromethyl-α,β unsaturated carboxylic acid ester[356] and ethyl bromofluoroacetate was condensed on a hexopyranos derivative to afford two diastereoisomeric monofluorinated adducts in a 3:1 approximate ratio (Scheme 12)

Scheme 12





These two intermediates were separately elaborated to give (2*S*,3*S*) and (2*R*,3*S*)-fluorocitric acid.[357]

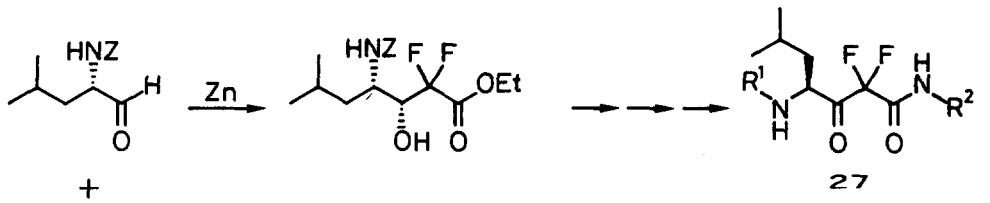
In most cases Reformatsky reactions have been performed starting from ethyl bromodifluoroacetate to afford α,α-difluoro-β-hydroxycarboxylic esters. On condensation with α-aminoaldehydes the formation of the *syn* products[358-361] is favoured and this stereochemical course can be rationalised in terms of chelation of zinc halide by the α-aminoaldehyde. The zinc derivatives formed starting from ethyl chlorodifluoroacetate or α-chloro-α,α-difluoroacetophenone behave in a similar manner, but yields are lower.[362] The same preference for *syn* products is observed when α-alkoxyimines are used as electrophiles (eq. 22), and this stereoselectivity can be rationalised by proposing the attack of the organometallic reagent on an α-chelated coordination species between the imine and zinc halide.[363] When α-hydroxyaldehydes are used as electrophiles,[364] the *anti* condensation products are formed preferentially[365,366] as predicted by Felkin's model for asymmetric induction (Scheme 13). The same stereochemical course has been observed for the Reformatsky reaction of bromodifluoromethylalkynes[367] and methyl iododifluoroacetate.[368,369] The highest diastereoisomeric excess is obtained by using the ketene silyl acetal prepared *in situ* by adding the appropriate silyl chloride to the zinc reagent formed from methyl iododifluoroacetate.[368-371] The ketene has also been employed for the synthesis of (+)-4,4-difluoroglutamic acid.

The initially formed 2,2-difluoro-3-hydroxycarboxylic esters of eq. 22 and Scheme 13 are useful intermediates for the synthesis of several biologically active compounds. 2'-Deoxy-2',2'-difluorocytidine **28** is an interesting anticancer agent. Various α,α-difluoroketone peptide analogues (**27**) have been shown to be effective "transition state analogue" inhibitors of several proteolytic enzymes (renin,[358,372-375] porcine pancreatic elastase,[376,377] human thrombin,[378] mung bean ATCase[379]). The nature of the R^1 and R^2 residues secures the target enzyme selectivity, while the α-fluoroketone moiety causes enzyme inhibition. Several peptidyl mono-, di-, and tri-fluoromethyl ketones[380,381] have shown a mechanistically similar enzyme inhibition (bovine chymotrypsin, porcine pancreatic elastase,[382] human leukocyte elastase,[383,384] acetyl-cholinesterase, carboxy peptidase A, pepsin[385]).

Chloroperfluorolefins are good electrophilic species and, for instance, the hydroxyl group of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose[386] easily adds to chlorotrifluoroethylene to give the fluoroether **29**, and the mercapto group of L-cysteine is easily combined with tetrafluoroethylene or chlorotrifluoroethylene to give **30a,b**. The 1,1-difluoroalkyl glucoside **29** is an effective enzyme-activated irreversible inhibitor of α-glucosidases, and the *S*-conjugates **30a,b** of cysteine are nephrotoxic and cytotoxic compounds.[387-390]

Fluorinated olefins have also been involved in cycloaddition reactions. The Diels-Alder reaction of a chiral ester of 2-trifluoromethylpropenoic acid has been employed in the synthesis of a precursor to 16,16,16-trifluororetinal,[391-393] while tetrafluoroethylene underwent a photochemical cycloaddition

Scheme 13



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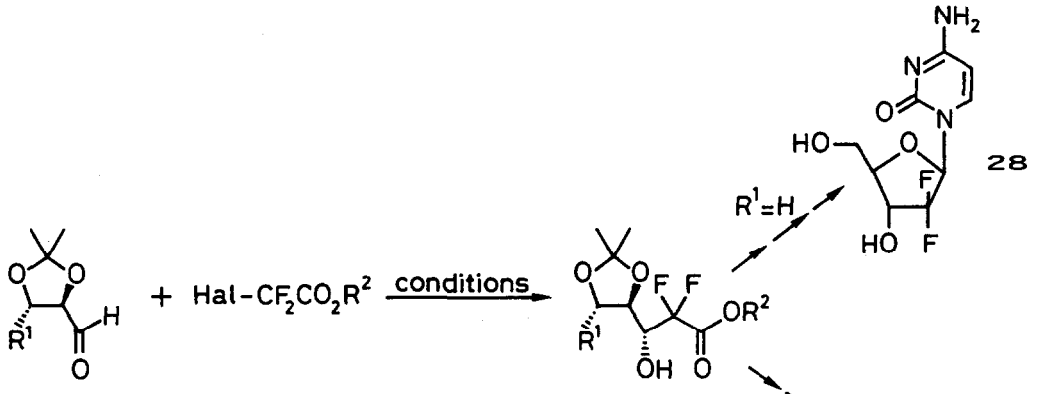
$Hal-CF_2CO_2Et$

Z	Hal	d.e.
t-BuOCO	Br	40
$PhCH_2OCO$	Cl	60



R^1	R^2	Hal	Conditions	Yield % (d.e.)
H	Et	Br	$Zn(Et_2O/THF)$	87(50)
H	Me	I	Zn(MeCN)	45(35)
H	Me	I	Zn(MeCN) then Et_3SiCl	74(80)
Me	Me	I	Zn(MeCN) then Et_3SiCl	90(88)

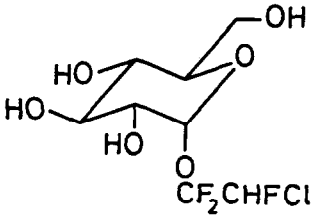
reaction with 3β-acetoxypregna-5,16-dien-20-one to afford a 16α,17α-cyclobutane adduct.[394]

In contrast to chloro- and bromo-polyfluoroalkenes, geminally fluorinated chloro-, bromo- and iodo-alkanes are poor alkylating agents and they have rarely been used as electrophilic species. The diastereoselective trifluoromethylation of chiral imide enolates has been performed by using iodotrifluoromethane in the presence of triethylborane.[395] The sodium enolate of a malonate derivative has

been alkylated with dichlorofluoromethane and the obtained product has been transformed into α-chlorofluoromethylornithine. The four enantiomers of this fluorinated aminoacid have been isolated in pure form through reversed-phase high-performance liquid chromatography with a chiral mobile phase.[35] The diastereoselective alkylation with chlorodifluoromethane of the lithium enolate of chiral amidines (obtained from α-amino acids and an optically pure prolinol derivative[396,397]) affords optically active α-difluoromethyl-α-amino acids.

Chlorodifluoromethane also alkylates sodium diethyl phosphite (Scheme 14) to give a diethyl difluoromethylphosphonate which has been transformed into a dinucleoside phosphate analogue (the *P*-deoxy-*P*-(difluoromethyl)thymidilyl(3'-5')thymidine) having the polar CF_2H group in place of the OH group of the natural phosphodiester linkage.[398] Similarly, other sodium dialkyl phosphites have been alkylated with bromodifluoromethylphosphonate esters (themselves prepared by a Michaelis-Becker reaction using dibromodifluoromethane) to give difluoromethanediphosphonate esters[399-401] which are used as isopolar, isosteric, and non-hydrolyzable analogues of the pyrophosphoric unit in several important biomolecules. For instance, several P^1,P^2- and P^2,P^3-fluoromethylene analogues of nucleoside triphosphates, **31a** and **31b,c** respectively, have been prepared and their biological properties studied.[402-409] Dibromodifluoromethane in the presence of tris(dimethylamino)phosphine brought about a smooth difluoromethylenation of the ester function of five- and six-membered carbohydrate lactones.[410,411] The difluoroenol ethers thus obtained have been hydrogenated and a stereospecific delivery of hydrogen from the convex face of the substrate afforded diastereoisomerically pure 2-difluoromethyl-tetrahydrofurans or -tetrahydropyrans. The difluoroenol ether moiety has also been alkylated and difluoromethylene linked C-glycosides were synthesized with high diastereoselection, but in low yields.

The difluoromethylenation reaction of the carbonyl group of a 17-ketosteroid has been carried out using difluoromethyldiphenylphosphine oxide[412] (synthesised from chlorodifluoromethane and diphenylphosphine oxide). This reagent failed with 2'-oxonucleosides, which required the employment of a modified Julia approach, i.e. the addition of the lithium derivative of difluoromethyl phenyl sulfone[413] followed by reductive elimination with samarium(II) iodide (eq. 23). A similar sequence employed *N*-methyl α-fluoromethyl phenyl sulfoximine for the fluoromethylenation reaction of 9-oxo-PGP_2.[414] Vinyl fluorides (E/Z mixtures) have also been prepared through a Horner-Wittig reaction of the carbanion of diethyl 1-fluoro-1-(phenylsulfonyl)methanephosphonate[415,416] (generated *in situ* from fluoromethyl phenyl sulfone and diethyl chlorophosphate) on sugar aldehydes and nucleoside ketones (eq. 23). Other reagents for



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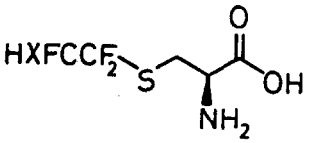
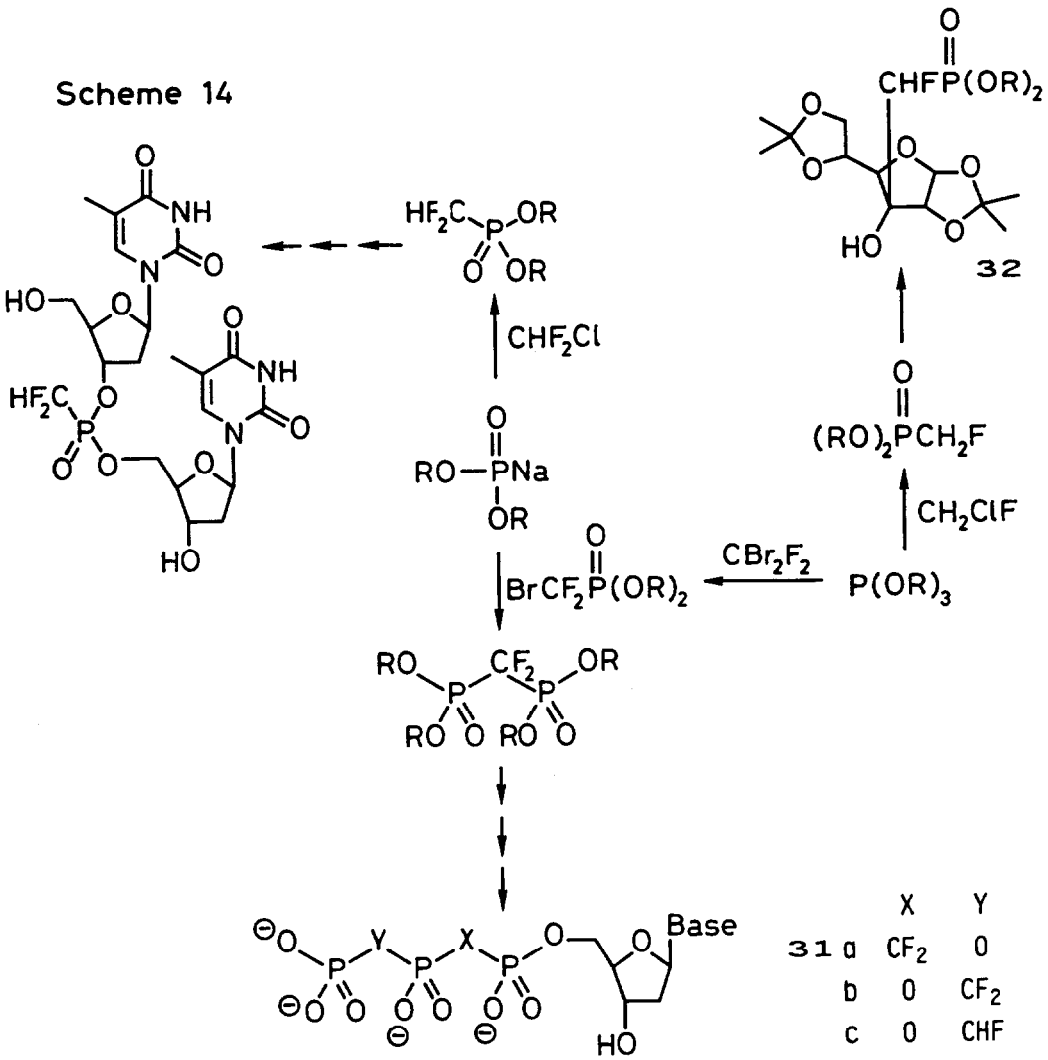


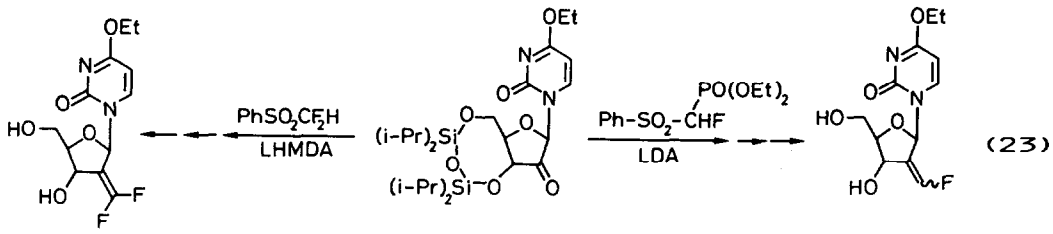
	X
30a	F
b	Cl

Scheme 14



fluoromethylenation of a carbonyl substrates are the fluoromethyl-triphenylphosphonium salts. On reaction with a 4-oxoproline derivative the ylids of these reagents give a mixture of (E)- and (Z)-4-fluoromethylene-L-proline in 4:5 ratio.[417,418]

Diisopropyl fluoromethylphosphonate is obtained by a Michaelis-Becker reaction of chlorofluoromethane with triisopropyl phosphite. Its lithium derivative reacts with a ribohexofuran-3-ulose derivative to give the two addition products **32** epimeric at the phosphonate α-carbon and resulting from selective attack from the less hindered *Si* face of the ketone (Scheme 14).[419] In contrast, a Wadsworth-Emmons reaction occurs when tetraethyl lithiumfluoromethylenebis-phosphonate is treated with



(23)

ribofuranoside aldehydes[420] or a 3-oxothreose.[421] The initially formed α-fluorovinylphosphonates are then hydrogenated to give α-fluoromethylenephosphonates useful in the study of glycolytic enzymes.

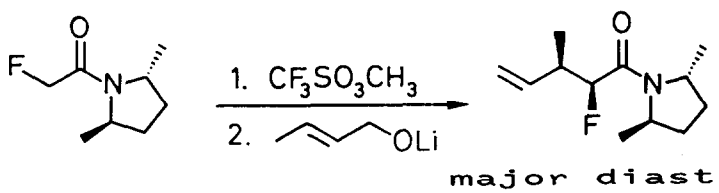
Mixed halofluoromethanes have also been used as fluorocarbene sources. On treatment with potassium *t*-butoxide chlorodifluoromethane produces $:CF_2$, which is trapped by the thio group of unprotected L-homocysteine to give the corresponding *S*-difluoromethyl product.[422] Fluorodiiodomethane and diethylzinc give a zinc-monofluorocarbenoid species which reacts with a chiral *N*-vinyl oxazolidone.[423,424] A *cis* fluorocyclopropyl amine is formed in good enantio- and diastereo-selectivity.

4.3.- Monofluorinated Compounds

When the key step in the synthesis of monofluorinated compounds is a carbon-carbon bond forming reaction, the source of the fluorocarbon framework is often the enolate of an α-fluorocarbonyl compound.

Ethyl fluoroacetate has been used as a two-carbon fluorinated synthon. The amide of fluoroacetic acid with (2*R*,5*R*)-2,5-dimethylpyrrolidine has been transformed into the *N,O*-ketene acetal of (*E*)-crotyl alcohol (eq. 24). This product has undergone an amide-acetal Claisen rearrangement at room temperature through a chair-like transition state with preferential *ul* approach from the *Si* face of the *N,O*-ketene acetal.[425] In another study, the aldol condensation of the lithium enolate of ethyl fluoroacetate (prepared from lithium hexamethyldisilazide) with (*R*)-2,3-*O*-isopropylideneglyceraldehyde has afforded a mixture of two stereoisomers having the same configuration at the newly formed hydroxylated stereocentre and opposite stereochemistries at the fluorinated carbon (eq. 25). This reflects the diastereofacial selectivity of the lithium enolates of ethyl fluoroacetate.[426]

The imines of fluoroacetone with the methyl ether of (*S*)-valinol or (*S*)-phenylalaninol have been used as chiral three-carbon synthons in alkylation reactions.[427] These imines have been regioselectively deprotonated and alkylated at the fluoromethyl group with moderate diastereoselectivity.



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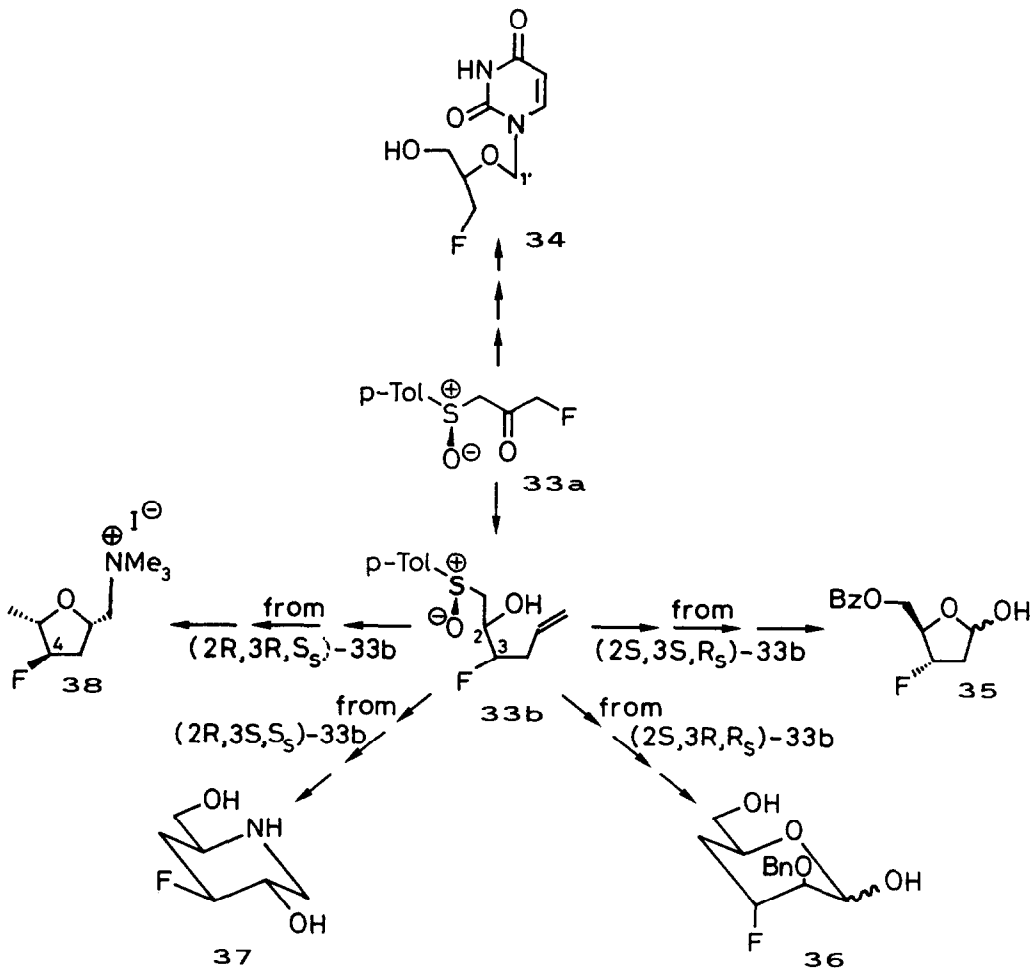
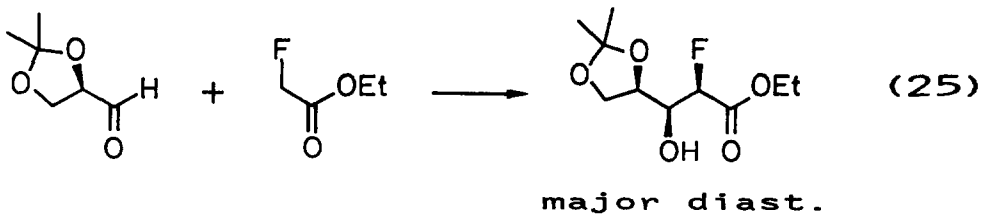
Scheme 15



Another fluorinated three-carbon synthon is α-fluoro-α'-sulfinylacetone[428] **33a**. Its carbon chain has been extended regioselectively at the fluoro- or sulfur-substituted termini through alkylation of the dilithium or monosodium derivative, respectively.[429] Alternatively, the carbonyl site can be either alkylated[430] or reduced[431,432] with high diastereoselectivity and under control of the configuration of the sulfur stereocentre. Different procedures for the removal of the auxiliary sulfoxide group from optically pure α-fluoro-α'-sulfinyl ketones and alcohols have been optimized and it has been possible to prepare fluoroorganic compounds containing various oxygen and nitrogen functionalities. For instance, α-fluoroepoxides[433,434] chiral at the fluorinated and oxygenated stereocentres, fluorohydrins[433,435,436] carrying cyano, oxime, hydroxylamino,[437-439] carboxymethyl, formyl, and hydroxymethyl groups, α-



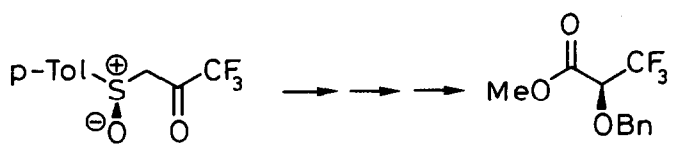
(25)

fluoroamines, α-fluoroalkylketones[440] carrying an alkyl, alkenyl, hydroxymethyl, or formyl residue have all been synthesised in enantiomerically and diastereoisomerically pure form.[441] These functionalities can be present either on acyclic carbon chains or on dihydropyran, tetrahydropyran,[442,443] or tetrahydrofuran[444,445] ring systems. Other preparations by similar methods have included the 1',2'-seco-2'-nor-nucleoside **34**,[446,447] the 2,3-dideoxy-3-fluoro-ribofuranose **35**[448], the 3,4-dideoxy-3-fluoro-lyxopyranose **36**,[449] the 1,3,4-trideoxy-3-fluoro-nojirimycin **37**,[450] and the 4-deoxy-4-fluoromuscarine **38**[451,452] (Scheme 15). Other diastereoisomers of these nucleosides, sugars, and alkaloids have also been prepared. Nucleosides containing the furanose **35** have proved to be highly active against the HIV virus, and fluoromuscarine **38** has showed affinity and relative efficacy similar to those of the parent unfluorinated alkaloid.

Various sulfinylmethyl ketones similar to **33a** but carrying a perfluoroalkyl instead of the fluoromethyl residue have also been prepared and elaborated into optically pure, sulfur-free, polyfluorinated products.[429,453,454] For instance, protected (*S*)-trifluorolactic acid has been synthesised starting from (*R*)-1-tolylsulfinyl-3,3,3-trifluoroacetone (eq. 26).[455,456]

The ultimate source of chirality in the synthesis of chiral sulfoxides is menthol, the two antipodes of which are cheap, commercially available products. As a consequence, both enantiomeric forms of the auxiliary sulfinyl group are easily available. Using this approach, it is always possible to synthesise the bioactive target compound with the desired absolute configuration.

Addition of the diacetone glucose modified titanium enolate of *t*-butyl acetate to the α-fluoroaldehyde **39** affords (eq. 27) the α-fluoroallylic alcohol **40a** in high optical purity.[457] Via an Overman rearrangement, this compound has been transformed into the α-fluoroallyl amine **40b,** which in turn was elongated to the full sequence of the neuropeptide substance P (SP) analogue **40c**. This fluoroolefin peptide isostere binds to the SP-receptor more than ten times more strongly than the unfluorinated analogue, thus proving the ability of the fluoroalkene moiety in **40c** to behave as a stable and effective dipeptide isostere.[458,459]



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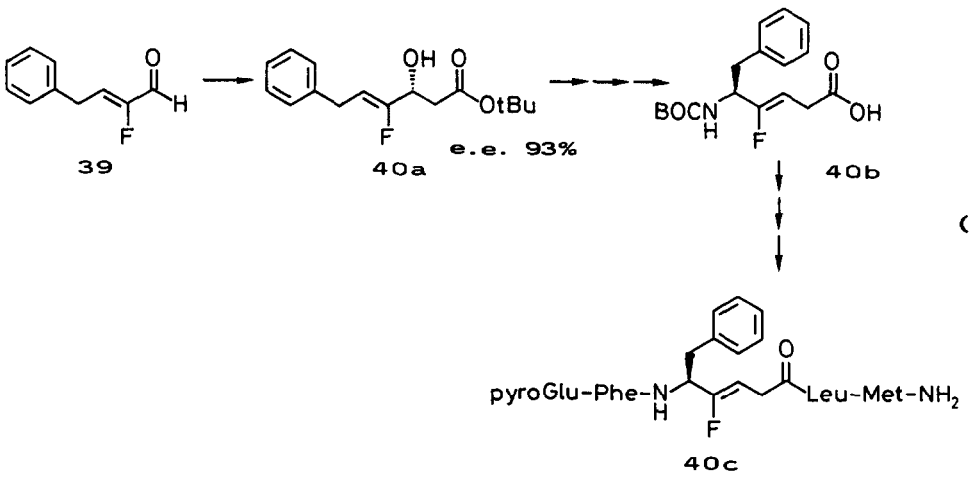
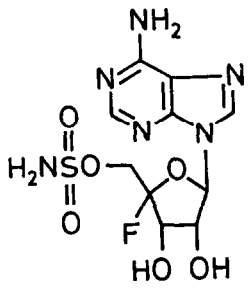


5.- ENZYMATIC PROCEDURES

The most common natural product containing fluorine is fluoroacetic acid, which is found in plants growing where the concentration of fluoride in the soil is high. Fluoroacetone and five other ω-fluorocarboxylic acids have been isolated from higher plants and they can be rationalised as metabolic products and/or biosynthetic precursors of fluoroacetate.

Fluoroacetyl CoA competes with acetyl CoA for the citrate (*Si*)-synthase in an enantio- and diastereo-selective process. *In vivo* and *in vitro* the enzyme catalyses the stereospecific abstraction of the pro-*S* proton of fluoroacetyl CoA, and the condensation of the anion on the *Si* face of oxaloacetate to give (2*R*,3*R*)-fluorocitric acid is greatly preferred over the other stereoisomers.[460-464] (2*R*,3*R*)-Fluorocitric acid is much more toxic than the other three possible isomers.[465-467] Citrate synthase accepts fluorooxaloacetate as a substrate and in this case too the preferential formation of the natural stereoisomer of fluorocitric acid is observed.[7a,460] Also, the catabolism of the two possible enantiomers of *erythro*-fluorocitric acid is different.



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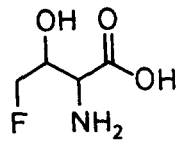


42

Two other chiral and naturally occurring compounds are nucleocidin **41**, a nucleoside carrying a fluorine atom on C-4' and endowed with interesting anti-trypanosomal activity,[468,469] and (-)-4-fluorothreonine **42**, which shows antimicrobial activity.[470]

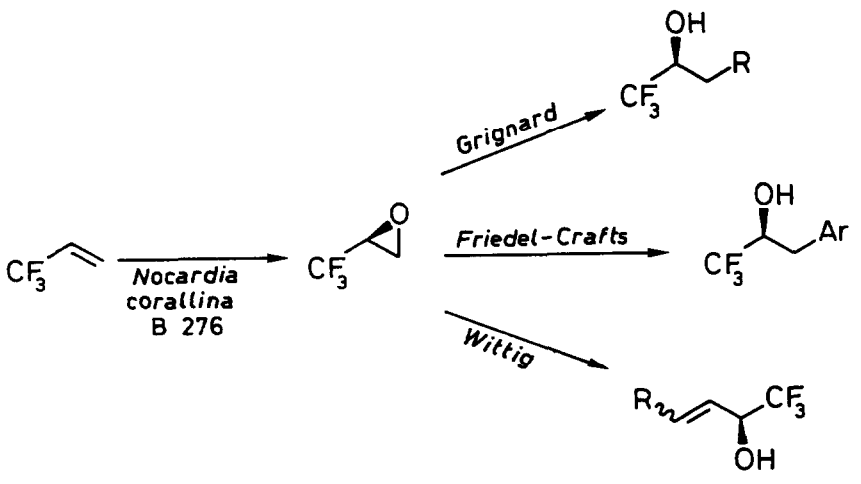
While the enzyme(s) forming the C-F bond in living organisms have not been studied in the detail,[471] a haloacetate halidohydrolase which is able to cleave the C-F bond has been purified and crystallised from *Pseudomonas sp.* strain A. It has been shown that this enzyme reacts preferentially with (*S*)-2-fluoropropionic acid to give D-lactic acid with inversion of configuration. The same stereochemical course was observed in the transformation of (*S*)-[2-$^2H_1$]-fluoroacetic acid into (*R*)-[2-$^2H_1$]-glycolic acid.[472] These results indicate a mechanism of cleavage of the strong C-F bond by the weak nucleophile H_2O with direct displacement of fluorine.

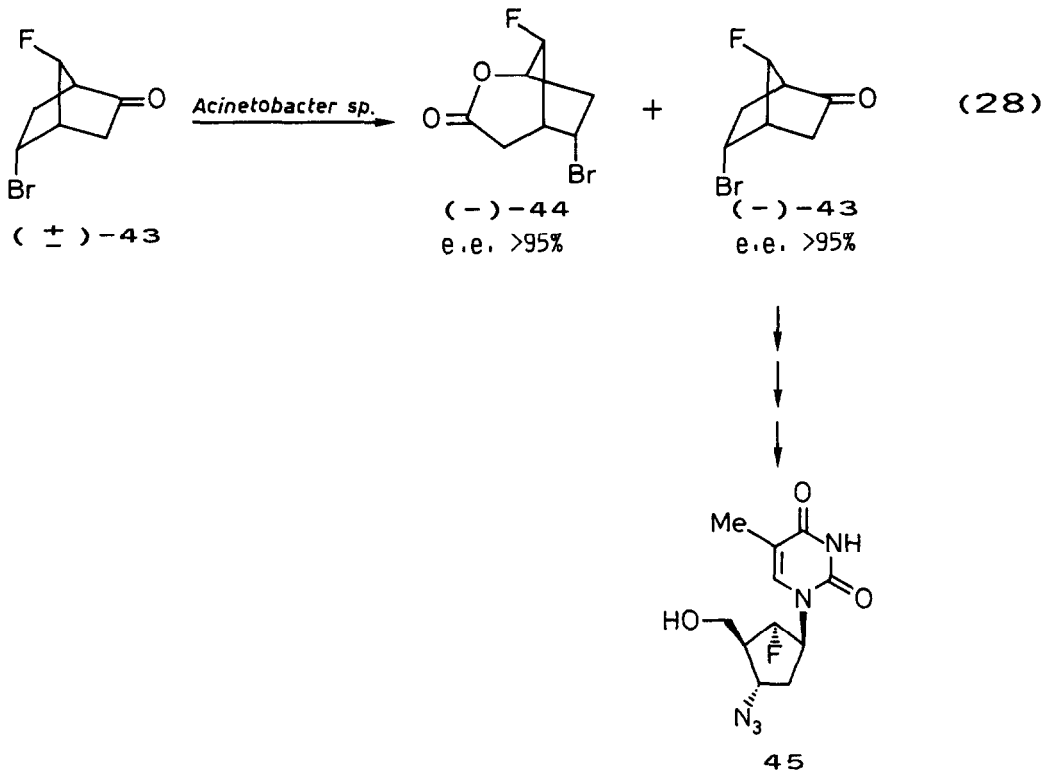
5.1.- Growing Microorganisms

While perfluorinated compounds are excreted unchanged by living organisms, partially fluorinated products can enter the biochemical pathway, and it often happens that a scalemic metabolite (catabolite) is formed by biotransformation of an achiral precursor. For instance, catabolism of the anticancer drug 5-fluorouracil[473,474] occurs with *trans* addition of hydrogen at the *Si*-face at C-5 and *Si*-face at C-6 of the pyrimidine ring and (*R*)-α-fluoro-β-alanine is formed selectively. (+)-Fluorosuccinic acid and (-)-4-carboxymethyl-4-fluorobutanolide have been isolated from the culture medium of a *Pseudomonas sp.* capable of growing on *p*-fluorophenylacetic acid as a sole carbon source.[475-477]

Systematic comparison of the hydroxylation positions of fluorinated substrates with the favoured hydroxylation sites in parent hydrogenated compounds shows that microbial oxidation at or adjacent to a fluorinated carbon is disfavoured.[478-480] Substitution of hydrogen by fluorine has often been exploited in attempts to protract the action of a drug by blocking the sites involved in oxidative degradation (so-called "obstructive halogenation"[481-486]).

Scheme 16



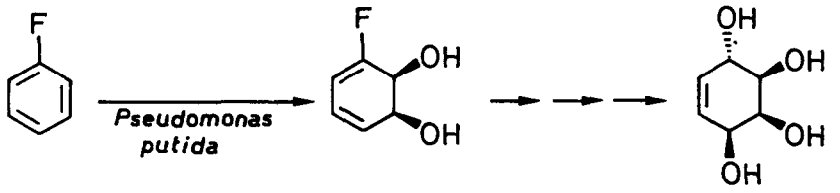


In some cases, however, microbial oxidation gives good yields of oxidation products, and interesting chirons have been prepared in this way.

3,3,3-Trifluoropropene has been oxidized to its (*S*)-epoxide in 75% e.e. by *Nocardia corallina* B 276.[487] Starting from this epoxide various trifluoromethylated alcohols have been prepared through regioselective Grignard, Friedel-Crafts, and Wittig-type reactions[488] (Scheme 16).

The monooxygenase enzyme system of *Acinetobacter* NCIB 9871 effected the kinetic resolution of the racemic ketone (±)-**43** by performing an enantioselective Baeyer-Villiger reaction (eq. 28).[489,490] The regiochemistry of the process is different from that found when peracids are used. Both the recovered (-)-**43** and the bicyclic lactone (-)-**44** show a high optical activity (>95%). The enantioselectivity of the microbial oxidation process is due to the presence of the halogen atoms since both enantiomers of bicyclo[2.2.1]heptan-2-one are oxidised by the bacterium. The recovered ketone (-)-**43** has been transformed into the antiviral carbocyclic nucleoside (+)-**45** with a fluoromethylene group replacing the oxygen atom of the ribose ring.

Some wild-type and mutant microbial strains defective in 3,5-cyclohexadiene-1,2-diol-1-carboxylic acid dehydrogenase (an oxidative enzyme on the catabolic pathway of benzenoids) have been used for the biotransformation of fluoroaromatic precursors to give chiral polyoxygenated fluoroorganic products in good yields.[491-493] No effective chemical process is available in order to perform the same transformation.



(29)

(1*S*,2*S*)-1,2-dihydroxy-3-fluoro-3,5-cyclohexadiene has been obtained by oxidation of fluorobenzene using *Pseudomonas putida*.[494] This chiron has been transformed into non-fluorinated (+)-conduritol c (eq. 29). The same microorganism oxidises *p*-fluorotoluene to (1*R*,2*R*)-6-fluoro-1,2-dihydroxy-3-methyl-3,5-cyclohexadiene.[495-498] Toluene, and *p*-chloro- and *p*-bromo-toluene also undergo *cis* dihydroxylation. The diol obtained from toluene is chiral and non racemic and the enantioselectivity of this biotransformation is the same of that observed for *p*-fluorotoluene. By contrast, the diols obtained from *p*-chloro- and *p*-bromo-toluene are racemic, showing that the size of the halogen atom and not its electronegativity is important for the enantioselectivity of this process.

When the three isomers of fluorobenzoic acid are biotransformed by the mutant strain BP of *Alcaligenes eutrophus*, a regio- and enantio-selective *cis* dihydroxylation occurrs across the C_1- C_2 bond, and all possible isomers of monofluoro 1-carboxy-1,2-dihydroxy-3,5-cyclohexadienes which differ in the position of the fluorine were obtained in optically active form.[499-501] The same regioselectivity was observed in the *cis* dihydroxylation of 3,4- and 3,5-difluorobenzoic acids by the mutant strain *Pseudomonas putida* JT 103.[502,503] The three isomeric 3,4-, 4,5-, and 3,5-difluoro-1,2-dihydroxy-2-carboxy-3,5-cyclohexadienes were obtained in optically active form and in high yields.

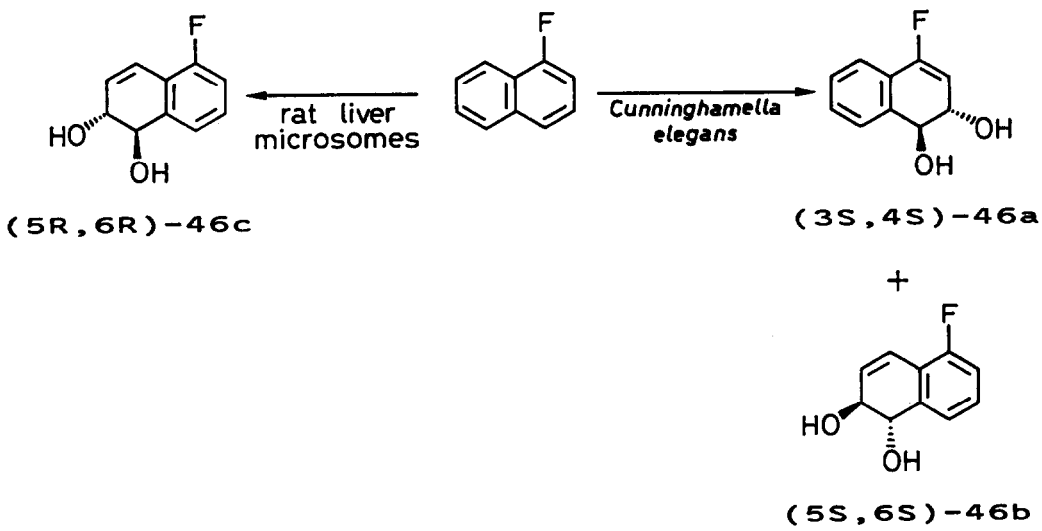
In the oxidation of aromatic substrates by bacteria (procaryotes) dioxygenases are involved and *cis*-diols are formed. In fungi and mammals (eucaryotes) the initial oxidation is catalysed by monooxygenases: arene-oxides are produced from which *trans* diols are formed.

The fungus *Cunninghamella elegans* transforms 1-fluoronaphthalene into *trans* (3*S*,4*S*)-3,4-dihydro-3,4-dihydroxy-1-fluoronaphthalene **46a** and the *trans* (5*S*,6*S*)-isomer **46b**, but for both products the enantiomeric excesses are low (≈ 20%) (Scheme 17). Conversely, rat liver microsome oxidation of 1-fluoronaphthalene affords regioselectively the *trans* 5,6-dihydroxylation product **46c** having the opposite absolute configuration to that produced by the fungus.[504]

The same microsomes oxidise 6-fluorobenzo[*a*]pyrene to the 7,8- 4,5-, and 9,10-dihydrodiols in >91% optical purity.[505-508] Several other fluorinated analogues of polycyclic aromatic hydrocarbons have been studied and it has been shown that fluorine effectively blocks oxidation at the double bond to which it is attached.

The reduction of some mono-[509,510] and poly-fluorinated[511] ketones has been realised in high enantiomeric excess using growing cultures of several microorganisms, despite the fact that α-fluoroketones are known to act as enzyme inhibitors. In some cases both enantiomers can be obtained in high chemical and optical yields by using different microorganisms.

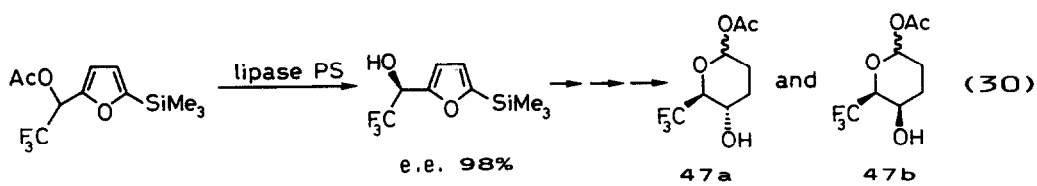
Scheme 17

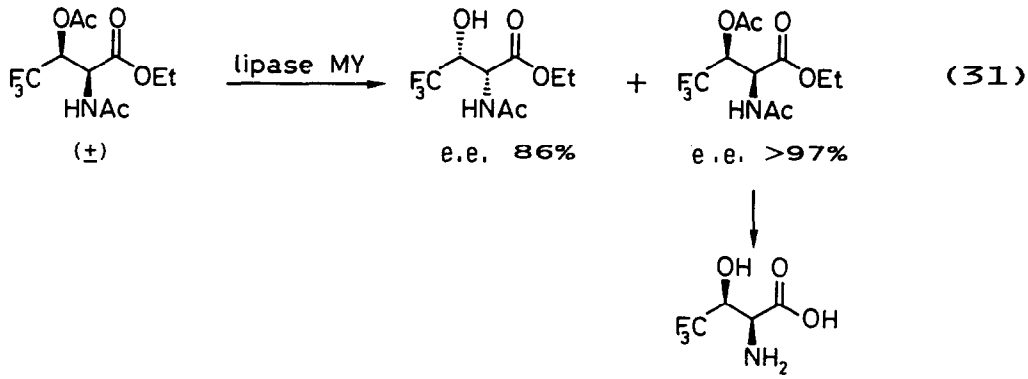


Enantioselective hydrolysis of the acetate of trifluoromethyl substituted cyanohydrins is achieved with *Bacillus coagulans*. The starting cyanohydrin acetate can be recovered in 30% yield and in optically pure form when incubation is performed with a ten-fold weight of dry cells.[512] Microbial asymmetric decarboxylation of fluorine-containing arylmalonic acid derivatives has been performed through incubation with *Alcaligenes brochisepticus*.[513]

5.2.- Hydrolytic processes

A wide range of trifluoromethyl carbinols carrying alkyl, aryl, heteroaryl, alkenyl, or alkynyl chains have been resolved by enantioselective hydrolyses of the corresponding esters (nearly always acetates) employing in most cases lipase MY (from *Candida cylindracea*) or lipase P (from *Pseudomonas fluorescens*). These two lipases show opposite enantioselectivities,[514,515] the former producing preferentially the alcohols having (*R*) absolute configuration.[516] The two hydrolyses in combination have often allowed both antipodes to be obtained in nearly pure form. In some cases cellulase (*Trichoderma viride*) has been used instead of lipase P in order to obtain the (*S*)-trifluoromethyl carbinol,[551,517] and the effect of enzyme immobilisation has been studied.[518]





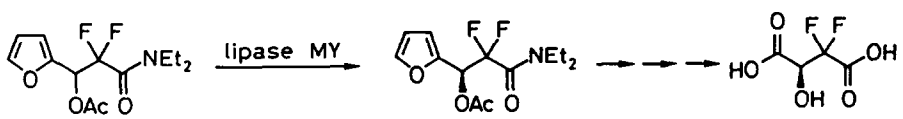
(31)

The presence of several functional groups in the substrate to be hydrolyzed (ketone, ester,[516] amide,[517] cyano,[519] sulfenyl, sulfinyl, and sulfonyl,[520] double or triple bonds,[521] ether[522]) does not interfere with the resolution process. Synthetic elaboration of these groups in the optically active alcohols obtained allowed the preparation of several polyfunctional molecules and some bioactive compounds (D-amicetose **47a** and D-rhodinose **47b**: eq. 30;[523] (2*S*,3*S*)-4,4,4-trifluorothreonine and its three possible stereoisomers: eq. 31[517]).

The same lipases have been employed for the resolution of 1,1-difluoroalkyl,[524] 1-fluoroalkyl,[525] chlorodifluoromethyl, chlorofluoromethyl,[514] difluoromethyl,[526] and fluoromethyl[527] carbinols. These resolution processes have been used, for instance, in the synthesis of optically pure (*S*)-β,β-difluoromalic acid (eq. 32),[524,528] (2*S*,3*S*)-4,4-difluorothreonine and its (2*R*,3*R*)-enantiomer.[529]

Obviously, fluorine can be present at either side of the ester moiety to be hydrolyzed; that is to say, the enzymatic hydrolysis of carboxylic esters can be used for the resolution not only of fluorinated alcohols, as described above, but also of fluorinated carboxylic acids. α-Trifluoromethylmandelic acid in 88% e.e. has been obtained by enantioselective cleavage of its methyl ester with *Aspergillus oryzae* protease at 40% conversion. At 60% conversion the recovered starting ester showed the same optical purity.[530] (*R*)-2-Trifluoromethyl-4-nitrobutyric acid has been isolated in optically pure form at 49% conversion of its benzyl ester with lipase P. The unreacted ester has been recovered and it was proven to be the pure (*S*) enantiomer.[531,532]

Besides α-trifluoromethylcarboxylic esters, α-monofluorinated carboxylic esters have also been resolved by this methodology. For example, the two enantiomers of 2-fluorohexanoic acid, an intermediate in the synthesis of prostaglandins and prostacyclins, are isolated in optically pure form starting from the ethyl ester using the bacterial lipase of *Pseudomonas fluorescens*.[533-535] The dissymmetrisation of diethyl 2-fluoro-2-methylmalonate through enantioselective hydrolysis of one of the two ester residues has been performed with opposite stereochemical results using lipases and cellulases.[536-538]



(32)

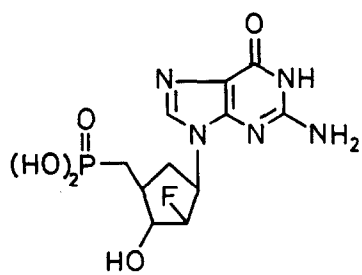
e.e. >99%

The optically pure α-fluoro-α-methylmalonate monoester so obtained has been transformed into several polyfunctional and monofluorinated compounds such as α-fluoro-α-methyl-β-keto esters[539] and -β-hydroxy esters,[540,541] dihydroxymonofluoroketones, and α-fluoro-β-amino acids.[542,543] Fluorinated analogues of angiotensin converting enzyme have also been prepared.[544]

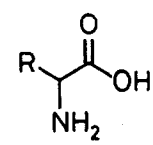
Phosphoric esters have also been resolved enzymatically. The 2'-fluorocarbocyclic nucleoside **48** has been isolated in non racemic form after incubation of the corresponding monoester with 5'-nucleotidase (EC 3.1.3.5) from *Crotalus atrox* venom.[545]

Hydrolytic enzymes have also been used to catalyze the Michael addition of oxygen, nitrogen, and sulfur nucleophiles to α- or β-trifluoromethylpropenoates. The products were usually formed in low to medium optical purity.[546-548]

The enzymatic resolution of fluorinated amino acids has been performed by hydrolysis both of an ester and an amide derivative of the amino acid. Specifically, chymotrypsine has been used with the isopropyl ester of *threo*-BOC-3-fluorophenylalanine[549] and with the methyl ester of 5-fluorotryptophan.[550] Lyophilized yeast has allowed the efficient resolution of the three nuclear monofluoro-substituted phenylalanine ethyl esters.[551] The *N*-trifluoroacetyl derivatives of 7-fluoro-, 4,7-difluoro-, and 5,7-difluoro-tryptophan **49a-c** were transformed into optically pure unprotected L-amino acids by treatment with carboxypeptidase A.[552] On chemical hydrolysis, the recovered unreacted amides afforded optically pure D-amino acids. Acylase I afforded enantiomerically pure L-*threo*-3-fluoroglutamic acid **49d** starting from the racemic *N*-acetyl derivative.[553,554] By similar enantioselective *N*-deacetylation processes the same enzyme allowed the preparation of L-*erythro*-3-fluoroglutamic acid (e.e. >90%), L-4-fluorohistidine **49e** (e.e. >98%),[555,556] ω-fluoro-L-isoleucine **49f** and its allo isomer.[557] Among trifluoromethyl substituted amino acids, α-trifluoromethylalanine and its β-analogue **50a**,[558] ω-trifluoromethyl-α-aminobutyric and valeric acids[559,560] (**50b** and **50c**, respectively), *S*-trifluoromethylcysteine **50d** and its *S*-difluoromethyl analogue[561] have all been resolved by action of an acylase on corresponding *N*-acetyl or *N*-trifluoroacetyl derivatives.

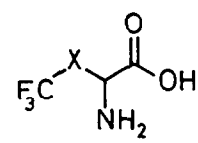


48



R

49 a 7-fluoroindol-2-yl
b 4,7-fluoroindol-2-yl
c 5,7-fluoroindol-2-yl
d -CHFCH$_2$COOH
e 4-fluoro-histidin-5-yl
f -CH(CH$_3$)CH$_2$CH$_2$F



X

50 a CH_2
b CH_2CH_2
c $CH_2CH_2CH_2$
d CH_2S

In other cases the resolution of racemic fluorinated amino acids into single pure enantiomers has been performed by chemical methods, i.e. formation and separation of diastereoisomeric derivatives. 3-Fluoro-2-deuterioalanine has been resolved with quinine,[562,563] and α-difluoromethylornithine with binaphthylphosphoric acids.[564] Fluorinated amino acids have also been resolved by formation of a dipeptide[565,566] or polypeptide with optically pure amino acids or through the same type of resolution applied to a suitable precursor.[567] This is the case, for instance, of 5,5,5-trifluoroleucine[568-570] and hexafluorovaline.[571,572] Some other important bioactive compounds such as isoflurane,[573-575] a commonly employed volatile anaesthetic, and a trifluoro analogue of captopryl,[576] have been obtained in optically pure form by chemical resolution.[577-584]

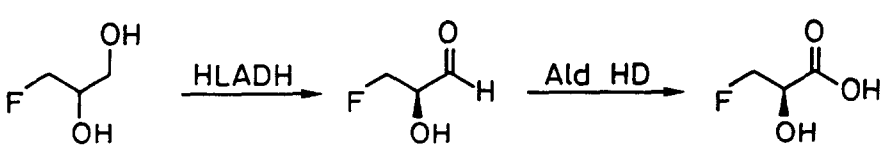
Another interesting approach to optical resolution is preferential crystallisation. A fundamental prerequisite for this kind of resolution is that the D,L-form is a racemic mixture (conglomerate, i.e. an eutectic mixture of D and L crystals) and not a racemic compound. Fenfluramine has been resolved through preferential crystallisation of salts with achiral acids.[585,586] Similarly, continuous resolution by preferential crystallisation of the benzenesulfonate salt of 3-fluoro-D,L-alanine-2d has afforded both enantiomers in high optical purity.[563] The D-form of this amino acid is an effective antibacterial drug.[587-589]

Much more interesting is the use of catalytic antibodies. Immunogenic conjugates prepared starting from specifically designed phosphonates have been used to induce catalytic antibodies for hydrolytic processes with the desired enantio- and diastereo-selectivity. 1,2- Or 1,3-diastereoisomeric mixtures of monofluoro and trifluoromethyl compounds have been resolved into single pure enantiomers having the *syn* or *anti* relative configuration.[590,591]

5.3- Oxido-reductases

In the great majority of enzymatic oxidoreduction reactions described in the literature, the fluorinated substrate is reduced and fluorine is not directly bound to the carbon(s) at which the reaction occurs.[592] An example of the few enzymatic reactions occurring with oxidation of the substrate is the enantioselective oxidation of 3-fluoro-1,2-propanediol by horse liver alcohol dehydrogenase (HLADH). The corresponding aldehyde is formed and further oxidised *in situ* to the enantiomerically pure (*R*)-β-fluorolactic acid (eq. 33) by yeast aldehyde dehydrogenase.[593] The use of immobilized enzymes has no effect on chemical or optical yields. Complementarily, (*S*)-β-fluorolactic acid can be obtained by the reduction of β-fluoropyruvic acid with L-lactate dehydrogenase.[594]

Other alcohol dehydrogenases (ADH) have been used successfully on fluorinated substrates. For instance, ADH from *Lactobacillus kefir* and *Thermoanaerobium brokii* reduces trifluoroacetophenone with complete and opposite enantioselectivity. The corresponding alcohols, having the (*R*) and (*S*) absolute configuration, respectively, are formed in good chemical yields.[595-597] ADH-catalysed reductions require NAD(P)H cofactors. It is interesting to observe that NADH itself[597] and some models[598-600] have been



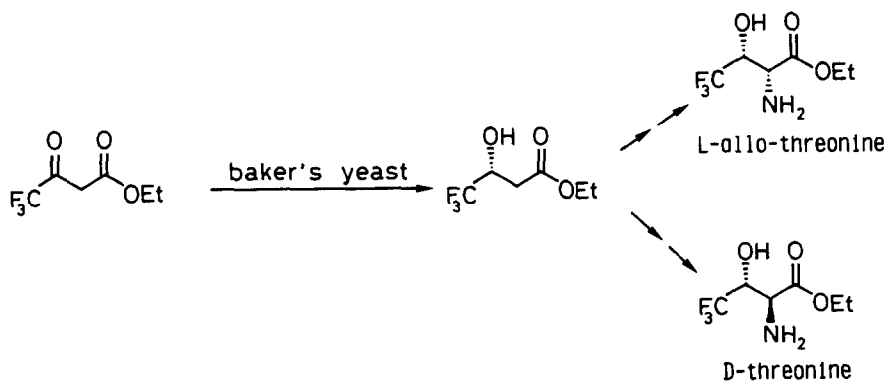
(33)

employed for the enantioselective reduction of fluorinated acetophenones, but the enantiomeric excesses of the isolated alcohols are lower than those obtained with the ADH systems.

The most commonly employed enzyme system in oxidoreduction reactions is baker's yeast. It has afforded the dithioacetal of (*S*)-β-fluorolactic aldehyde in nearly pure form through reduction of the dithioacetal of β-fluoropyruvic aldehyde.[601] Several other monofluorinated substrates have been effectively processed, e.g. α-fluoroacetophenone ((*R*)-alcohol, e.e. 97%),[602] α-fluoro-α'-sulfenyl-, or sulfinyl-, or sulfonyl-acetone ((*S*)-alcohols in all cases, e.e. >97%, 89%, and 87%, respectively),[511,520] 2-fluoro-1,5-diketones, (e.e. 5-42%).[603] Ethyl 2-fluoroacetoacetate affords a mixture of *syn* and *anti* 2-fluoro-3-hydroxybutyrates. The enantiomeric excess of *syn* isomer is high (92%) while that of the *anti* product is significantly lower (44%).[604] In contrast, both *syn* and *anti* ethyl 2-fluoro-2-methyl-3-hydroxybutyrates were formed in nearly optically pure form (e.e. >98%) by reduction of non-enolizable and enantiomerically pure ethyl (*R*)-2-fluoro-2-methyl-3-oxo-butyrate and its (*S*)-enantiomer, respectively. This implies that the hydride enters from the *Re*-face of the carbonyl independently of the configuration of the adjacent fluorinated carbon.[540]

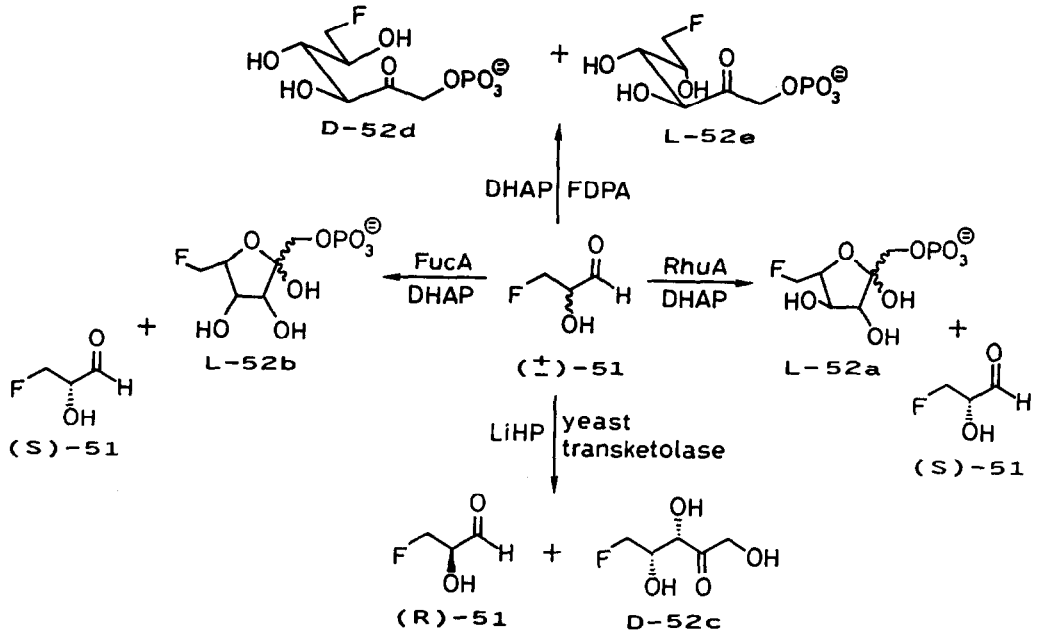
Several perfluoroalkyl substituted ketones have been reduced by baker's yeast.[605-610] An alkyl-perfluoroalkyl ketone is reduced preferentially with respect to a dialkyl ketone. For instance, 1,1,1-trifluoro-2,4-pentanedione afforded (*S*)-5,5,5-trifluoro-4-hydroxy-2-pentanone in high regio- and enantio-selectivity .[611] Furthermore, perfluoroalkyl substituted allylic alcohols can be obtained in medium to high optical purity from the corresponding α,β-unsaturated ketones if the perfluorinated chain is located on the carbon-carbon double bond.[612] Saturated alcohols are formed starting from alkenyl perfluoroalkyl ketones.

Finally, fermenting baker's yeast reduced ethyl 4,4,4-trifluoro-3-oxobutyrate to the corresponding (*R*)-3-hydroxybutyrate on a preparative scale. The enantioselectivity of the process is not high (45%), but the optically pure product (e.e. >98%) can be obtained on crystallisation.[604,613] This trifluorohydroxybutyrate has been efficiently transformed into several other trifluoromethylated products[614] such as butyro- and valero-lactones,[615] ethyl trifluoroglycidate[616,617] and, more interestingly, D-4,4,4-trifluorothreonine and its L-allo-isomer (eq. 34).[618,619]



(34)

Scheme 18



When trifluoroethanol and an α,β-unsaturated ketone or ester were treated with baker's yeast, γ-hydroxy-γ-trifluoromethyl ketones or esters were formed through a carbon-carbon bond forming reaction.[620] Chemical yields were low, but high e.e.s were obtained.

Purified enzymes perform the same processes in a more efficient way.[621] The transcarboxylase catalysed carboxylation of 3-fluoropyruvic acid is stereospecific as (2*R*,3*R*)-3-fluoromalic acid is isolated exclusively after *in situ* reduction, with malate dehydrogenase, of the initially formed 3-fluorooxaloacetate.[622] L-Rhamnulose 1-phosphate aldolase (RhuA) and L-fuculose 1-phosphate aldolase (FucA) perform a highly enantio- and diastereo-selective addition of dihydroxyacetone phosphate (DHAP) to racemic 3-fluorolactic aldehyde **51** (Scheme 18). Both microbial aldolases display an overwhelming kinetic preference for (*R*)-3-fluorolactic aldehyde. Starting from the racemic substrate supplied in excess, a single step preparation of 6-deoxy-6-fluoro-L-fructose 1-phosphate L-**52a** (95% yield) and L-tagatose 1-phosphate L-**52b** (86% yield) has been performed with absolute and relative control of configuration at three contiguous chiral centres.[623] Obviously, the recovered fluorolactic aldehyde **51** is enriched in the (*S*)-antipode. (*R*)-3-Fluorolactic aldehyde can be obtained in optically pure form through kinetic resolution with yeast transketolase.[624] In fact, this enzyme catalyses the reaction of lithium hydroxypyruvate (LiHP) exclusively with the (*S*)-enantiomer of racemic 3-fluorolactic aldehyde to give 5-deoxy-5-fluoro-D-xylulose D-**52c** and unreacted optically pure (*R*)-**51**. No similar enantioselectivity for the substrate has been shown by fructose diphosphate aldolase (FDPA),[625] which catalyses an aldol condensation between DHAP and both enantiomers of 3-fluorolactic aldehyde. This reaction is stereospecific in the sense that exclusively the pro-*R* proton of DHAP is removed and a 1:1 mixture of 6-deoxy 6-fluoro-D-fructose 1-phosphate and -L-sorbose 1-phosphate, D-**52d** and L-**52e**, respectively, is formed.

6.- CONCLUSIONS

Fluoroorganic, bioactive compounds in enantiomerically pure form are of great importance in order to assemble a detailed description of the recognition of fluorine containing molecules by biological receptors.

When the introduction of a single fluorine atom in a molecule is performed following the approach of the functional group interchange (viz. substitution of fluorine for hydroxyl or halogen) *nucleophilic* sources of fluorine are used. By contrast, direct fluorination of a substrate (viz. substitution of fluorine for hydrogen) is realised using *electrophilic* sources of fluorine.

DAST is the source of fluoride anion more commonly employed for the replacement of hydroxyl by fluorine. The chemical yields are often high, but a stereochemical disadvantage of the process is the fact that the leaving group generated *in situ* at the alcohol carbon atom (through reaction of DAST with the hydroxyl group) is rather prone to undergo S_N1 processes or to be involved in neighbouring group participations. FARs Present the same drawbacks, so that new reagents having a similar chemical reactivity, but a cleaner stereochemical profile would be useful.

An alternative approach to optically active alkyl fluorides is the kinetic resolution of racemic alcohols through a fluorodehydroxylation reaction. A chiral variant of DAST would effect this kind of transformation. Only one compound of this type (viz. **14a**) has been reported and other reagents able to perform highly enantioselective fluorodehydroxylation reactions are very desirable.

The "naked" fluoride anion is a powerful nucleophile. The poor reactivity frequently described in organic reactions is due to the fact that the fluoride anion has a marked proclivity for becoming hydrated, a process which causes a consistent decrease in nucleophilicity. The preparation and use of really anhydrous fluorides is presently troublesome. An easier availability of "naked" fluorides would probably allow milder reaction conditions to be employed and higher chemical and optical yields to be obtained.

The traditional reagents for electrophilic fluorination have a limited shelf-life, and are often highly aggressive, sometimes explosive, toxic, unstable, and hygroscopic. Recently, compounds containing the N-F functionality have been developed as alternatives for these hazardous reagents. *N*-fluorosulfonamides and, above all, *N*-fluorobissulfonimides are the most promising compounds from both chemical and stereochemical point of view as the stability and the reactivity of these reagents are suitably balanced. The handling of these agents does nor require any special apparatus and electrophilic fluorination reactions can now be included in a multistep synthesis as routinely and plainly as any other organic transformation.

The total asymmetric synthesis of fluorinated, bioactive compounds can now take advantage of the fact that some fluorinated chirons are commercially available (e.g. ethyl (*R*)-4,4,4-trifluoro-3-hydroxybutyrate) and others can be easily prepared in hundred gram scale (e.g. (*R*) and (*S*)-1-fluoro-3-tolylsulfinylacetone). The specific effect of the presence of a fluorine atom or a fluorinated residue on the stereochemical course of most reactions still needs to be studied before some predictive generalisations can be assembled.

It is now apparent that although fluoroorganic compounds are practically xenobiotic substances, the presence of this halogen does not prevent other functional groups present in the molecule from undergoing the usual biotransformation processes. While of great interest, the enzyme-catalysed, asymmetric formation and cleavage of the carbon-fluorine bond have not yet been explored.

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