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Bioorganic and Medicinal Chemistry of Fluorine

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and
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FOREWORD

In 1886, Henri Moissan achieved the isolation of elemental fluorine, and this discovery was awarded twenty years later by the Nobel Prize (1906). At the time of this discovery, Moissan was working in a place that was not geared toward this kind of research: the Faculty of Pharmacy in Paris. These studies were certainly not oriented toward potential commercial products, and Moissan could not imagine the important applications that took place one century later in the field of pharmaceuticals. Indeed, pharmacy and more generally life sciences have become major fields in fluorine chemistry. This story is instructive in the current debate between pure and applied research.

For decades, fluorine was a laboratory curiosity and it was studied mainly by mineral chemists. As is often the case, it was coincidence and not planned research that gave rise to fluorine chemistry. The development of the organic chemistry of fluorine is a direct consequence of the Manhattan Project: in order to build nuclear weapons, the isotopic enrichment of natural uranium into its radioactive isotope was needed. For this purpose, the chosen process involved gas diffusion, which required the conversion of uranium into gas: uranium hexafluoride (UF_6) was thus selected. In order to produce UF_6 gas on a large scale, fluorhydric acid and elemental fluorine were needed in industrial quantities. This was the birth of the fluorine industry.

Some powerful companies, such as Dupont de Nemours, took advantage of these new possibilities in inorganic chemistry and in the field of polymers. Indeed, new materials with exceptional properties were developed, and some fluorinated polymers are now famous under their trademark names (e.g., Teflon™, GoreTex™).

Actually, it was in the early 1950s that the organic chemistry of fluorine really emerged. Within only two or three years, some major applications were developed such as fluorinated general anesthetics and the antitumor properties of fluorouracil.

Above all, Fried found out that introducing fluorine in corticosteroids had tremendous effects on their biological properties. After this discovery, this family of compounds became major drugs.

The study of fluorouracil and of fluorocorticosteroids showed that the presence of a single fluorine atom in a molecule could deeply modify its biological properties. At a conceptual level, this was a determining step.

Despite these great discoveries, for a long time fluorine chemistry remained more oriented toward the field of materials than toward medicinal chemistry. This can be explained by the fact that a traditional source of inspiration often comes from nature, and organofluorine compounds are almost absent as natural products. Moreover, the only one known at that time was fluoroacetic acid, a potent poison.

The organic chemistry of fluorinated compounds (and bioorganic chemistry) is a relatively young field that only emerged some thirty years ago. Since the 1990s, the achievements in this field have been extremely fast and important, and organic chemistry of fluorinated compounds has reached a level of sophistication in line with other sectors of bioorganic and medicinal chemistry.

In the beginning, organic chemistry of fluorinated compounds was mainly oriented toward aromatic and heterocyclic chemistry. This explains the prominence of fluorinated aromatic moieties in pharmaceuticals and crop science products. Nevertheless, great methodological improvements have been achieved in fluorination and trifluoromethylation techniques over the last few years, and new reagents and building blocks have been developed. This has led to important advances that allow research of more ambitious targets. As a consequence, an exceptional number of fluorinated drugs and agrochemicals with increasing variety and structure complexity are being used or are in development. The percentage of fluorinated compounds on the pharmaceutical market has increased from 2% in 1970, to 8% in 1980, to 13% in 1990, and to 18% in 2000, with six drugs in the top 12. It is worth noting that fluorinated compounds are found in various domains of the pharmacopoeia. They are also found in the field of biocompatible materials and in that of agrochemicals, which will not be considered in this book. Indeed, among agrochemicals, fluorinated compounds represent almost 50% of the market (3% in 1970, 10% in 1980, and 28% in 1990).

This book is intended for chemists who are interested in bioorganic and medicinal chemistry. Its aim is to give an overview of the various applications of fluorinated compounds in these areas. *Bioorganic and Medicinal Chemistry of Fluorine* is divided in two main parts: the first one deals with generalities concerning the specific properties of fluorinated compounds and their preparation; the second part is dedicated to the different classes of fluorinated compounds involved in bioorganic chemistry and to their biological properties.

In Chapter 1, the main effects resulting from the introduction of fluorine atoms into a molecule are recalled. Chapter 2 focuses on the specific methods used to prepare fluorinated compounds, while Chapter 3 surveys the potential role of fluorine atoms in the biological activity of a molecule.

The second part of this book is composed of five chapters successively dedicated to fluorinated analogues of natural products, to fluorinated amino acids and peptides, and

to saccharidic derivatives. Chapter 7 deals with fluorinated enzyme inhibitors. The primary drugs containing fluorine atoms that are, already on the market or in development, are the subject of the last chapter.

Despite the quantity of collected data over the last fifty years, many questions remain about the effects induced by the presence of fluorine atoms on biologically active molecules. Indeed, the frequency of fluorine in pharmaceuticals has generally stemmed from structure–activity studies rather than rational predictions. In this book we attempt to rationalize and comprehend the role of fluorine in bioactivity.

The vastness of the field as well as its rapid evolution means that this book cannot (and does not mean to) be exhaustive. The choice of subjects was subjective and perhaps arguable. We hope this will stir the reader's imagination and interest to venture further into the field.

A number of people have made production of this book possible. We acknowledge Bruno Figadère, who was with us at its origin. During this work, Bernard Badet, Jean-Daniel Brion, Micheline Charpentier-Morize, Philippe Durand, Michel Langlois, Thierry Lequeux, André Loupy, and Patrick Rollin helped us with inspired suggestions. We are grateful to Françoise Lesquibe for her help with the references.

We would also like to thank the authors of the various reviews and books that really helped us. Among them, Kenneth Kirk, Klaus Burger, Tomoya Kitazume, Valery Kukhar, Vadim Soloshonok, Philip Edwards, Bruce Smart, and Takashi Yamazaki are especially acknowledged.

PREFACE TO THE ENGLISH EDITION

This book was originally written in French and published in 2005 under the title *Chimie bioorganique et médicinale du fluor* (EDP Sciences/CNRS Editions). Shortly after publication, it became clear that an English version of this book would be of high interest to the scientific community. During international symposiums and lectures abroad, numerous colleagues expressed their enthusiasm for this idea, and this prompted us to start. Two years later, the work was finished and *Bioorganic and Medicinal Chemistry of Fluorine* was born. A simple glance at the title could lead readers to think that it is just a translation of the original work. Actually, it is more a "Second Edition" as there are several points of improvements: (1) references have been updated to spring 2007 for some chapters (2004 for the original edition); (2) some paragraphs have been completely modified for clarity; and some new sections have been added.

Finally, we are honored that the publication of this book almost meets the 100th anniversary of Henri Moissan's Nobel Prize.

Jean-Pierre Bégué
Danièle Bonnet-Delpon

Julien Legros
Châtenay-Malabry, June 2007

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GENERAL REMARKS ON STRUCTURAL, PHYSICAL, AND CHEMICAL PROPERTIES OF FLUORINATED COMPOUNDS

This chapter deals with modifications of the physical and chemical properties of an organic molecule, which are induced by the replacement of hydrogen atoms by fluorines. These changes in the physicochemical properties play an important role in the behavior of the molecule when it is put into a biological environment.

Compounds with a few fluorine atoms (arbitrarily, from a single F to a C_2F_5 group) are called "lightly fluorinated" molecules and are the focus of bioorganic and medicinal chemistry. In these compounds, the presence of fluorine atoms severely modifies their chemical reactivity, but it has only a modest influence on their physical properties. In contrast, the physical characteristics of "highly fluorinated" (perfluorinated) molecules are strongly affected with regard to their "hydrogenated analogues." Despite their important applications in the biomedicinal field (e.g., biocompatible materials and polymers, surfactants, gas carriers), such compounds are only marginally considered in this book. However, some physicochemical aspects of perfluorinated molecules are introduced in this chapter to better comprehend the properties of lightly fluorinated molecules.

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

1.1 STRUCTURAL EFFECTS

Most of the effects induced by the presence of fluorine atoms in a molecule come from both the structure and the fundamental atomic properties of the fluorine atom (Table 1.1). Because of its electronic structure $1s^2\ 2s^2\ 2p^5$, fluorine has very specific properties, as indicated by the extreme values of the atomic parameters given in Table 1.1.[1–3]

The very high ionization potential[1] and the low polarizability[2] of the fluorine atom imply that fluorinated compounds have only weak intermolecular interactions. Thus, perfluoroalkylated compounds have very weak surface energies, dielectric constants, and refracting indexes.

The very high electronegativity of fluorine[3], its small size, the excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon, and the presence of three lone pairs of electrons mean that a fluorine atom borne by a carbon atom is always, on an inductive level, an electron-withdrawing substituent. Bonds are always strongly polarized from the sp^3 carbon (δ^+) to the fluorine (δ^-). These features associated with the low polarizability of the fluorine atom, implies that the C—F bond has a relatively important ionic character and a stronger energy than the bond between carbon and the other halogens.

The dipolar nature of the C—F bond in lightly fluorinated molecules gives a polar character to these molecules[4]. Consequently, their physico-chemical properties can be quite different from those of hydrocarbon compounds and from those of the corresponding perfluorinated compounds.

In brief, the effects of fluorination on the molecular properties stem from the combination of the atomic properties of the fluorine atom: strong electronegativity, small size, excellent overlap of the 2s or 2p orbitals with the corresponding orbitals of carbon, and very strong bond with carbon.

Table 1.1 Atomic parameters of fluorine atom[1,2,3]

Atom	Ionization Potential (kcal/mol)	Electron Affinity (kcal/mol)	Atom Polarizability (Å^3)	Van Der Waals Radii (Å)	Pauling's Electronegativity χ_p
H	313.6	17.7	0.667	1.20	2.20
F	401.8	79.5	0.557	1.47	3.98
Cl	299.0	83.3	2.18	1.75	3.16
Br	272.4	72.6	3.05	1.85	2.96
I	241.2	70.6	4.7	1.98	2.66
C	240.5	29.0	1.76	1.70	2.55
N	335.1	− 6.2	1.10	1.55	3.04
O	314.0	33.8	0.82	1.52	3.44

1.2 PHYSICAL PROPERTIES

1.2.1 Boiling Point

Highly fluorinated molecules have a nonpolar character and an extremely low polarizability, inducing only weak intra- and intermolecular interactions. As a consequence, perfluorocarbons behave almost like ideal liquids: they are very compressible and have very high vapor pressure. For example, the physical properties of perfluorohexane, heptafluorohexane, and hexane are reported in Table 1.2.[1] The effect of the polar character of the hemifluorinated compound (heptafluorohexane) on the dielectric constant value is remarkable.

Except in some rare cases, the boiling points[1] of perfluorinated compounds, functionalized or not, are always lower than those of their hydrogenated analogues Table 1.3). Conversely to what is observed with the halogenated analogues, branching has only a minor effect on the boiling point. Indeed, perfluoroisopentane has a boiling point (bp) close to that of *n*-fluoropentane, while the bp of isopentane is much less than that of *n*-pentane.

The bp of a perfluoroalkane is only 25–30 °C higher than that of the rare gas with the same molecular weight. This illustrates the "perfect" fluid character of these compounds, resulting from the low intermolecular interactions.

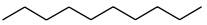
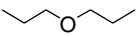
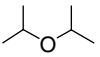
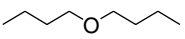
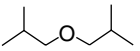
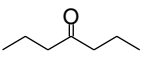
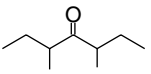
While the boiling points of chloro- and bromomethanes always increase according to the number of halogen atoms, this correlation does not exist in the case of fluoromethanes. The bp increases from CH_4 to CH_2F_2 and then decreases until CF_4 (Table 1.4).[1] Indeed, a parallelism exists between boiling points and dipolar moments. A partially fluorinated compound will exhibit nonnegligible intermolecular interactions according to the importance of the dipolar moment (Table 1.5).[1]

Fluorinated compounds, even the lightly fluorinated ones, have a high vapor pressure with respect to those of their hydrogenated analogues. Fluorinated molecules are often volatile, even when the boiling point is relatively high. Consequently, careful

Table 1.2 Comparative physical properties of *n*-hexanes (perfluorinated, hemifluorinated, and non fluorinated hexanes)[1]

Property	C_6F_{14}	$CF_3(CF_2)_2(CH_2)_3H$	C_6H_{14}
Boiling point (°C)	57	64	69
Heat of vaporization ΔH_v (kcal/mol)	6.7	7.9	6.9
Critical temperature T_c (°C)	174	200	235
Density, d^{25} (g·cm^3)	1.672	1.265	0.655
Viscosity, η^{25} (cP)	0.66	0.48	0.29
Surface tension, γ^{25} (dyn/cm^{-2})	11.4	14.3	17.9
Compressibility, β (10^{-6} atm^{-1})	254	198	150
Refractive index, $n_D{}^{25}$	1.252	1.292	1.372
Dielectric constant, ε	1.69	5.99	1.89

Table 1.3 Effect of fluorination on boiling points[1]

				
bp (°C)	"F"	29.3	30.1	29.5
	"H"	36.1	27.9	9.5
				
bp (°C)	"F"	144		53
	"H"	174		81
				
bp (°C)	"F"	56		54
	"H"	90		69
				
bp (°C)	"F"	111		98
	"H"	142		122
				
bp (°C)	"F"	75		72
	"H"	143.5		123.7
				
bp (°C)	"F"	81		
	"H"	82		

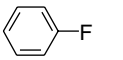
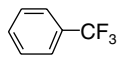
	bp (°C)		bp (°C)
			85
CF_3-COOH	78		105
CH_3-COOH	118		
CCl_3-CF_3	43		112
CCl_3-CH_3	75		

Table 1.4 Boiling points of halomethanes[1]

Compound	bp (°C)	Compound	bp (°C)	Compound	bp (°C)
CH_4	−161	CH_4	−161	CH_4	−161
CH_3F	−78.6	CH_3Cl	−24.2	CH_3Br	3.6
CH_2F_2	−51.6	CH_2Cl_2	40.1	CH_2Br_2	98.2
CHF_3	−82.2	$CHCl_3$	61.3	$CHBr_3$	149.5
CF_4	−128	CCl_4	98.2	CBr_4	189.5

Table 1.5 Dipole moments (μ) and boiling points of fluoromethanes and fluoroethanes[1]

Parameter	CH_4	CH_3F	CH_2F_2	CHF_3	CF_4	CH_3CH_3	CH_3CF_3	CF_3CF_3
μ (D)	0	1.85	1.97	1.65	0	0	2.32	0
bp (°C)	−161	−78	−52	−82	−128	−89	−47	−78

handling of fluorinated compounds is required during isolation to avoid possible accidental inhalation of these toxic substances.

1.2.2 Surface Tension and Activity

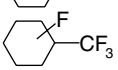
The surface tension γ measures the molecular forces that oppose the extension of the area of a liquid dropped on a surface. A perfluoroalkane always has a surface tension lower than that of the corresponding alkane (Table 1.6).[1,5,6] Perfluoroalkanes are able to wet any kind of surface. Perfluoroamines and -ethers also have low surface tensions (15–16 dyn/cm^2).[1]

Fluorinated surfactants lower the surface tension of water more strongly than their nonfluorinated analogues. Fluorinated surfactants reduce the superficial pressure of water from 72 to 15–20 dyn/cm^2 while a nonfluorinated agent only decreases the value to 25–35 dyn/cm^2 (Table 1.6).

Perfluorocarbons bearing a polar hydrophilic head are very active surfactants.[4b] Indeed, the presence of fluorine atoms strongly lowers the critical micelle concentration (CMC) of an amphiphilic compound. Moreover, fluorination generally has important effects on micellization phenomena, especially on the size and shape of formed micelles.

Hemifluorinated compounds $F(CF_2)_m—(CH_2)_nH$ often have a particular behavior. Because of their strong polarity, these compounds are able to form micelles in fluorocarbon as well as in hydrocarbon media.[5]

Table 1.6 Surface tension γ (dyn·/cm^2) and CMC (mM) values of perfluorinated compounds[1,5,6]

Compound	γ (dyn/cm^2)	Compound	γ (dyn/cm^2)	CMC (mM)
$CH_3—(CH_2)_4—CH_3$	17.9	$CF_3—(CF_2)_6—CO_2H$	15.2	2.8
$CH_3—(CH_2)_4—CH_2F$	19.8	$CHF_2—(CF_2)_6—CO_2H$	21.8	
$CH_3—(CH_2)_4—CF_3$	17.9	$CF_3—(CF_2)_7—CO_2NH_4$	14.8	6.7
$CF_3—(CF_2)_4—CHF_2$	12.6	$CF_3[OCF_2CF(CF_3)]OCF_2—CO_2NH_4$	17.5	7.0
$CF_3—(CF_2)_4—CF_3$	11.4	$C_8F_{17}CH_2[(C_2H_4O)_3CH_3]_2$	19	0.012
	23.3			
	15.4			

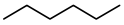
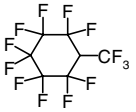
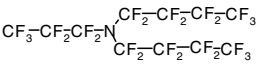
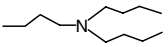
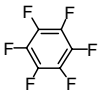
1.2.3 Polarity-Solubility

Paradoxically, fluorinated compounds are found among the least polar compounds (perfluorocarbons) as well as among the most polar ones (fluorinated alcohols), according to the empirical scale of Middleton (P_s). Some representative examples of fluorinated solvents and related hydrogenated compounds are given in Table 1.7.[7] Perfluorocarbon compounds, almost apolar, are nonmiscible with both water and hydrocarbon compounds. They are able to dissolve only compounds with very low cohesive energies, such as gases and highly fluorinated molecules.

This very specific ability of perfluorinated compounds to dissolve gases has found an application in oxygen carrier liquids (short-time blood substitutes). A perfluorocarbon dissolves three times more oxygen than the corresponding hydrocarbon, and ten times more than water. This property can be explained by the presence of large cavities in the liquid and by the weak intermolecular interactions of the medium, and not by specific interactions.

Replacing some of the fluorine atoms by hydrogen atoms increases the polarity.[4a] Hydrofluorocarbons are more polar than the corresponding perfluorocarbons. They can also be even more polar than their hydrocarbon analogues.[8]

Table 1.7 Middleton polarity index (P_s) of fluorinated and nonfluorinated compounds[7]

Compound	P_s	Compound	P_s
CF_3–CF_2–CF_2–CF_2–CF_2–CF_3	0.00		2.56
	0.46		3.34
	0.68		3.93
CF_2Cl—$CFCl_2$	3.22	$CHCl_2$—$CHCl_2$	9.23
$CFCl_3$	3.72	$CHCl_3$	4.64
CF_3Cl_3	3.22	CH_3Cl_3	7.03
	4.53		6.96
CF_3—COOEt	6.00	CH_3—COOEt	6.96
	7.86		8.94
CF_3—CH_2OH	10.2	CH_3—CH_2OH	8
CF_3—CHOH—CF_3	11.1	CH_3—CHOH—CH_3	7.85
		H—COOH/H_2O_2 50%	10.64

1.2.4 Lipophilicity

Lipophilicity is of prime importance in the design of drugs. Indeed, it controls many parameters such as absorption, biological barrier passage (and consequently transport into organs and cells), and also interaction with the macromolecular target (cf. Chapter 3).

In the case of fluorinated molecules, it is important to differentiate the lipophilic character from the hydrophobic character. Both these characters are in tune for nonfluorinated molecules, but they diverge when the number of fluorine atoms increases in a molecule. It is generally recognized that fluorination induces an increase in the lipophilicity. However, this has only been demonstrated for aromatic compounds, and more specifically when fluorine atoms are in the α position of atoms, or groups bearing π electrons (Table 1.8).[4a] Conversely, the presence of fluorine atoms in an aliphatic molecule provokes a decrease in the lipophilicity, while it can enhance the hydrophobicity. This phenomenon is so important that highly fluorinated molecules are not soluble in organic solvents or in water and constitute a third phase.

The confusion between these two characteristics is common in medicinal chemistry. It comes from the usual empirical measurement of the lipophilicity, which is the logarithm of the partition coefficient between 1-octanol and water (log P). This parameter gives a representative overview of a compound absorbed by a lipidic membrane, an essential datum in medicinal chemistry. It is often considered that the higher the log P value is, the more lipophilic the compound is. Actually, the log P value is only a measurement of relative solubility. Considering that the solubility of a fluorinated substance decreases more in water than in octanol, this measurement leads one to think that fluorinated compounds are more "lipophilic." Actually, this represents the relative lack of affinity of fluorinated compounds for both phases.

Table 1.8 shows some Hansch–Leo π values for aromatic compounds ($\pi = \log P_{C_6H_5X} - \log P_{C_6H_5X}$ for substituted benzenes).[9] Note that the effects of fluorination can be relatively important (e.g., C_6H_5—SO_2CF_3 is ~150 times more lipophilic than C_6H_5—SO_2CH_3).

Table 1.8 Hydrophobic Hansch–Leo π values (log $P_{C_6H_5X}$—log $P_{C_6H_6}$)[9]

Substituent	π (log P_X – log P_H)	Substituent	π (log P_X – log P_H)
F	0.14	SCH_3	0.61
Cl	0.71	SCF_3	1.44
NO_2	–0.27	SO_2CH_3	–1.63
CH_3	0.56	SO_2CF_3	0.55
CF_3	0.88	$NHSO_2CH_3$	–1.18
CH_3CH_2	1.02	$NHSO_2CF_3$	0.92
CF_3CF_2	1.89	CH_3–C=O	0.02
OH	–0.67	CF_3—C=O	0.55
OCH_3	–0.02	CH_3—CO—NH—	–1.27
OCF_3	1.04	CF_3—CO—NH—	0.08

Table 1.9 Octanol–water partition (log *P*) of aliphatic compounds[9,10]

Compound	log *P*	Compound	log *P*	
CH_3—CH_3	1.81	CH_3—$CHCl_2$	1.78	
		CH_3CHF_2	0.75	
$CH_3(CH_2)_3CH_3$	3.11	$CH_3(CH_2)_3CH_2F$	2.33	
Compound	log *P*	Compound	log *P*	Δlog *P*
CH_3CH_2OH	−0.32	CF_3CH_2OH	0.36	0.68
CH_3—CH_2CH_2OH	0.34	CF_3—CH_2CH_2OH	0.39	0.05
CH_3—$CH_2CH_2CH_2OH$	0.88	CF_3—$CH_2CH_2CH_2OH$	0.90	0.02
CH_3-$CH_2CH_2CH_2CH_2OH$	1.40	CF_3—$CH_2CH_2CH_2CH_2OH$	1.15	−0.04
CH_3—$CH_2CH_2CH_2CH_2CH_2OH$	1.64	CF_3—$CH_2CH_2CH_2CH_2CH_2OH$	1.36	−0.28

For aliphatic molecules, the data are rarer. Nevertheless, partial fluorination lowers the log *P* value, conversely to aromatic molecules. For alcohols, the situation is more complex: the log *P* value is dependent on the position of fluorine atoms and on the chain length (Table 1.9).[9, 10]

The log *P* value strongly depends on the solvent system chosen as a reference (e.g., cyclohexane/water versus octanol/water), since associations and hydrogen bonds are highly depending on the nature of the solvent. This is highlighted in the case of functionalized fluorinated molecules, where fluorination strongly modifies hydrogen bonding (Table 1.10).[9]

Trifluoromethyl ketones, which are enzyme inhibitors, constitute an interesting example: the log *P* value depends on the equilibrium between hydrate, hemiketal, and ketone and the equilibrium is itself less important than the solvent. The solubility of each of these forms also depends on the solvent's nature. For these reasons, the observed log *P* values are often difficult to interpret.

Table 1.10 Solvent effects on solvent–water partition[9]

Compound	log *P* (octanol/water)	log *P* (cyclohexane/water)
C_6H_5—OH	1.48	−1.00
C_6F_5—OH	3.23	−0.52
Compound	Log *P* (octanol/water)	Log *P* (hexane/water)
CH_3CO—CH_2—CO—CH_3	0.26	0.02
CH_3CO—CH_2—CO—CF_3	0.29	−0.50
Compound	log *P* (Et_2O/water)	log *P* (benzene/water)
CH_3—COOH	−0.36	−1.74
CF_3—COOH	−0.27	−1.89

1.3 EFFECTS ON ELECTRONIC PROPERTIES AND REACTIVITY

In a molecule, fluorine atoms influence bond energies, electronic distribution, acidity, hydrogen bonds, steric interactions, and the stability of intermediate entities in a transformation. These factors, which have great influence on chemical reactivity, are examined.

1.3.1 Effects of Fluorination on Bond Energies and Reactivity

The C—F bond is the strongest bond that a carbon atom can form with another atom. For example, the C—F bond is 25 kcal/mol stronger than the C—Cl bond. Moreover, the strength of the C—F bond increases with the number of fluorine atoms borne by the carbon, conversely to what occurs with the other halogens (Table 1.11).[8, 11] α-Fluorination does not have much influence on the C—H bonds, but it increases the strength of the C—F, C—O, and C—C bonds. For example, in the bis(trifluoromethyl) ether CF_3—O—CF_3, the C—O bond is 22 kcal/mol stronger than that of dimethyl ether. The C—C bond of trifluoroethane is more than 10 kcal/mol stronger than that of ethane, and also stronger than that of hexafluoroethane (Table 1.11). Strengthening of the C—F bonds by fluorination explains the great stability of the CF_3 groups. In contrast, β-fluorination strongly increases the C—H bond strengths (Table 1.12).[8] The C—H bond in $(CF_3)_2$C—H is 15 kcal/mol stronger than in $(CH_3)_2$C—H. However, β-fluorination has little effect on C—F bonds.

This strengthening of C—F, C—H, and C—O bonds, through α- or β-fluorination, gives fluoroalkyl compounds a significantly greater chemical, thermal, and enzymatic

Table 1.11 Bond dissociation energy of methanes, ethanes, and halogenoethers[8,11]

	$D°$(C—X) (kcal/mol)							
Compound	H	F	Cl	Br	CH_3	CF_3	OCF_3	OCH_3
CH_3—X		108.3	82.9	69.6	88.8	101.2		83.2
CH_2X_2		119.5	81.0	64				
CHX_3		127.5	77.7	62				
CX_4	104.3	130.5	72.9	56.2				
CF_3—X	106.7	130.5	87.1	70.6	101.2	98.7	105.2	

Table 1.12 C—X bond dissociation energies of halogenoethanes[8]

	$D°$(C—X) (kcal/mol)			
X	CH_3CH_2—X	CH_3CF_2—X	CF_3CH_2—X	CF_3CF_2—X
H	100.1	99.5	106.7	102.7
F	107.9	124.8	109.4	126.8
Cl	83.7	—	—	82.7
Br	69.5	68.6	—	68.7
I	55.3	52.1	56.3	52.3

inertness compared to their nonfluorinated analogues. Highly fluorinated, or perfluorinated, polymers exhibit very high thermal and chemical stabilities, which justify their use in the field of biocompatible materials, volatile anesthetics, and artificial blood.

The C—F bond strength renders the aliphatic fluorides much less reactive than the corresponding chlorides in S_N1 or S_N2 reactions (from 10^{-2} to 10^{-6}). In fluoroalkenes, the C—F bond is also strong: the more fluorine atoms there are, the stronger the π double bond is. In general, the reactivity of these double bonds decreases with electrophiles while it increases with nucleophiles.

1.3.2 Effects of Fluorination on the Electronic Repartition of a Molecule

Due to the inductive effect, fluorine is always an electron-withdrawing substituent. Nevertheless, it can be electron-donating through resonance. Fluoroalkyl groups always behave as electron-withdrawing substituents. The bond polarization is given in Figure 1.1.

When bonded to an unsaturated carbon atom or to an arene, the fluorine atom exerts an inductive electron-withdrawing effect ($\sigma_I > 0$) and an electron-donating effect through resonance ($\sigma_R < 0$), both being very superior to the effects of the other halogens (Figure 1.1).[12] The values of the Hammet parameters σ_I and σ_R of some fluorinated substituents are reported in Table 1.13.[1,13,14,17]

The effect of fluorination on the reactivity of the ketone carbonyl group is important. Applications in enzymology are given in Chapters 3 and 7. Nucleophiles such as water, alcohols, and, amines add easily to fluoroaldehydes and fluoroketones, providing stable adducts (e.g., hydrates, hemiketals). Trifluoroacetaldehyde (fluoral) is commercialized only under its stable forms: hydrate and hemiketal. The great electrophilicity of the carbonyl is commonly attributed to an increase in the positive charge of the carbonyl (charge control). However, *ab initio* calculations on

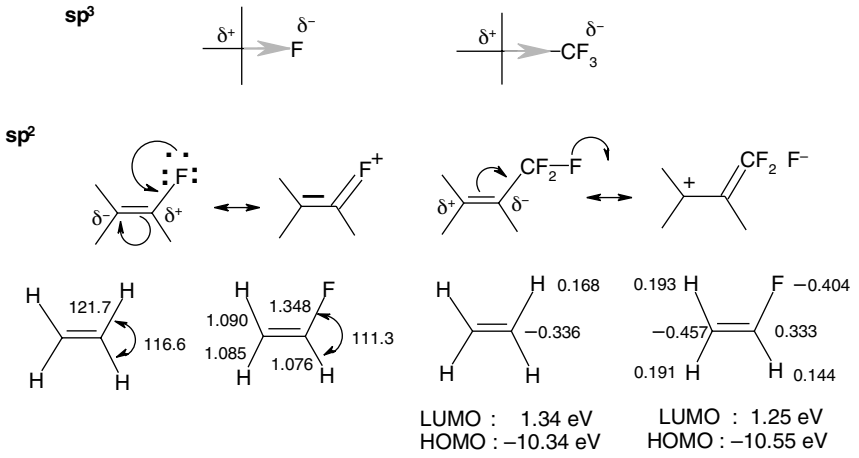


Figure 1.1 Fluorination electronic effects.[12]

Table 1.13 Hammet's electronic constants of fluorinated substituents[1,13,14,17]

Substituent	σ	$\sigma_{inductive}$	$\sigma_{resonance}$	Substituent	σ	$\sigma_{inductive}$	$\sigma_{resonance}$
F	3.10	0.52	−0.46	CH_3O		0.29	−0.43
Cl		0.47	−0.24	CF_3O		0.39	−0.18
Br		0.44	−0.22	CH_3S		0.23	−0.16
NO_2		0.56	0.22	CF_3S	2.73	0.42	0.02
OH		0.29	−0.43	$CH_3\ SO_2$		0.48	0.16
CH_3		0.04	−0.15	$CF_3\ SO_2$	4.41	0.73	0.31
CH_2F-	1.17			$CH_3\ SO_2NH$		0.42	−0.21
CHF_2-	2.0			CF_3SO_2NH		0.49	−0.10
CF_3	2.60	0.42	0.10	$(CF_3SO_2)_2\ N$		0.70	0.10
CH_3CH_2		0.05	−0.11	C_6H_5	0.60	0.08	−0.1
CF_3CH_2	0.90	0.14	−0.05	$F-C_6H_4-$	0.63		
CF_3CF_2		0.41	0.11	$CF_3-C_6H_4-$	0.96		
$CF_3-CF_2-CF_2-$	2.83			C_6F_5	1.50	0.25	0.02
				C_6H_5-CO-	2.20		
				CN		0.56	0.08

fluoroacetaldehydes have shown that the charge on the carbonyl does not vary significantly, while the length of the C=O bond and the negative charge of the oxygen atom are lowered by the fluorination (Figure 1.2).[15] Different type of computational studies show that the electrophilicity may result from a significant lowering of the carbonyl's LUMO (orbital control) (Figure 1.3).[15,16]

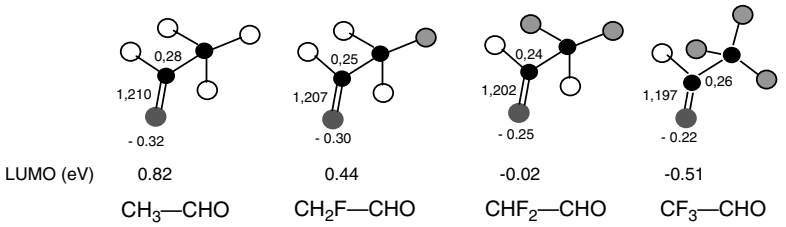


Figure 1.2 Fluoroacetaldehydes: length of C=O bond and electronic repartition.[15]

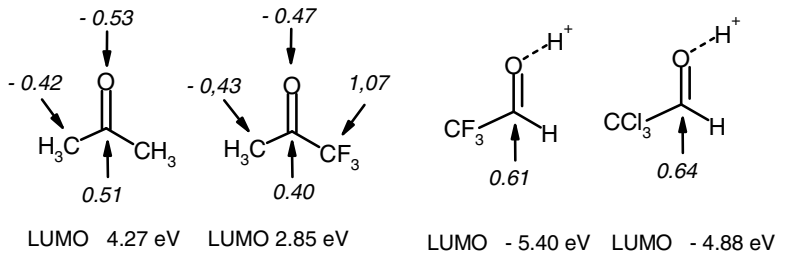


Figure 1.3 Calculated charge density (HF-31G**) and LUMO energy of acetone and acetaldehydes.[16]

1.3.3 Acidity, Basicity, and Hydrogen Bond

1.3.3.1 Acidity Fluoroalkyl groups are strong electron-withdrawing substituents; consequently, the acidity of neighboring hydrogen atoms is greatly increased (Table 1.14).[8,17–20] pK_a of carboxylic acids, alcohols, and imides are reported in Table 1.15 and Figure 1.4. In the same manner, fluorination largely lowers the basicity of amines: perfluorinated secondary amines are not able to afford hydrochlorides, and perfluorinated tertiary amines show a behavior close to that of perfluorocarbon compounds. This inertness is essential for their applications (biocompatible emulsions).[1]

1.3.3.2 Hydrogen Bond In spite of its strong electronegativity and its lone pairs of electrons, fluorine is a poor acceptor of hydrogen bond. This is due to the low polarization of its S and P electrons.[1] The calculation of the strength of the hydrogen bond C—F···H—O shows that it is approximately two times weaker than the —O···H—X (~2.4 kcal/mol).[21]

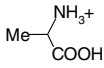
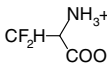
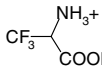
Most of the examples of H···F bonds reported in the literature concern intramolecular hydrogen bonds (fluoroalcohols, fluorophenols, and fluoroanilines) (Figure 1.5).[1] At this point, it is important to recall that the criterion to determine the existence of hydrogen bond with F is an interatomic distance between 2.0 and 2.3 Å, equal to or less than the sum of the atomic radii.

Hydrogen bonds between fluorinated substrates and biological macromolecules have been postulated in some enzyme–substrate complexes. However, it is rather difficult to determine if these hydrogen bonds really exist: other factors may stabilize the conformation corresponding to the short H···F interatomic distance observed. Indeed, this conformation can be favored by other factors (e.g., other stronger hydrogen bonds, gauche effect), without participation of an H···F interaction to stabilize the supramolecular structure.[22] The existence and possible

Table 1.14 pK_a and ΔG_{acid} calculated values of fluorinated compounds[8,17]

Compound	pK_a	Compound	pK_a
CHF_3	30.5	CH_3—COOMe	24
$CHCl_3$	24.4	CH_2F—COOEt	21
CF_3—CHF_2	28.2	CHF_2—COOEt	25
CF_3—$CHCl_2$	24.4	$CH_2(NO_2)_2$	3.63
$(CF_3)_3CH$	21	$CHF(NO_2)_2$	7.70
Compound	ΔG_{acid} (kcal/mol)	Compound	ΔG_{acid} (kcal/mol)
$(C_6H_5)_3CH$	352.8	$CH_2(CN)_2$	328.3
$(C_6F_5)_2CHC_6H_5$	328.4	CH $(CN)_3$	293
$(C_6F_5)_3CH$	317.6	$C_6H_5CH_2CN$	344.1
$(CF_3)_2CH_2$	343.9	$C_6F_5CH_2CN$	327.6
$(CF_3)_3CH$	326.8	$(C_6F_5)_2CHCN$	312.4

Table 1.15 pK_a, pK_b, α_2^H and β_2^H values of fluorinated compounds[17, 18]

Acidity	pK_a	α_2^H	β_2^H
CH_3—COOH	4.76	0.550	0.42
CH_2I—COOH	3.2		
CH_2Br—COOH	2.9		
CH_2Cl—COOH	2.9		
CH_2F—COOH	2.6		
CF_2H—COOH	1.3		
CF_3—COOH	0.5	0.951	
C_6H_5—COOH	4.21	0.588	0.42
C_6F_5—COOH	1.75	0.889	
	2.4	2.3	1.2
	2.3		
	1.3		
CH_3COOCH_3	28.2		
CH_2FCO_2Me	21		
CHF_2CO_2Me	25		

Acidity	pK_a	α_2^H	β_2^H
CH_3CH_2OH	15.9	0.33	0.44
CF_3CH_2OH	12.4	0.57	0.18
$CH_3CHOHCH_3$	16.1	0.32	0.47
$CF_3CHOHCF_3$	9.3	0.771	0.03
$(CH_3)_3$—COH	19.0	0.32	0.49
$(CF_3)_3$C-OH	5.4	0.862	
C_6H_5—OH	10.0	0.596	0.22
C_6F_5—OH	5.5	0.763	0.02
Succinimide	9.6	0.493	
F_4–succinimide	2.1	0.86	

Basicity	pK_a	β_2^H
$CH_3CH_2NH_2$	10.7	0.70
$CF_3CH_2NH_2$	5.9	0.36
$C_6H_5NH_2$	4.3	0.38
$C_6F_5NH_2$	0.36	
CH_3COCH_3		0.48
CF_3COCF_3		0.24

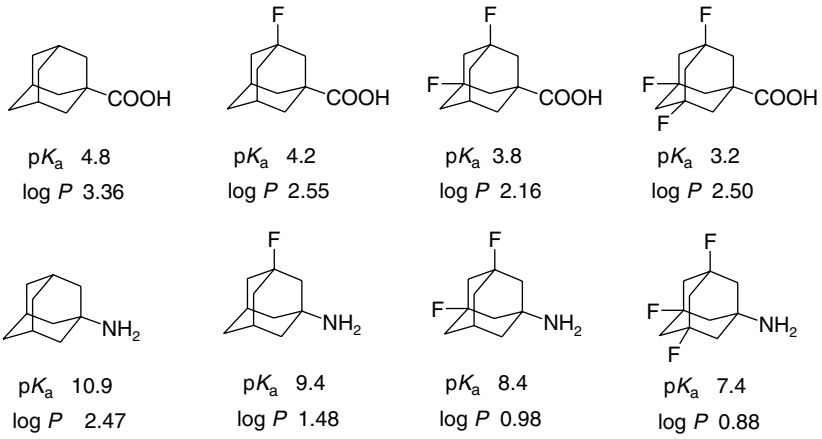


Figure 1.4 Fluorination impact on pK_a and log P of substituted adamantane.[20]

role of an H···F bond in the interactions between fluorinated substrates and biological macromolecules still remain an open question (cf. Chapter 3).

Conversely, numerous examples of coordination between a metallic ion and fluorine atoms borne by carbons can be found in the literature.[1,19, 23–27] However, the demonstration of this interaction is often indirect and is based either on theoretical calculations or on data linked to the reactivity or the stereochemistry (Figure 1.5).

If the fluorine atom itself is only slightly involved in hydrogen bonds, its inductive effect plays a very important role in the ability of neighboring functional groups to give or to accept hydrogen bonds. The presence of fluorine atoms enhances the ability of a neighboring function to donate a hydrogen bond (α_2^H) (acidity) and lowers its ability to accept hydrogen bond (β_2^H) (basicity) (Table 1.15). Thus, fluorinated alcohols are powerful donors of hydrogen bonds, but, conversely to nonfluorinated alcohols, they

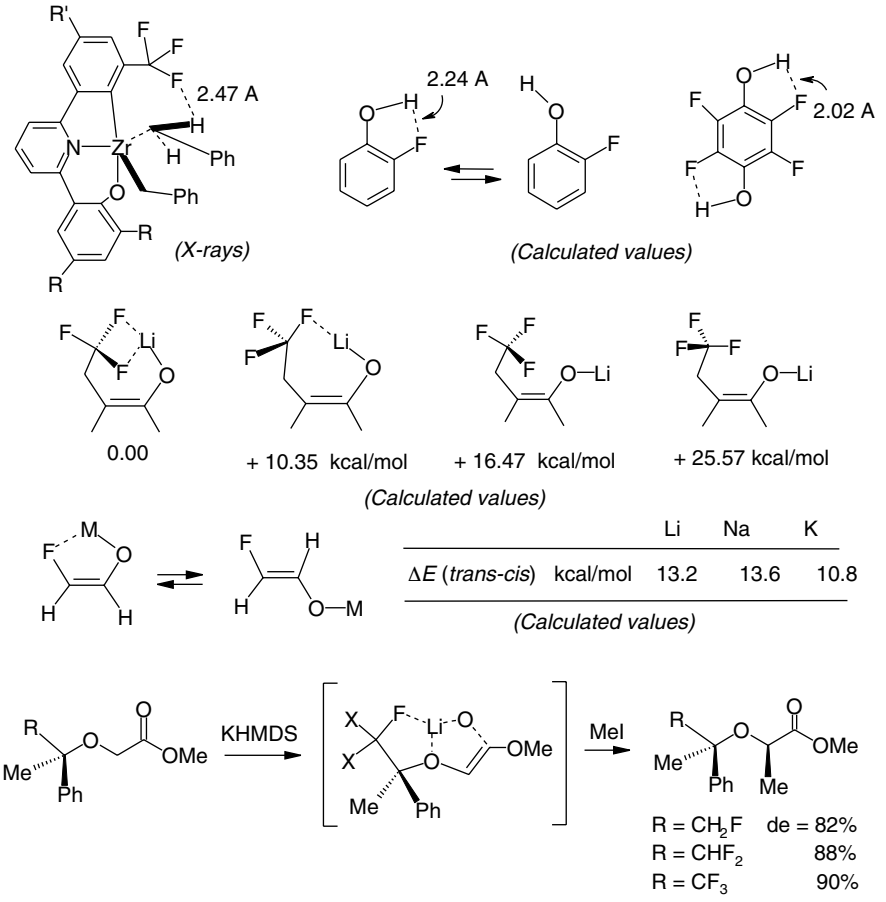


Figure 1.5 Typical examples of F···H and F···metal bonds.[1, 23–25, 30]

Table 1.16 Van der Waals radius (r_v) and bond length[1]

X	Electronegativity	r_v (Å)	Bond Length C—X (Å)
H	2.2	1.20	1.09
F	4.0	1.47	1.39
Cl	3.0	1.75	1.77
O	3.5	1.52	1.43
N	1.70	1.55	—
C		1.70	1.54

are extremely poor acceptors. Since they are poor nucleophiles, they are very useful polar solvents in organic synthesis.[28] Hydrofluorocarbon molecules can also be hydrogen bond donors, as fluorine atoms enhance the acidity of neighboring hydrogens.[29] It will be shown later that hydrogen bonds play an important role in the anesthetic properties of fluorocompounds (cf. Chapter 3).

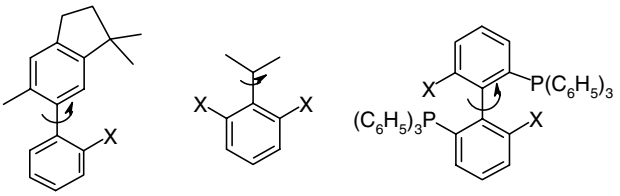
1.3.4 Steric Effects

Whereas the van der Waals radius of the fluorine atom is the smallest one after that of hydrogen, its volume is actually closer to that of oxygen (Table 1.16).[1] Note that if the volume is an intrinsic property, steric effects are dependent on the observed phenomena. They frequently appear in dynamic processes. This allows comparison of steric parameters of various groups, fluorinated or not. These parameters show that the CF_3 group is at least as bulky as an isopropyl or isobutyl group (Table 1.17).[1,31,32] These data are confirmed by the values of the rotation, or of inversion barriers, of fluorinated diphenyl-type compounds (Figure 1.6).

Table 1.17 Steric parameters of fluorinated and nonfluorinated substituents[1,32]

Substituent	E_s^0	A	v
H	0.00	0.00	0.00
F	−0.46	0.15	0.27
OH	−0.55	—	—
CH_3	−1.24	1.17	0.52
$(CH_3)_2CH$	−1.76	2.1	0.76
$(CH_3)_2CHCH_2$	−2.17	—	0.98
CFH_2	—	1.59	—
CF_2H	—	1.85	—
CF_3	−2.40	2.4	0.91
C_2F_5		2.65	—
$(CH_3)_3C$	−2.78	<3.9	—

[1] E_s, Taft steric values.[9a]; A, values from the axial–equatorial conformational equilibrium in cyclohexane v, Charton steric parameters.[9b]



X	Δ *G* (kcal/mol)	Δ *G* (kcal/mol)	Δ *G* (kcal/mol)
H	10.6	2.0	22
F	14.2	6.9	> 35
CH_3	19.3	12.8	> 30
CF_3	22.2		
$CH(CH_3)_2$	22.2		

Figure 1.6 Axial rotation barrier values.[1]

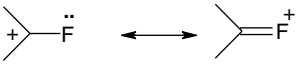
1.3.5 Fluorination Effects on the Stability of Reaction Intermediates (Carbocations, Carbanions, and Radicals)

1.3.5.1 Carbocations The effect of the presence of fluorine atoms on the stability of a carbocation is depending on whether they are borne by the α carbon or the β carbon. When the fluorine atom(s) is borne by the charged carbon, the charge is stabilized by one of the lone pair of fluorine atoms, despite the destabilizing electron-withdrawing effect. This competition between the two effects (mesomere and inductive effects) defines the stability order of fluoromethyl cations (Figure 1.7).[33, 34] Nevertheless, an alkyl group is better at stabilizing a carbocation than a fluorine atom. Mono- and difluorinated methyl carbocations are used in synthesis (Nazarov reaction and cyclialkylation).[35] Fluorinated carbocations with carborane anions can be studied in the solid state.[36]

The presence of fluorine strongly destabilizes a carbocation centered on the β carbon because only the inductive effect takes place.[34, 37] The effect on solvolysis or protonation reaction of double bonds can be very important.[18, 37] The destabilization of carbenium and alkoxycarbenium ions plays an important role in the design of enzyme inhibitors (cf. Chapter 7) and in the hydrolytic metabolism of active molecules (cf. Chapter 3).

1.3.5.2 Carbanions Although the presence of a fluorine atom in the α position has a stabilizing influence through the inductive effect, the repulsion induced by the

Back donation stabilization of fluoropropyl cation



Order of stability of fluoromethyl and fluoroethyl carbocations

$^{+}CH_3 < {}^{+}CF_3 < {}^{+}CH_2F < {}^{+}CF_2H \approx {}^{+}CH_2CH_3 << {}^{+}CF_2CH_3 \approx {}^{+}CHFCH_3$

Figure 1.7 Stability order of fluoroalkyl carbocations (gas phase).[34]

CF_3H	$CF_3(CF_2)_5CF_2H$	$(CF_3)_2CFH$	$(CF_3)_3CH$
pK_a 30.5	30	20	11

Figure 1.8 α-and β-Fluoro carbanions.

lone electron pair is destabilizing. As a consequence, α-fluorination stabilizes carbanions less than the other halogens[39]: the acidity of haloforms decreases from bromoform ($pK_a = 22.7$) to chloroform ($pK_a = 24.4$) and to fluoroform ($pK_a = 30.5$).

Furthermore, the repulsion between the electron pairs of fluorine atoms is responsible for the pyramidal structure of the carbanion derived from fluoroform. The inversion barrier of the anion is $\sim$100 kcal/mol, while that of CH_3^- is only 2 kcal/mol. As the acidity of fluoroform is 10^{40} times higher than that of methane, the role of the pyramidal form in stabilizing the carbanion CF_3^- is essential.

On a thermodynamic level, the presence of fluorine atoms in the β position strongly stabilizes the anions (planar or not) either by inductive effect or by negative hyperconjugation (Figure 1.8).

With regard to nonfluorinated olefins, the great reactivity of fluoroolefins toward nucleophiles comes from both a higher electrophilicity of the double bond, and from the stabilization of the carbanion, resulting from the addition of the nucleophile, by β-fluorine atoms.[40]

The stabilization of a carbanion brought by α- or β-fluorine atoms is thermodynamic. Indeed, because of the great reactivity of carbanions toward elimination of a fluoride ion, they may have short lifetimes: α-fluorinated carbanions easily undergo α-elimination processes to carbenes, while β-fluorinated carbanions undergo β-elimination reactions.

The α-elimination process is a very fast and effective reaction of trifluoromethyl carbanions (Figure 1.9).[41] Consequently, the corresponding organometallic species (Li, Mg) cannot be used in organic synthesis. When the carbon-metal bond is close to a covalent bond, the anionic species is more stable, but has almost no reactivity toward electrophiles. Zinc, and especially silicon, derivatives constitute the best compromises.[42] When the fluoroalkyl chain is longer, organometallics are more stable and can be used in synthesis (Figure 1.10).[43]

The β-elimination reactions are also very frequent and they are typical of the chemistry of fluorinated compounds. They play an important role in synthesis and also

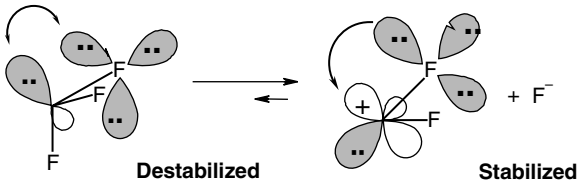


Figure 1.9 Stabilizing and destabilizing interactions of CF_3^- anion and CF_2 carbene.

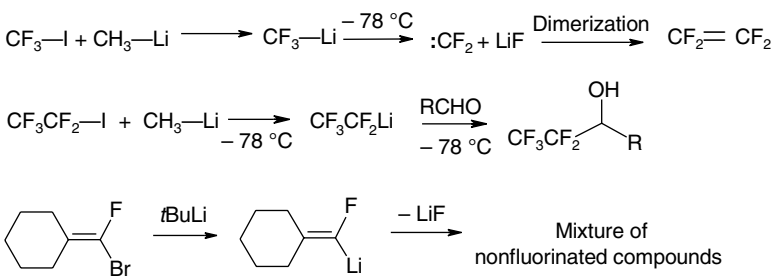


Figure 1.10 α-Elimination process of fluoride anion.[44]

in the design of irreversible enzyme inhibitors (mechanism-based inhibitors). The development of a negative charge on the β-position of a fluorine atom may induce the loss of a fluoride ion through an $E1_{CB}$ or a concerted mechanism.

Along the same line, the reactions of vinyl fluorides with nucleophiles often involve addition–elimination processes. The addition reaction generates a carbanion, and this latter induces the loss of a fluoride. As the loss of a fluoride ion is irreversible, the equilibrium is displaced toward the formation of the carbanion and, consequently, the reaction is very efficient. These reactions are often concerted ones (Figure 1.11).

In contrast to α-elimination, β-elimination processes are very common in reactions involving fluoroalkyl compounds and perfluoroolefins (Figure 1.11).

1.3.5.3 Effects on S_N1 and S_N2 Substitution Reactions The difficulty in performing S_N1 or S_N2 substitution reactions on the α, β, or even γ positions of CF_3 or fluoroalkyl groups is an important and typical feature of the reactivity of fluoro compounds.

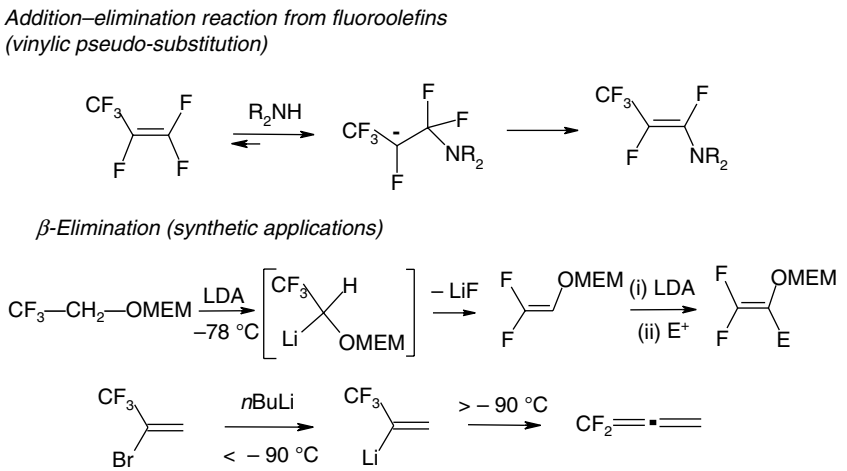


Figure 1.11 β-Elimination reactions with fluorinated compounds.[44–46]

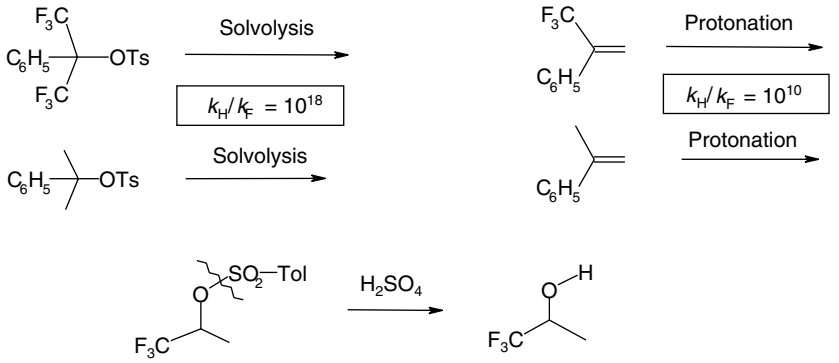


Figure 1.12 CF_3 effect on S_N1 type reactions of tosylates and on protonation of fluoroolefins.[38, 48]

Generally, an electron-withdrawing group strengthens the bond that is susceptible to cleavage during the substitution reaction. Moreover, a fluoroalkyl group strongly destabilizes a carbenium ion in the α position. As a consequence, the presence of a fluoroalkyl group makes S_N1 substitution reactions very difficult to achieve (Figure 1.12).[38, 47] The solvolysis reactions of tosylates are much slower than those of nonfluorinated tosylate analogues.[38] It has been demonstrated that the hydrolysis of the tosylate of trifluoropropanol in a concentrated sulfuric acid medium does not occur at the expected C—O bond but at the O—S bond (Figure 1.12).[48]

The inductive effect is *a priori* unfavorable for an S_N2 substitution. Moreover, the strengthening of the C—X bond disfavors its cleavage. Furthermore, the electronic as well as the steric repulsion phenomena inhibit the attack of the nucleophile. An important decreased rate is observed in the S_N2 reactions on carbons bearing a fluoroalkyl or CF_3 group (Figure 1.13).

It is important to note that the substitution of trifluoromethyl and perfluoroalkyl halides goes through a specific process. The displacement of the halogen atom never occurs via the usual S_N1 or S_N2 processes; rather it occurs either via a halophilic attack and a monoelectronic transfer ($S_{NR}1$)[13, 49] or via an α-elimination of a fluoride ion and a process involving a carbene.

1.3.5.4 Free Radicals The inductive effect of fluorine atoms destabilizes radicals.[50] For electronic reasons, fluorination has an important impact on

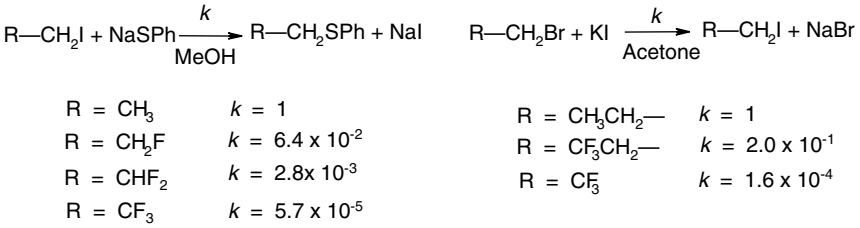


Figure 1.13 CF_3 effect on S_N2 reaction.[1]

Table 1.18 Inversion barrier of methyl and fluoromethyl radicals and dissociation energy of C—H bond of fluoromethanes[51]

Radical	CH_3	CH_2F	CHF_2	CF_3
Inversion barrier (kcal/mol)	—	~1	7	25
Dissociation energy of C—H bond (kcal/mol)	105 ± 0.2	101 ± 2	103 ± 2	107 ± 1

the structure of α-fluorinated radicals.[50] While the methyl radical is planar, the pyramidal character increases with the number of fluorine atoms. Like the CF_3^- carbanion, the $CF_3^\bullet$ radical is pyramidal. Since the inversion barrier is low, stabilization of the $CH_2F^\bullet$ and the $CHF_2^\bullet$ radicals can occur through resonance (Table 1.18).

The β-fluorinated radicals, such as the α-trifluoromethyl ones, are also destabilized due to the inductive effect. The dissociation energy grows from CH_3CH_2—H (97.7 kcal/mol) to CF_3CH_2—H (102.0 kcal/mol).[50, 52]

However, in radical reactions, the stability of radicals plays only a minor role with respect to polar and steric effects. The addition of fluoroalkyl radicals is mainly governed by orbital factors, and the polar effects play a major role in the processes.[50] The trifluoromethyl radical, which is a model of the electrophilic radical, reacts 10 times faster with ethylene than with tetrafluoroethylene, which is more electron poor. In contrast, the methyl radical reacts 10 times faster with tetrafluoroethylene than with ethylene.[50] Data on the relative speeds of addition of fluorinated radicals onto styrene and methylstyrene are collected in Table 1.19.[53] The addition of fluoroalkyl radicals onto electron-rich olefins is of great importance from a synthetic point of view. The abstraction of hydrogen by the fluoroalkyl radical is also governed by polar effects. Another important difference with regard to hydrocarbon radicals is the fact that dismutation reactions and fluorine atom migrations are rare. One of the consequences, for example, is, the formation of fluoro-polymers with very high molecular weights during radical polymerization.

Table 1.19 Absolute rate constants of addition of fluoroalkyl radical to styrene and methylstyrene[53]

	$k_{addition}/10^6\ M^{-1}\ s^{-1}$	
Radical	$C_6H_5C{=}CH_2$	$C_6H_5C(CH_3){=}CH_2$
$CH_3CH_2CH_2CH_2CH_2^\bullet$	0.12	0.06
$CH_3CH_2CH_2CF_2CH_2^\bullet$	0.52	0.98
$CH_3CH_2CH_2CH_2CHF^\bullet$	0.46	
$CH_3CH_2CH_2CH_2CF_2^\bullet$	2.7	3.3
$CF_3^\bullet$	53	87
$CF_3CF_2CF_2^\bullet$	43	78

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2

OVERVIEW ON THE PREPARATION OF FLUORINATED COMPOUNDS

Due to the specificity of organofluorine compounds, their synthesis and reactivity can sometimes be disconcerting for the organic chemist. The traditional techniques of fluorination involve unusual reagents that are often hazardous and corrosive (e.g., elemental fluorine, fluorhydric acid, sulfur tetrafluoride). Consequently, these chemicals are difficult to handle and special lab equipment is required. Moreover, they are often poorly selective and incompatible with elaborated or fragile substrates. Thus, chemists have been obliged to synthesize the elaborated molecules required for medicinal chemistry starting from a few available basic materials that already contain fluorine. These starting compounds are often intermediates, or secondary products, from industrial processes, coming especially from the field of polymers.

Chemists have prepared numerous small molecules, so-called building blocks or synthons, from these industrial intermediates, as a package of starting chemicals. At the same time, they have successfully developed the required synthetic methodologies, allowing access to more complex molecules. Indeed, in this approach, it is necessary to take into account the specific reactivity of organofluorine compounds, since the electronic structure of the fluorine atom modifies the chemical reactivity of the molecule. These effects are even stronger when the number of fluorine atoms is important with respect to the molecular weight of the molecule. These difficulties have reinforced the reputation of singularity that is commonly attributed to organofluorine chemistry.

Two approaches are thus possible for synthesizing an elaborated molecule containing one or several fluorine atoms. The first one is the synthesis of a nonfluorinated precursor of the target molecule with further introduction of the fluorine atoms at a late

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

stage of the synthesis, by using fluorination or trifluoromethylation techniques. The second strategy involves the synthesis of the target compound starting from fluorinated building blocks. The chemist should then be able to make use of either of these two strategies to synthesize the target via the most straightforward route.

The chemistry of fluorinated compounds has undergone a huge and very fast evolution during the last few decades. New easy-to-handle fluorinating and trifluoromethylation reagents have been discovered, and considerable improvements have been accomplished in these fields. Also, the number of building blocks has greatly increased, and the improvements in synthetic methodology are considerable. These great advances have led to the synthesis of numerous fluorinated molecules with complex structures, including chiral ones.[1, 2] The synthesis of fluorinated compounds is largely dependent on industry for access to the starting materials (reagents and building blocks). The elimination of an industrial source for environmental reasons (e.g., chlorofluorocarbons, CFC) or for industrial strategic reasons may disqualify a synthetic arsenal or a preparation process. This chapter does not describe in detail all the methods that the medicinal chemist can use to prepare fluorinated molecules. The goal is just to highlight the main points and to clarify the synthetic methods that are reported in this book. Thus, this chapter offers a survey of the arsenal available for the synthesis of compounds with a few fluorinated atoms. Along this line, reviews are preferentially cited with respect to the original works. However, some significant examples are given as illustrations.

The synthesis of fluorinated aliphatic compounds is the main topic of this chapter. Indeed, numerous aromatic fluorinated products are available commercially. Moreover, in contrast to aliphatic molecules, their synthesis has not undergone significant evolution in the last few years. The synthesis of highly fluorinated compounds is also not considered here, since these compounds are much more involved in the formulation sciences than in medicinal chemistry. In this chapter, the synthesis of fluorinated compounds is dealt with in the following order: monofluorinated, then difluoromethylated, and finally trifluoromethylated molecules.

2.1 PREPARATION OF MONOFLUORINATED COMPOUNDS

Three strategies are used to prepare a monofluorinated compound:

1. Creation of a carbon–fluorine bond through reaction of a fluoride anion (nucleophilic fluorination).
2. Creation of a C–F bond by means of an F^+ cation (nucleophilic fluorination).
3. Creation of a carbon–carbon bond starting from a synthon that already has a C–F bond.

2.1.1 Nucleophilic Fluorination

The main reagents for nucleophilic fluorination are the metal and ammonium fluorides, the DAST reagent and its analogues, and the amine complexes of fluorhydric acid.

2.1.1.1 Fluorides The small size (radius = 1.47 Å) and the low polarizability of the fluoride ion favor its basic character to the detriment of its nucleophilic character as a reagent. Moreover, the fluoride ion is generally strongly solvated (hydration energy = 123 kcal/mol), which renders F^- poorly reactive. For these reasons, nucleophilic reaction by means of a metal fluoride is not always an easy thing. Displacement of a sulfonate or of a halide can be achieved by a metal fluoride (e.g., K^+, Cs^+, Ag^+) or a quaternary ammonium: $Bu_4N^+F^-$ (TBAF) or $Bu_4N^+HF_2^-$ (TBABF). But the reaction has to be conducted in aprotic medium in the presence of a crown ether or another cation complexing agent (e.g., glyme). However, dissociating media and solvents also enhance the basicity of the fluoride anion, thus favoring the competitive elimination reaction. In order to reinforce the reactivity of fluoride ions, anhydrous metallic fluoride ions (nonsolvated) can be utilized. This is the reason why many activation methods (e.g., dehydration, use of a supported reagent, fluoride relay, catalysis) have been described.[3] Nevertheless, the preparation of such anhydrous reagents may be difficult, and substitution reactions are not always easily reproducible.[3]

2.1.1.2 HF–Amine Complexes Complexes of fluorhydric acid (HF) with pyridine or alkyl amines (Et_3N, Et_2NH) are often utilized as reagents in nucleophilic fluorination reactions such as the opening of oxiranes,[4] the bromofluorination of double bonds in the presence of NBS, or the diazotation/fluorination of amines with sodium nitrite (the Balz–Schiemann-like reaction) (Figure 2.1).[6]

2.1.1.3 The DAST Reagent DAST (diethyl amino sulfur trifluoride) is the main reagent for nucleophilic fluorination (Figure 2.2). Other more stable, related reagents, such as Deoxofluor™ and DFMBA, are now available.[8–10] These reagents allow the direct transformation of a C–OH bond (alcohol) to a C–F bond (fluoride). The reaction is effective with primary, secondary, and tertiary alcohols. These reactions are often stereoselective and take place with inversion of the configuration. However, the cationic character of the substitution is often very pronounced. In some

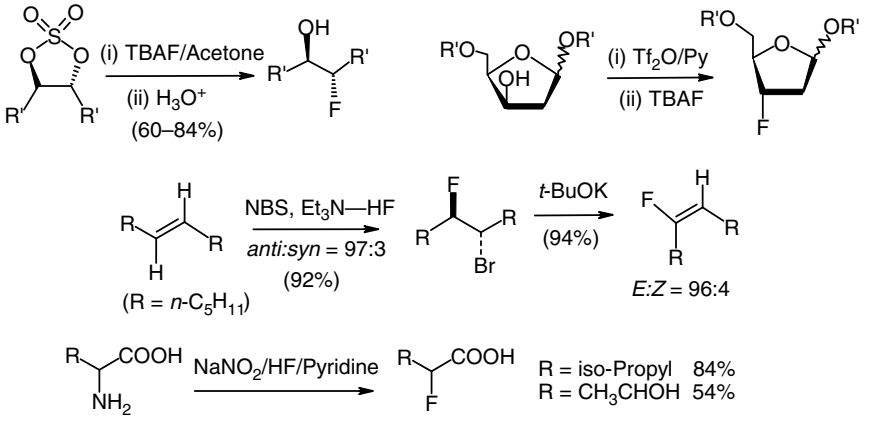

Figure 2.1 Examples of nucleophilic fluorination with fluorides or with HF–amine complexes.[5–7]

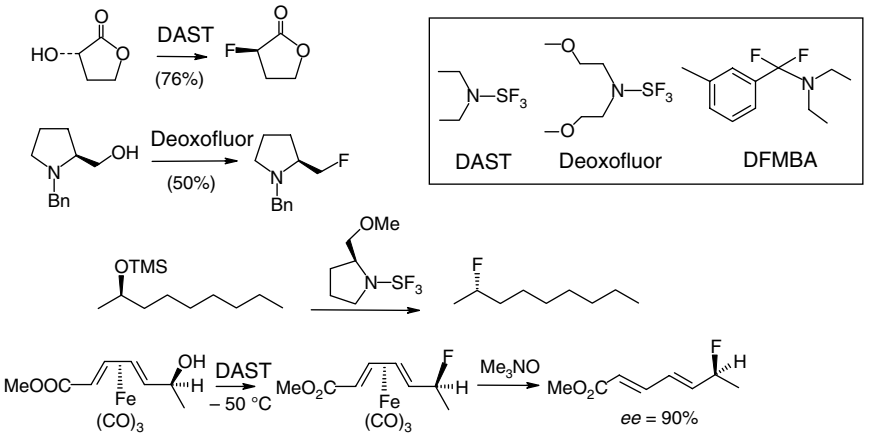

Figure 2.2 Fluorination with nucleophilic reagents (e.g., DAST, Deoxofluor).[9–13]

cases, this leads to rearrangements or to retention of the configuration when there is participation of neighboring groups (cf. Chapter 6). The synthesis of nonracemic tertiary fluorides has been reported in the case of fluorination of dienic alcohols that are complexed with iron tricarbonyl.[11]

2.1.2 Electrophilic Fluorination

During the last few years, considerable improvements have appeared in the field of electrophilic fluorination. This is due to the discovery of new stable and easy-to-handle reagents: 1-(chloromethyl)-4-fluoro-1,4-diazonia [bicyclo[2.2.2]octane bis(tetrafluoroborate)] (F-TEDA-BF_4 or Selectfluor™)[14] and F-*N*-sulfonimides (NFSI, NFOBS) (Figure 2.3).[15] Most of these reagents are commercially available and have revolutionized the electrophilic fluorination field. They are safe and easy to use and allow, under mild conditions, the fluorination reaction of aromatic rings and heterocycles (nucleic bases and nucleosides), of sulfoxides and sulfonamides, of carbonyl derivatives, of enol ethers,[14, 16] of amino acids, phosphonates, alkenes, and glycols,[14, 15] and of allyl and aryl silanes.[17]

Catalytic enantioselective fluorination has recently emerged. Both organocatalysis and metal catalysis have been successfully developed.[18] Chiral N–F reagents have been prepared or formed *in situ* starting form a chiral amine derivative and a classical N–F reagent (*vide supra*).[18] These reagents allow the enantioselective fluorination of

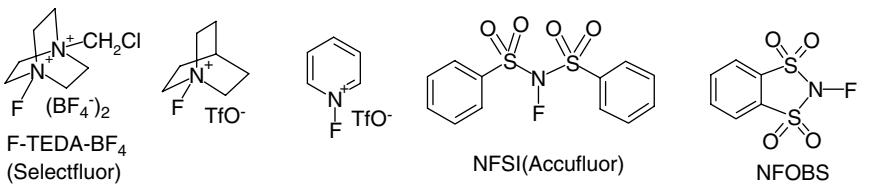

Figure 2.3 Electrophilic fluorination reagents.[14, 15]

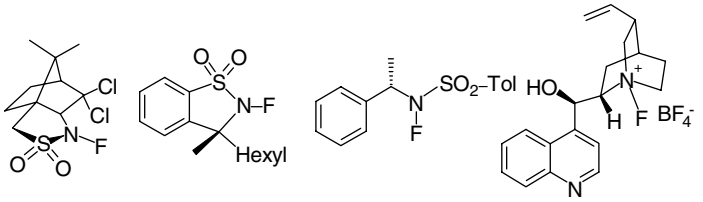

Figure 2.4 Asymmetric electrophilic fluorination reagents.

ketone enolates (Figure 2.4). Among them, the N–F derivatives of *Cinchona* alkaloids seem to be the most promising ones, and excellent *ee* have been obtained with some substrates (Figure 2.5).[19–23] The use of other chiral amines has recently been reported in the literature.[24]

The asymmetric fluorination of enolates by means of chiral metal complexes has been reported with Selectfluor™ in the presence of a chiral Lewis acid derived from TADDOL ($TiCl_2$/TADDOL), or with F-*N*-sulfonimide (NFSI) with palladium complexes and chiral phosphines.[18b, 25–27]

The fluorination of enolates of ketone, amide, or hydrazone bearing a chiral auxiliary (SAMP, Evans oxazolidine) with nonchiral fluorination reagent (*N*-fluoro sulfonimides, *N*-fluoropyridine) occurs with excellent diastereoselectivities.[15, 28]

Asymmetric electrophilic fluorination has already found application in medicinal chemistry. For example, the enantioselective synthesis of a fluorooxindole, Maxipost™ (BMS-204352), has been reported. This compound is an effector for opening calcium channels and is currently in development for the treatment of cerebral ischemia (Figure 2.5).[29]

These improvements have led to the sidelining of older reagents, which were often hazardous and difficult to handle, such as hypofluorites (CF_3OF, CH_3COOF) and XeF_2.[30, 31] However, elemental fluorine is still industrially used, for example, in the synthesis of 5-fluorouracil (5-FU) (Figure 2.6).[30b] There is also a renewal of interest in the use of F_2. This is due to the commercialization of efficient generators that produce a very dilute F_2 gas in nitrogen, thus avoiding the storage and handling problems and need for special equipment in laboratories.[30a]

Aromatic fluorination involves analogous methods to those used in the aliphatic series. The most utilized methods are electrophilic fluorination (F_2, N—F reagents) and nucleophilic fluorination through the Balz–Schiemann reaction (diazotation in the presence of fluoride ion). This latter method is of prime importance in industry.[32] When the aromatic ring is activated by one or several electron-withdrawing groups, the replacement of a lost group by a fluoride ion is efficient.[30c]

2.1.3 Formation of Carbon–Carbon Bonds Starting from Monofluorinated Synthons

The only monofluorinated synthons that are available are monofluoroacetic acid and its derivatives (esters, thioacetate, bromofluoroacetate) and halogenofluoromethanes ($CHCl_2F$).

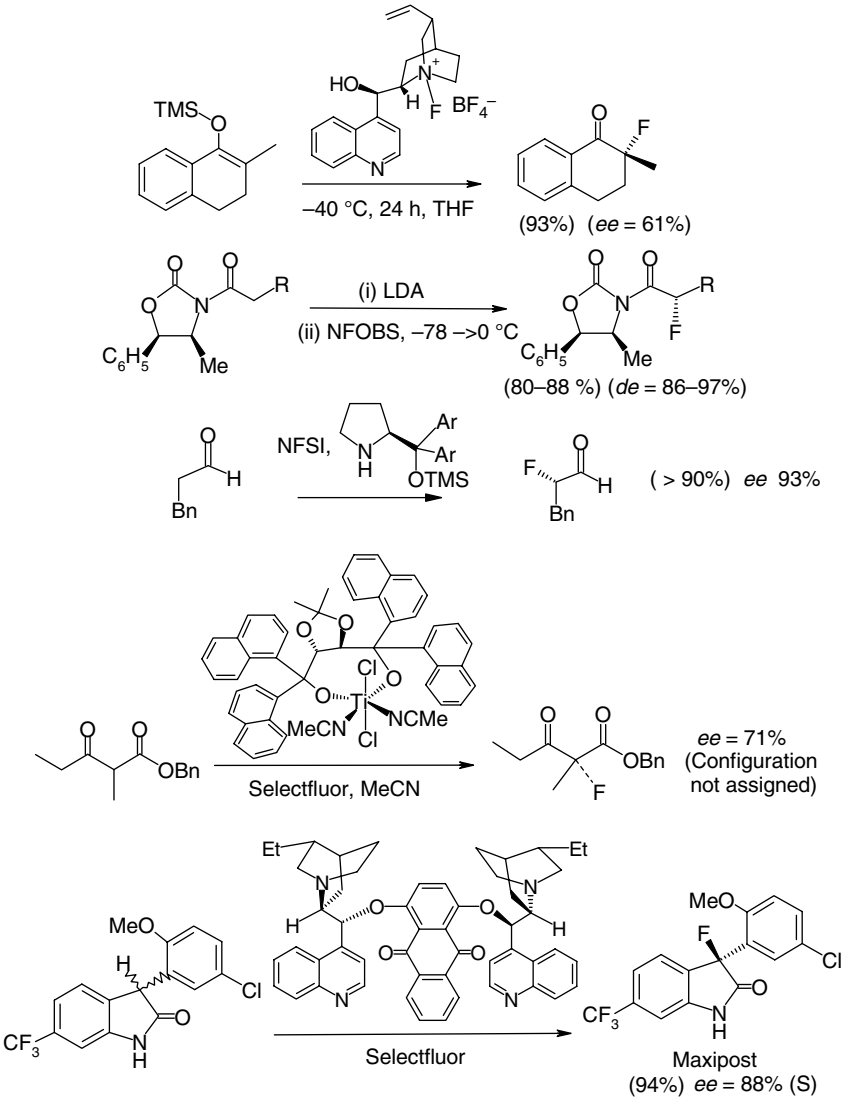

Figure 2.5 Examples of asymmetric electrophilic fluorination.[19–29]

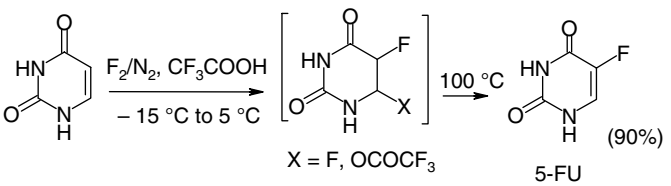

Figure 2.6 Preparation of 5-fluorouracil.[30b]

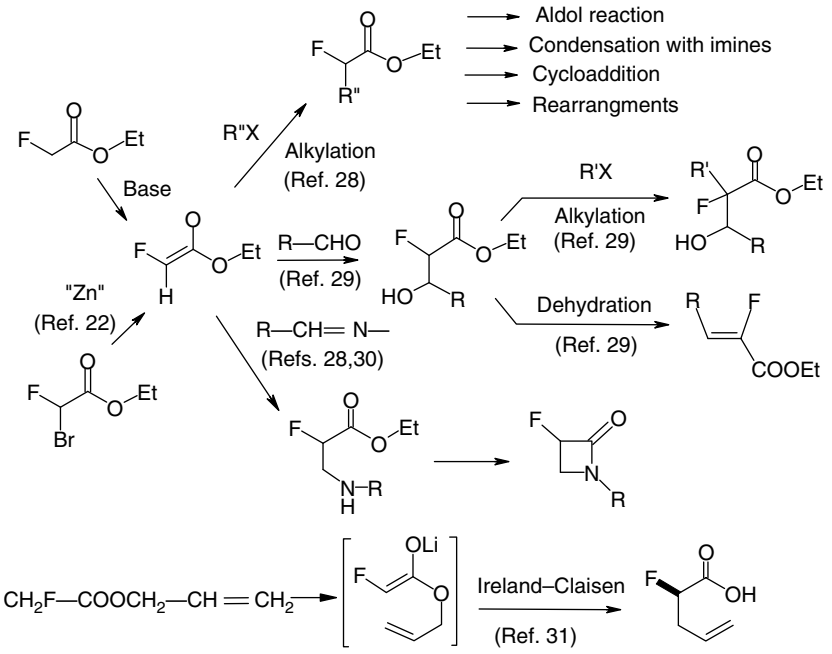

Figure 2.7 Reaction of enolates of esters derived from monofluoroacetic acid.[33–36]

In spite of their high toxicity, the derivatives of fluoroacetic acid are the starting molecules of many syntheses.

The enolates of fluoroacetate or fluorothioacetate esters are generated either through deprotonation with a lithium amide or by an *in situ* reduction of ethyl bromofluoroacetate with zinc.[33] These enolates can undergo diverse reactions with electrophiles (Figure 2.7):

- Alkylation[33] that leads to monofluoroesters, whose enolates provide the same possibilities as the anions of monofluoroacetates.
- Aldolization (eventually asymmetric) with aldehydes that afford adducts that can be further alkylated or dehydrated.[34]
- Condensation with imines to afford β-lactams. These latter ones can also be obtained by cycloaddition of the same imines with the keten stemming from fluoroacetyl chloride.[35]
- Ireland–Claisen rearrangement,[36] in the case of anions of allyl fluoroacetates.

Fluoroacetates can also react as electrophiles: they can acylate organometallic derivatives to afford monofluoroketones[37] or fluoro-β-ketosulfones.[38] This type of reactivity is also found with di- and trifluoroacetates (*vide infra*).

Ethyl fluorophosphonate is commercially available; it is prepared through a Michael–Arbuzov reaction between triethyl phosphite and ethyl bromofluoroacetate.

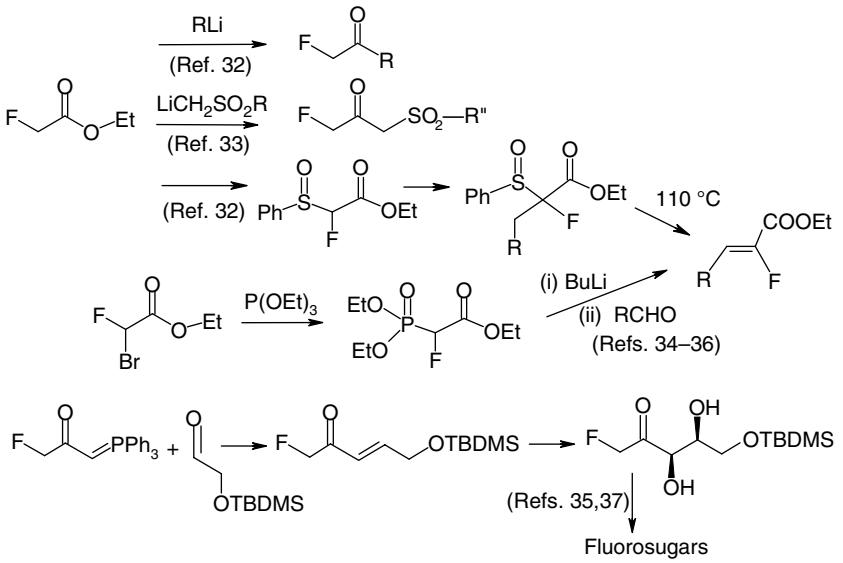

Figure 2.8 Examples of the reactivity of some derivatives of monofluoroacetic acid.[37–42]

This compound allows the stereoselective preparation of α,β-unsaturated-α-fluoro esters with (*E*) configuration (Figure 2.8).[39, 40] However, the stereoselectivity can depend on the nature of the base used.[41] Fluoroacetylphosphorane reacts with aldehydes to afford ethylenic monofluoromethyl ketones (Figure 2.8).[40, 42]

Vinyl fluorides can also be prepared starting from difluorovinyl compounds via the loss of a fluorine atom by an addition–elimination process, as illustrated in Figure 2.9.[43–45]

***Remark*:** *Preparation of monofluoroalkenes*. Monofluoroalkenes are interesting substrates for cyclopropanation and for Diels–Alder reactions.[46] They are also used as a nonhydrolyzable mimic of the peptidic bond (cf. Chapters 3 and 7). The main preparations of fluorinated olefins are as follows:

- Elimination reactions of vicinal halofluorides, fluorhydrins, or β-fluorosulfoxides.
- Reaction of a fluorophosphonate with an aldehyde that provides *E*-α-fluoro-α, β-esters.
- Addition–elimination processes of a vinylic fluorine, from *gem*-difluoroalkenes.[47]
- Electrophilic addition across triple bonds with iodotoluene difluoride in the presence of Et_3N,HF complex, followed by Sonogashira or Heck reaction.[48]

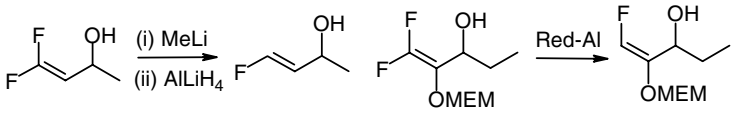

Figure 2.9 Examples of selective defluorination.[44, 45]

- Cross-coupling reactions (Sonogashira or Heck reactions) of 1-bromo-1-fluoroalkenes, which are generally prepared through the reaction of an aldehyde with $CFBr_3$ and PPh_3.[48, 49]
- Diethylzinc-promoted Wittig reaction.[50]

2.2 PREPARATION OF DIFLUORINATED COMPOUNDS

2.2.1 Nucleophilic Fluorination

The carbonyl of aldehydes and ketones can be transformed into a *gem*-difluoro group. This transformation can be performed either directly with DAST[51] or in an indirect manner by treating the corresponding thioacetal or hydrazone with an oxidant (NBS, dibromohydantoin, etc.) in the presence of a source of fluoride ions (e.g., HF–pyridin complex or TBABF prepared from TBAF and KHF_2).[52, 53]

The halogen–fluorine exchange with an HF–amine complex allows the transformation of a *gem*-dichloro goup into a difluoro group. While this reaction is difficult to initiate in nonactivated positions, it is efficient in the benzylic position and in the α position of functional groups (e.g., esters, phosphonates) (Figure 2.10).[54, 55]

2.2.2 Electrophilic Fluorination

In the presence of several equivalents of N–F-type reagents,[14, 15] it is possible to perform the difluorination of enolates of ketones, amides, and enamines.[56–58] The difluorination of nucleosides has also been performed with Selectfluor (Figure 2.11).[59]

2.2.3 Starting from Di- and Trifluoromethyl Compounds

2.2.3.1 Difluoromethylation with a Halogenodifluoromethane The halogenodifluoromethanes (CF_2XY, X,Y = halogen or hydrogen) are important

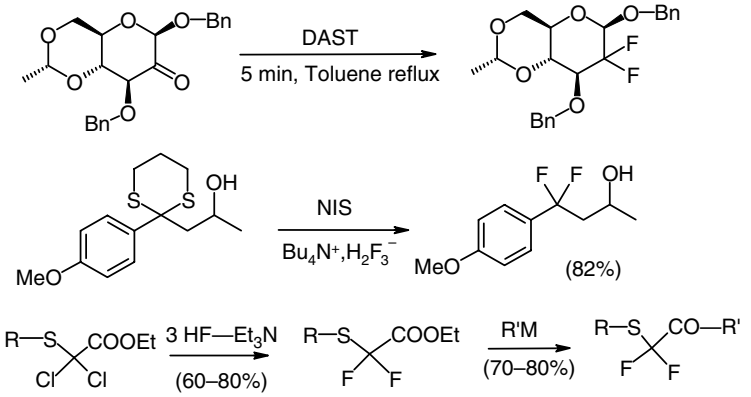

Figure 2.10 Nucleophilic difluorination.[51–54]

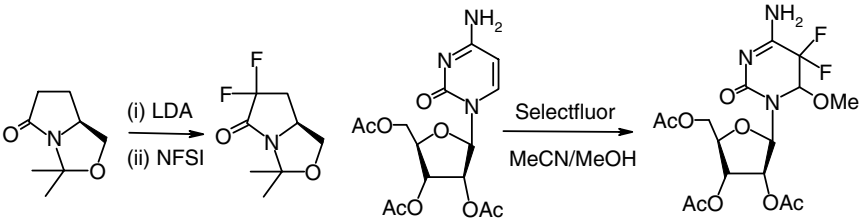

Figure 2.11 Examples of electrophilic difluorination.

difluoromethylation and difluoromethylenation agents.[60] They can react in different ways:

- As electrophilic reagents with enolates.
- As precursors of ylide to afford difluorovinylic compounds.
- As free radicals that can add on double bonds.
- As carbenes to afford *O*- and *S*-difluoromethyl derivatives and difluoro cyclopropanes.

Some examples are shown in Figure 2.12.

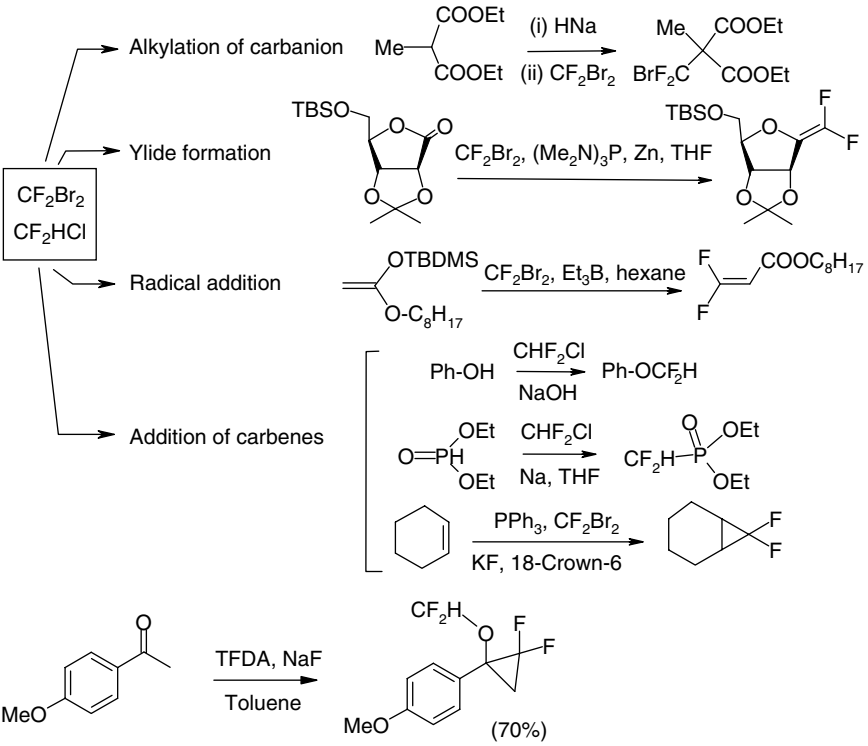

Figure 2.12 Difluoromethylenation and difluoromethylation reactions with halogenodifluoromethanes.

The alkylation of carbanions with halogenodifluoromethane (CF_2Br_2, $CHClCF_2$) permits an efficient introduction of CF_2Br and CF_2H. The bromine atom can then be reduced through a radical path. This method of introducing a CF_2H group has been applied successfully for the synthesis of β-difluoromethyl amino acids (cf. Chapter 4).[61]

The difluoromethylene ylides react with carbonyl derivatives (aldehyde, lactone) to afford *gem*-difluoromethylene compounds.[40, 62] They are generated starting from halogenodifluoromethane with triphenylphosphine (or trisaminophosphine) or starting from zinc and a phosphonium salt (or a phosphine oxide).[40, 63, 64]

The radical addition of CF_2Br_2 on olefins (activated or not) leads to difluorobromomethyl and difluoromethyl compounds.[65]

Difluorocarbenes can be generated from halogenodifluoromethane in the presence of a base. They provide efficient access to O–CF_2H and S–CF_2H-substituted molecules, starting from alcohols, phenols, and sulfides,[60, 66] and to difluorocyclopropanes starting from olefins.[67, 68] With triethyl phosphite, they afford the difluoromethylphosphonate whose corresponding anion (also accessible starting from diethyl bromodifluorophosphonate) is an important synthetic intermediate.[65] A preparation of difluorophosphonates that avoids the use of halogenodifluoromethanes has recently been described.[55] One can also generate these difluorocarbenes starting from bromo- or chlorodifluoroacetic acids[69, 70] or even trifluoroacetic acid.[71]

Difluorocarbene, generated from fluorosulfonyldifluoroacetate, adds on double bonds and aromatic or vinylic ketones, affording fluorinated cyclopropanic ethers.[72]

Difluoroethylene and trifluorobromoethylene are also starting molecules to access difluorinated molecules through organometallic approaches (e.g., metallation, palladium-catalyzed coupling) (*vide infra*).[73–75]

2.2.3.2 Starting from Halogenodifluoroacetic Acids Ethyl chloro-, bromo-, and iododifluoroacetates, as well as the corresponding difluorophosphonates, are powerful reagents for difluoromethylenation through radical, anionic, and electrophilic pathways.

The radicals generated from esters of halogenodifluoroacetic acid or halogenodifluorophosphonic acid add onto olefins and enolates.[65, 76, 77] When these reactions are intramolecular, they afford tetrahydrofurans.[78] In the presence of copper dust, ethyl bromodifluoroacetate can couple with aromatic and vinyl halides or can add onto Michael acceptors (Figure 2.13).[79]

The Reformatsky reagent, prepared from ethyl bromodifluoroacetate, adds onto aldehydes and imines (Figure 2.14). This method for introducing a CF_2CO_2Et moiety has been widely applied in medicinal chemistry.[80–82] The presence of the Wilkinson catalyst ($RhCl(PPh_3)_3$) in the medium renders the reaction efficient with ketones as substrates.[83] When the reaction is performed on a substrate bearing a chiral auxiliary (such as *N*-methyl ephedrine), the reaction proceeds with good diastereoselectivity.[84–86] This Reformatsky approach can also be performed in the solid phase.[87] Similar reactions can also be realized with zinc derivatives generated from chlorodifluoromethylketone[88a] or by using tetrakis(dimethylamino)ethylene

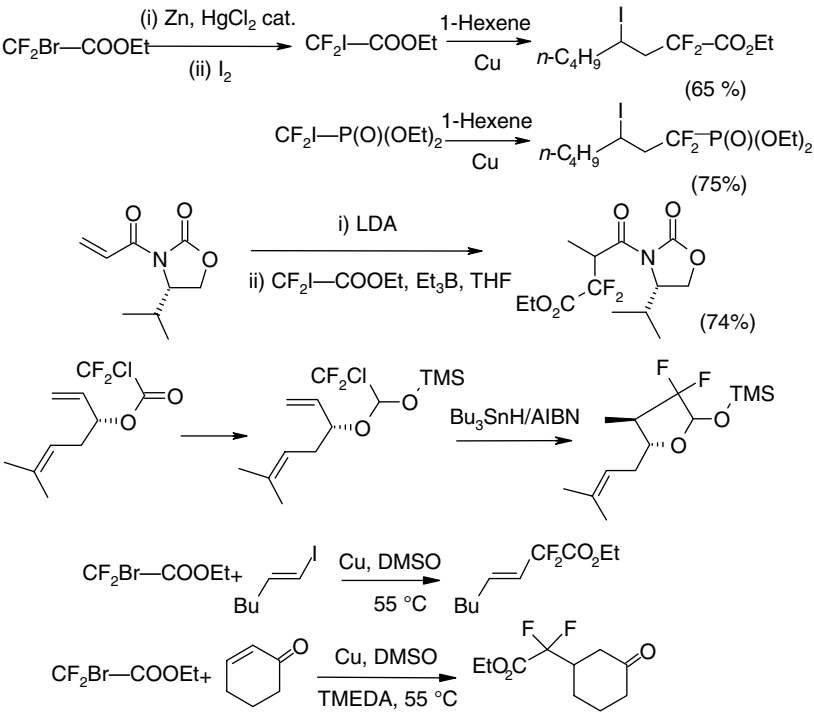

Figure 2.13 Radical additions of iododifluoroacetate and of iododifluorophosphonate.[76–78, 79]

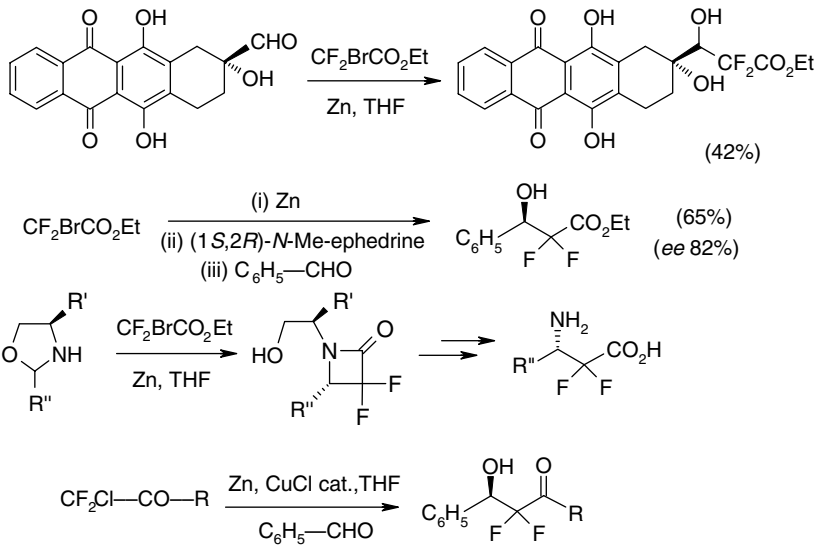

Figure 2.14 Addition of $ZnCF_2CO_2Et$ on aldehydes and imines.[80–88]

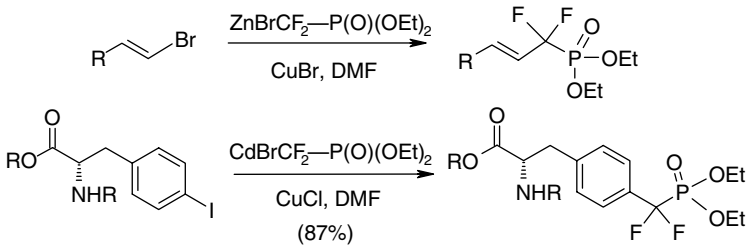

Figure 2.15 Coupling reaction of ethyl bromodifluorophosphonates.[90, 91]

as a reducing agent.[88b] Isopropyl bromodifluoroacetate can be coupled directly to vinylic organometallic-derived zirconium compounds, in the presence of a Ni(0) catalyst.[89]

Most of these reactions have been extended to ethyl bromodifluoromethyl phosphonate (Figure 2.15).[90, 91] However, conversely to the anions of difluoroacetate, lithiated anions of diethyl difluoromethylphosphonate are easily generated through the deprotonation of ethyl difluoromethyl phosphonate. They are frequently used for the synthesis of difluorophosphonates (cf. Chapter 7).[40, 92]

Esters of chlorodifluoroacetic acids, like the esters of monofluoroacetic acid, can acylate anions (e.g., organometallic derivatives, enolates, lithiated sulfones). They lead to chlorodifluoromethylketones and to β-ketosulfones and β-ketoesters which have the —CF_2 motif (Figure 2.16).[93, 94]

Difluoroacetic acid and its derivatives (esters, aldehyde) are excellent reagents for introducing a difluoromethyl group. However, because they are expensive, they are used relatively infrequently. Their reactivity is close to that of trifluoroacetic derivatives.[95, 96]

2.2.3.3 Starting from Difluoroallylic and Difluoropropargylic Derivatives Just like the esters of bromodifluoroacetic acids, difluoroallylic and difluoropropargylic bromides (via organometallic derivatives) can add onto aldehydes and couple with activated halides (Figure 2.17).[97]

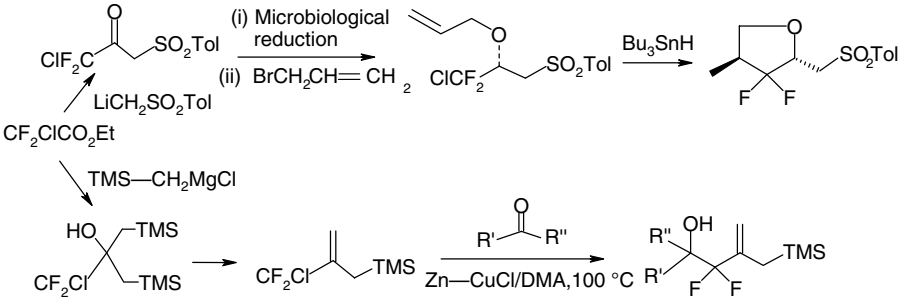

Figure 2.16 Nucleophilic addition on the ethyl chlorodifluoroacetate.

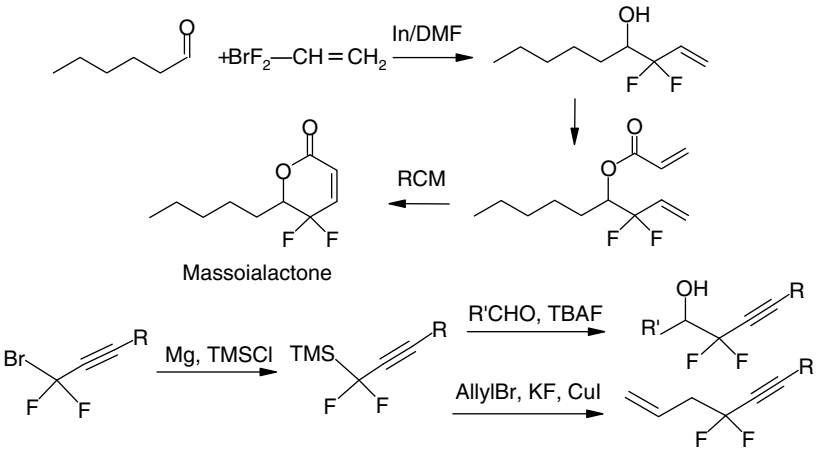

Figure 2.17 Reaction of fluorinated allyl and propargyl bromides.

2.2.3.4 Starting from the Difluoromethyl Phenyl Sulfone The nucleophilic difluoromethylation of aldehydes and ketones (enolizable or not) and of alkyl halides can be performed by using the anion of difluoromethyl phenyl sulfone. When using LHMDS as a base in a THF/HMPA solvent mixture, the reaction is also efficient with enolizable ketones and aldehydes. The CF_2H group is set free by reductive elimination of the sulfonyl group. Elimination in basic medium affords the corresponding 1,1-difluoroalkene (Figure 2.18).[98]

2.2.3.5 Starting from Trifluoromethyl or Bromodifluoromethyl Compounds (β-Elimination Pathway) As mentioned in Chapter 1, the development of a negative charge on the carbon in the α position of a CF_3 group can be accompanied by the loss of a fluoride ion, or of a bromide ion in the case of a CF_2Br group. This so-called β-elimination reaction allows preparation of *gem*-difluoroolefins and of difluoromethylenic compounds in an efficient manner. Trifluoroethanol, trifluoroacetic, and bromodifluoroacetic acid derivatives and trifluoromethyl styrene are the most common precursors of functional difluoroolefins (e.g., difluoroenoxysilanes).

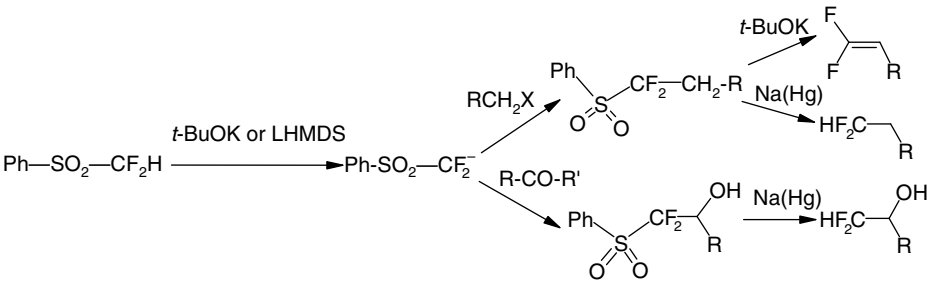

Figure 2.18 Difluoromethylenation reaction with difluoromethyl phenyl sulfone.

These difluoromethylenation reagents constitute a very important class of building blocks.

(a) Starting from Trifluoroethanol Trifluoroethanol is an industrial material, available at relatively low cost. The deprotonation and metallation of its derivatives generate the corresponding difluorovinyl anions.[99] However, stabilization of these anions is required to use them in synthesis. It is achieved either by a heteroatom (e.g., the intramolecular stabilization by a heteroatom of the lithiated enolate; Figure 2.19) or by a transmetallation (B, Cu), affording a more stable organometallic compound (Figure 2.20).[74, 100–102]

The stabilization by a heteroatom of the lithiated enolate can be realized by using carbamates and methylmethoxyethers (MEM) of trifluoroethanol. As shown in Figure 2.19, these enolates are powerful tools for the synthesis of difluorocompounds, especially to access difluorosugars.[74, 100–103]

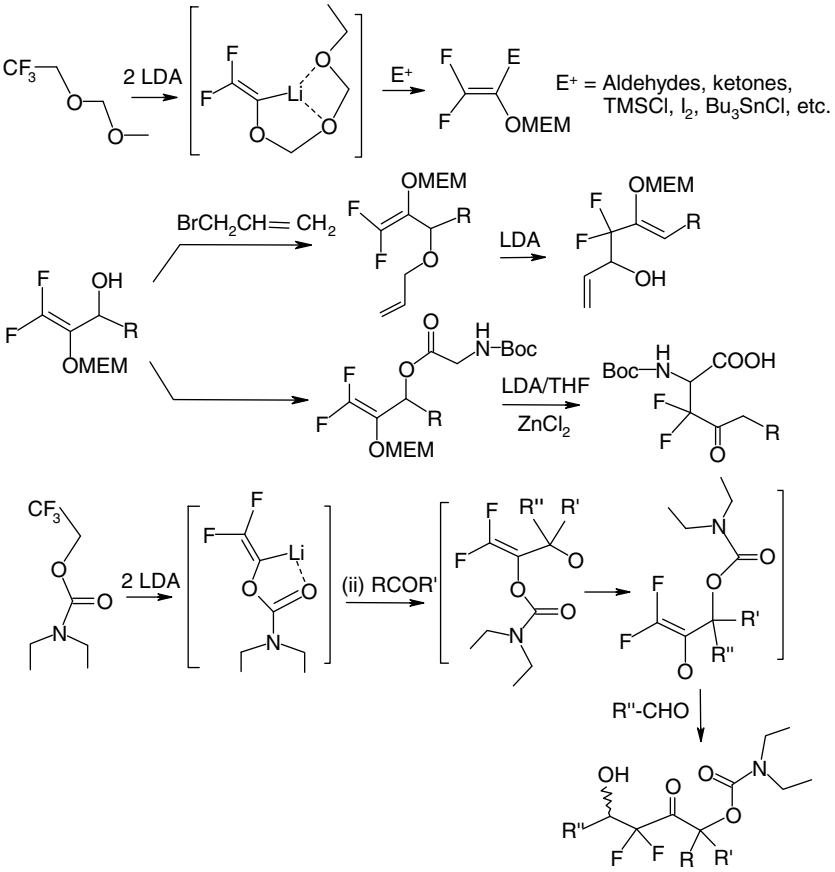

Figure 2.19 Difluorovinyl lithium enolates stabilized by heteroatom.[100–102]

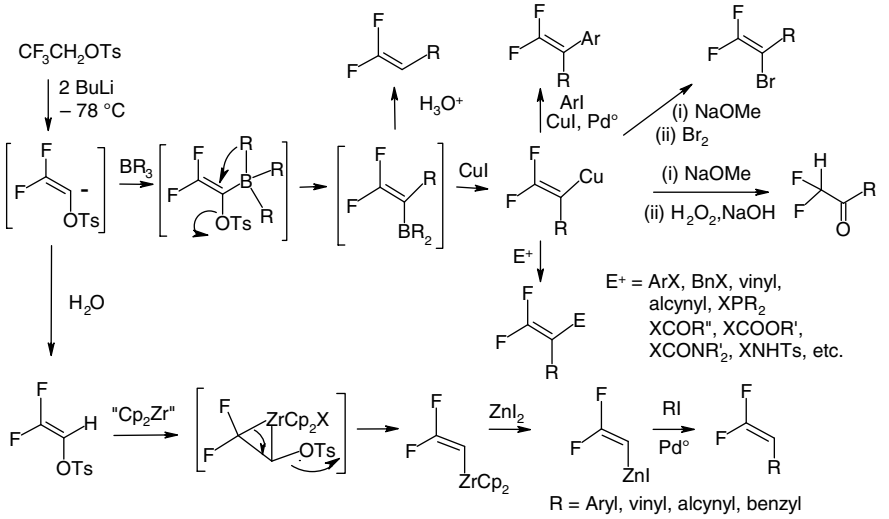

Figure 2.20 Synthesis starting from the tosylate of trifluoroethanol.[74, 102]

The transmetallation of the lithiated anion, generated from the tosylate of trifluoroethanol, is performed at low temperature with a borane or with cyclopentadienylzirconium. A further transmetallation affords a second organometallic species that is more stable or more reactive (zinc or copper) and that has a broader synthetic potential (Figure 2.20).[74, 102]

(b) Starting from Trifluoromethylstyrene An addition–elimination process, occurring from an activated trifluoromethylated olefin, leads to the formation of a *gem*-difluoroolefin. The example of trifluoromethylstyrene illustrates the synthetic interest of this reaction. Organolithiated molecules afford substituted difluorostyrenes, eventually functionalized as allylic difluorinated amines (Figure 2.21).[104, 105]

(c) Difluoroenoxysilanes Difluoroenoxysilanes are powerful reagents for difluoromethylenation. They were originally prepared from halodifluoroketones.[106]

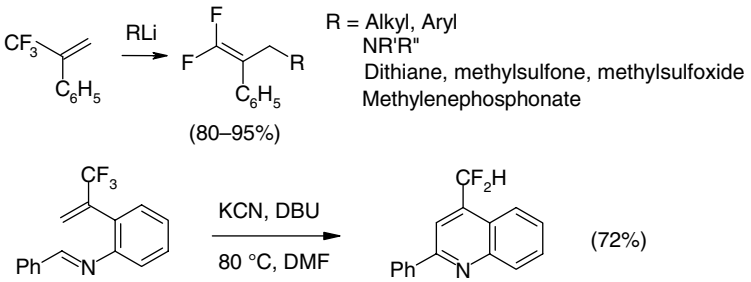

Figure 2.21 Reactions with trifluoromethylstyrenes.[104, 105]

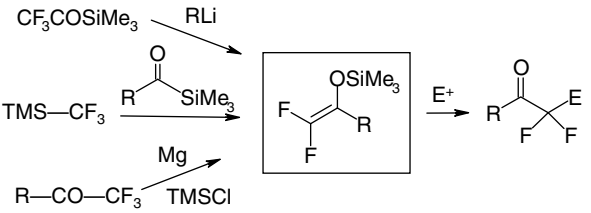

Figure 2.22 Preparation of difluoroenoxysilanes from trifluoromethyl compounds.[107–109]

Now they are prepared from trifluoromethyl compounds according to two pathways. The first one involves a Brook rearrangement with adducts obtained from trifluoromethylketones, trifluoroacetylsilanes, or acylsilanes and a Ruppert reagent (CF_3TMS).[107, 108] The second pathway is the reduction of a trifluoromethylketone, either by electrochemical reaction or by using Mg(0) in the presence of TMSCl. This latter method has become commonplace for aromatic ketones (Figure 2.22).[109, 110] Whatever the method used to prepare difluoroenoxysilanes, these compounds react as nucleophiles with an electrophile (e.g., allylic acetates, aldehydes, oxonium ion precursors) in the presence of Lewis acids.[111] Difluoroenoxysilanes are important for the synthesis of difluoro-*C*-glycosides and difluoro-*C*-disaccharides,[112] and also to prepare difluorinated analogues of terpenes and diterpenes (Figure 2.23).[107, 108, 112–114]

Although difluoroenoxysilanes are typical nucleophiles, they can also react with other nucleophiles via their oxidation into radical cations. The oxidative homocoupling and the cross-coupling with heteroaromatics and alcohols proceeds very well in the presence of Cu^{2+} triflate as the oxidizing reagent (Figure 2.24).[111a]

A difluorinated analogue of the Danishefsky diene has been prepared by reductive defluorination with Mg(0) of an α,β-unsaturated trifluoromethylketone. Its use in a hetero-Diels–Alder reaction (including asymmetric version) can lead to oxygen- and nitrogen-containing heterocycles (Figure 2.25).[115]

The reduction of trifluoromethylimines with Mg(0) affords *N*-silyl difluoroenamines.[116, 110] These synthons are very interesting for the preparation of difluoro-β-amino alcohols and of difluoro amino acids (cf. Chapter 4). They can also add onto radicals, react with sulfur ylides to afford difluoromethylaziridines, or even undergo intramolecular ene reactions (Figure 2.26).[117]

Silylacetals of difluoroketene have an important synthetic potential and constitute an alternative to the Reformatsky reagent generated from ethyl bromodifluoroacetate.[118] They are prepared by reduction by a bromo-, iodo-di-, or trifluoroacetate in the presence of a trialkylsilylchloride. Despite the fact that they are difficult to prepare, they behave similar to their nonfluorinated analogues (aldolization reactions, conjugated addition, etc.) (Figure 2.27).[119]

The isolation of the silylacetal ketene is required when the reaction is catalyzed by a chiral Lewis acid. However, due to its instability, isolation yields of the compounds are very low. Reaction of difluoroketene silylacetal with electrophiles affords adducts with excellent *ee* (Figure 2.28).[120] The instability of these difluoroketene silylacetals is due to the facile migration of the silyl group from oxygen to carbon, affording

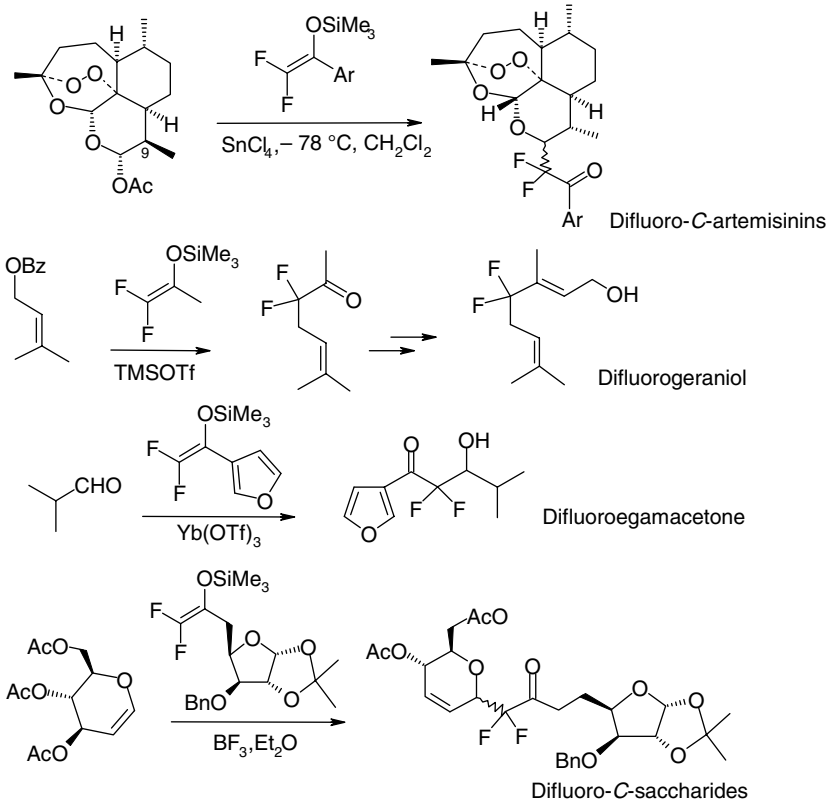

Figure 2.23 Synthesis of fluorinated analogues of natural compounds prepared by means of difluoroenoxysilanes.[107, 108, 112–114]

trimethylsilyl difluoroacetate.[120] This latter compound is more stable than the corresponding silyl ketene acetal. Trimethylsilyl difluoroacetate can also be prepared either by electrochemical reduction of a chlorodifluoroacetate in the presence of TMSCl[121] or, like difluoroenoxysilanes, by magnesium-promoted reduction (Figure 2.28).[122, 123] This silane reacts with electrophiles (e.g., aldehydes, imines, activated halides) in the presence of fluoride ions. Nevertheless, it is less reactive than difluoroketene silyl acetal.[111, 121]

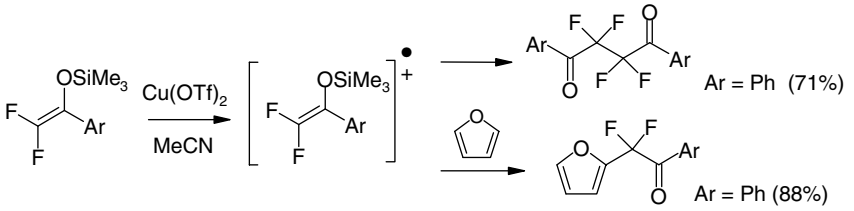

Figure 2.24 Oxidative coupling of difluoroenoxysilanes.[111a]

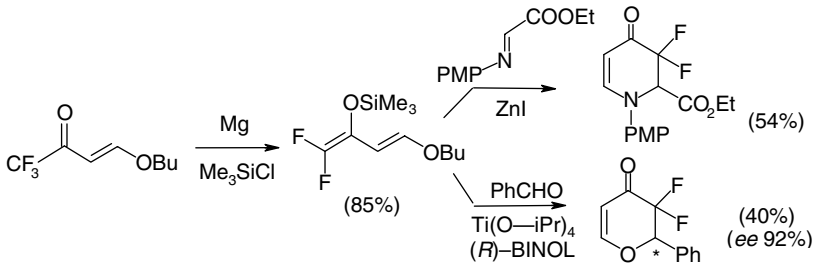

Figure 2.25 Use of difluorinated Danishefsky dienes.[115]

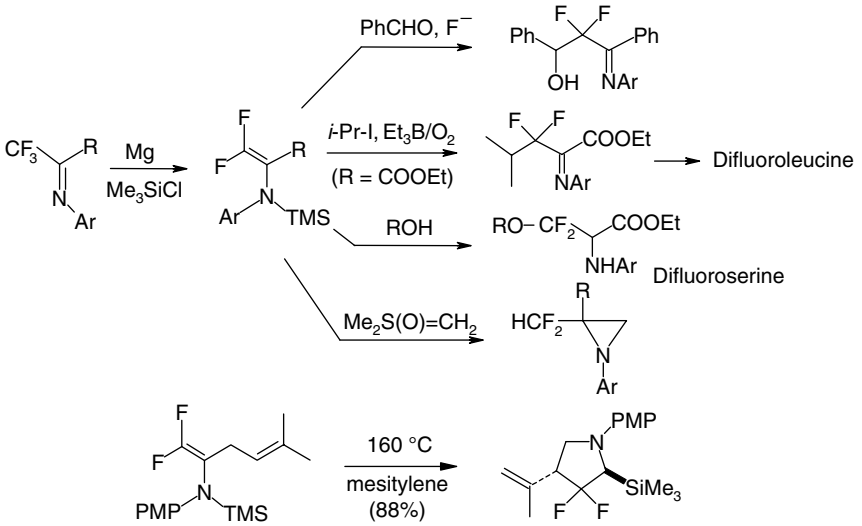

Figure 2.26 Synthetic applications of *N*-silyl difluoroenamines.[116, 117]

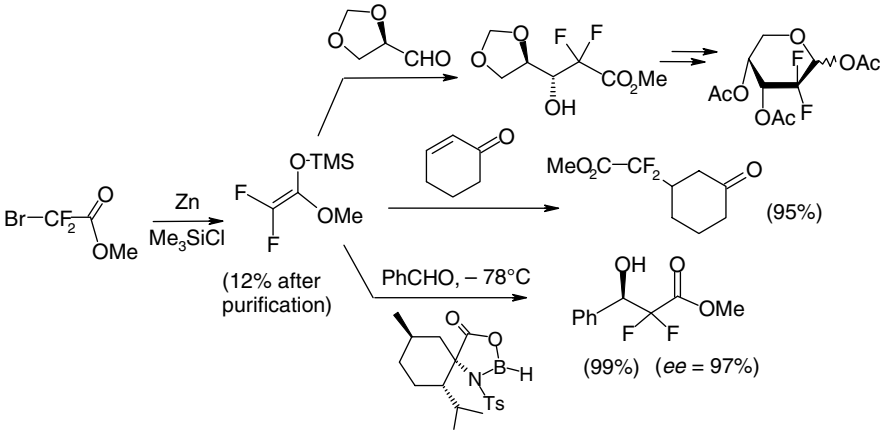

Figure 2.27 Preparation and reaction of silylacetal of difluoroketene.[118–120]

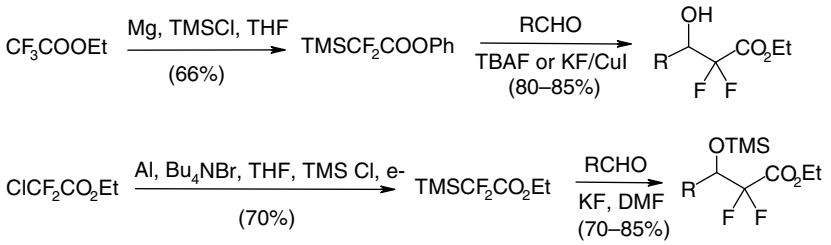

Figure 2.28 Preparation and reaction of trimethylsilyldifluoroacetate.

***Remarks*:** *Preparation of difluorophosphonates.* The preparation of difluorophosphonates is detailed in Chapter 7 (enzyme inhibitors). It is worth noting that it has been the topic of a recent review.[124]

Preparation of gem-difluoroallenes. gem-Difluoroallenes can be synthetized by metal-promoted reduction of dihalogenolefins, or by Shapiro reaction of trifluoromethylketone hydrazones.[125]

2.3 PREPARATION OF TRIFLUOROMETHYL COMPOUNDS

2.3.1 Fluorination

The conversion of a carboxylic group into CF_3 with SF_4[126] and the chlorine–fluorine exchange from a trichloromethylated derivative with SbF_3 or HF in aromatic series are important industrial processes.[127] However, they are not valuable at the laboratory level: SF_4 is toxic and hazardous, and special apparatus is required to utilize HF. On a bench scale, oxidative desulfurization-fluorination allows the transformation of dithiocarbonates and xanthates into —CF_3 or –OCF_3 groups. This reaction is performed under mild conditions with a source of fluoride ion (HF–pyridine or TBA + $H_2F_3^-$) in the presence of an oxidative agent (NBS or dibromohydantoin (DBH)).[128] The terminal CF_3 group can be introduced by this method (Figure 2.29). Examples with labeled ^{18}F have also been reported.[129]

The addition of a fluoride ion onto an activated difluoroolefin is also an efficient method to prepare trifluoromethylated compounds (Figure 2.30).[130, 131]

2.3.2 Nucleophilic Trifluoromethylation

Due to the poor efficiency of trifluoromethylated organometallic derivatives as trifluoromethylating reagents, nucleophilic trifluoromethylation has remained unattractive for a long time. Indeed, in the absence of stabilization, the trifluoromethyl anion is very unstable and is quickly transformed into difluorocarbene (cf. Chapter 1). When the carbon–metal bond is "relatively covalent," the organometallic species becomes more stable but it is then less reactive toward an electrophile.[132] On the synthetic level, only zinc and copper derivatives have found real applications in aromatic and heterocyclic series.[127, 133] The discovery of the Ruppert reagent

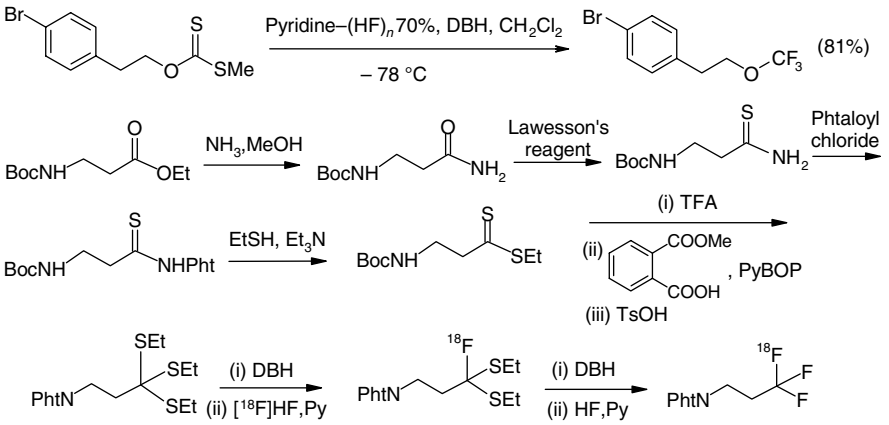

Figure 2.29 Trifluorination through oxidative desulfurization-fluorination process.[128, 129]

(trifluoromethyltrimethylsilane, CF_3TMS) has been a major breakthrough in the field, and the nucleophilic trifluoromethylation of carbonyl derivatives has become a powerful method.[134–136]

2.3.2.1 Trifluoromethylation with Ruppert Reagent The efficiency of this reagent is due to the fact that the chain reaction does not involve the transfer of a free CF_3^-, but goes through a pentacoordinated silicon intermediate in which the negative charge brought by the CF_3 is involved in a labile σ bond with the silicon. The chain reaction is initiated by a fluoride ion, but it is the alcoolate stemming from the addition of the CF_3 group that ensures the propagation (Figure 2.31). The product of the reaction is an *O*-silylated product (the desilylation occurs only if the quantity of fluoride ion used is significant).[134, 135] The solvent of the reaction is commonly THF, and the fluoride ion source is tetrabutyl ammonium fluoride (TBAF). However, other Lewis bases, such as lithium carboxylate and amine oxide, are able to initiate the reaction.[137] The nature of the initiator or the source of fluoride and the choice of the

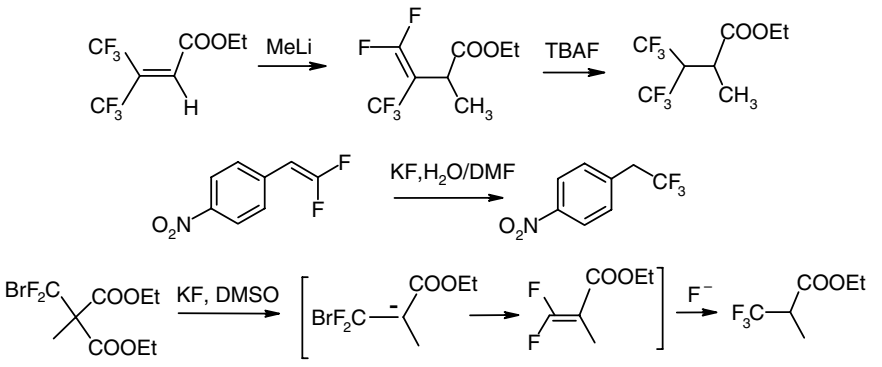

Figure 2.30 Conversion of a CF_2 group into CF_3.[130, 131]

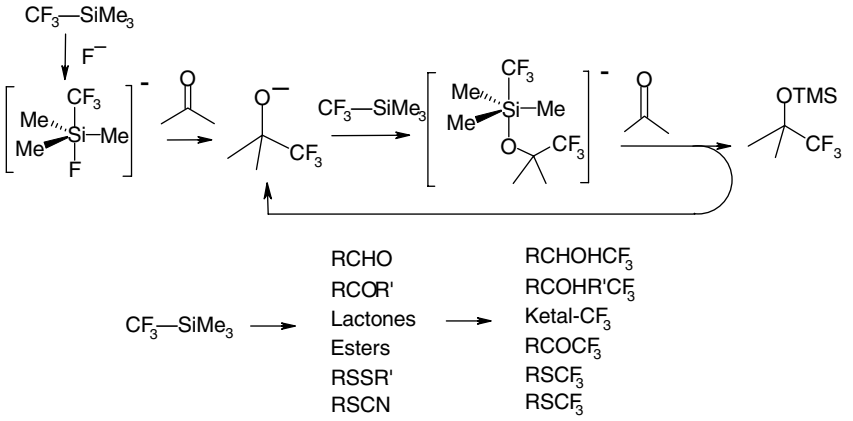

Figure 2.31 Nucleophilic trifluoromethylation with Ruppert reagent.

solvent have a major role in the success of the reaction, in particular, in the case of poor reactive substrates such as esters.[138] CF_3TMS reacts easily with aldehydes and ketones of very diversified structures (e.g., steroids, carbohydrates) (Figure 2.32).[134] Imides, oxazolidinones, lactones, and activated esters also react, albeit less easily.[134, 139] Nonactivated esters are not reactive under classical conditions. Nevertheless, with fluoride cesium in a strictly anhydrous medium (neat or in pentane), they afford trifluoromethylketones.[140] This reaction has also been extended to α-amino esters.[140] Among nitrogen-containing molecules, only aldimines,[141] activated imines, and

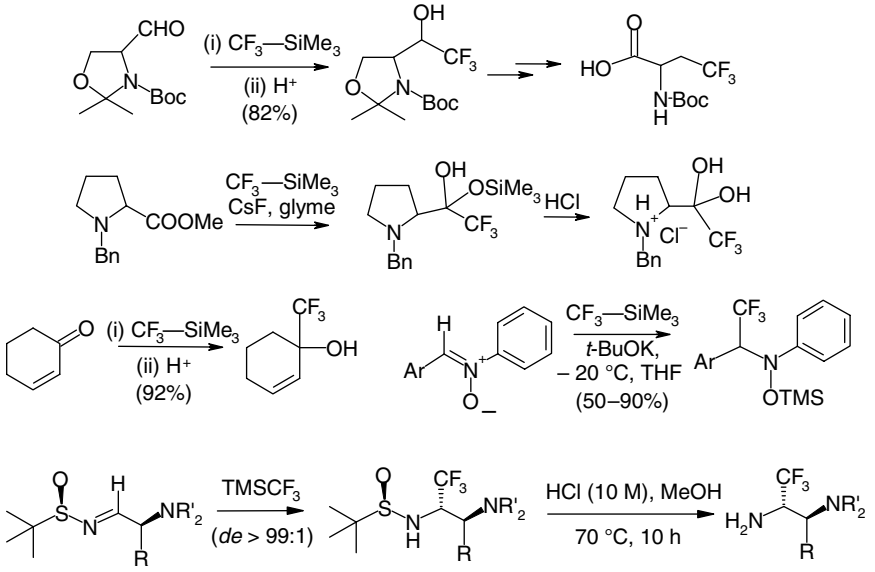

Figure 2.32 Examples of trifluoromethylation with Ruppert reagent.

nitrones react with the Ruppert reagent.[142] The reaction can be rendered easier when it is performed in the presence of a silylating agent such as TMS-imidazole.[143] CF_3TMS also reacts easily with thiocyanates and disulfides to afford CF_3S compounds.[144] The asymmetric addition of the Ruppert reagent has been performed by means of chiral quaternary ammonium fluoride catalysts, such as *Cinchona* alkaloids. However, enantioselectivity is often relatively modest.[145, 146] Nevertheless, efficient diastereoselective trifluoromethylation of chiral *t*-butylsulfinimides has been achieved.[136, 147]

Some other fluoroalkyl derivatives of silicon (e.g., $ArCF_2TMS$, $ClCF_2TMS$, RfTMS, C_6F_5TMS) have been prepared and used as fluoroalkylating reagents. Unfortunately, their reactivity is much lower than that of CF_3TMS, and they have not found important synthetic applications.[148]

2.3.2.2 Alternatives to the Ruppert Reagent Despite the huge improvement brought by the Ruppert reagent, the quest for new trifluoromethylating reagents is still very active, for diverse reasons. First, CF_3TMS is prepared from CF_3Br (Halon 1301). While this gas is utilized in various industrial areas (e.g., fire extinguisher, calorie carrier fluids), it is now banned because of its effect on the depletion of the ozone layer. Production of Halon 1301 will surely decrease dramatically and, consequently, its selling price will increase dramatically. Another reason is the fact that most of the attempts to perform enantioselective trifluoromethylation with CF_3TMS have been disappointing.

The quest for new trifluoromethylating reagents has begun with the search for a new precursor for the preparation of $TMSCF_3$ (instead of CF_3Br). The first candidate is fluoroform (CHF_3).[149] Indeed, when an aldehyde is treated with fluoroform and a strong base in DMF, trifluoromethylation occurs. However, fluoroform is a gas that is not convenient for use in laboratories. Moreover, the strong basic medium required for the generation of the fluoroform anion can be a source of problems with sensitive substrates.[150] Taking into account that the tetrahedral intermediate of this reaction (i.e., the adduct resulting from the addition of CF_3 on the DMF) could also be generated by the addition of an amine onto fluoral, an approach using fluoral has been developed (fluoral hydrate is an industrial chemical largely available and easy to use). Finally, fluoral (*O*,*N*)-silylacetals are able to transfer the trifluoromethyl group onto the carbonyl of aldehydes and nonenolizable ketones so strong basic conditions could be avoided (Figure 2.33).[151, 152]

It has recently been shown that when the tetrahedral intermediate of the reaction is cyclic, it is a better donor of nucleophilic CF_3. These cyclic intermediates can be generated intramolecularly from trifluoroacetamides or trifluorosulfinamides derived from *O*-silylated ephedrine. These reagents are able to trifluoromethylate aldehydes and ketones, even in the case of enolizable substrates, as a strong base is not required (Figure 2.34).[153] However, while the source of CF_3 is chiral, there is no chirality transfer to the addition product, and the replacement of ephedrine by other chiral amino alcohols did not show any improvement.[154] Similar to asymmetric trifluoromethylation with the Ruppert reagent, only the use of a fluoride salt of cinchonine can increase the enantioselectivity.[145, 146]

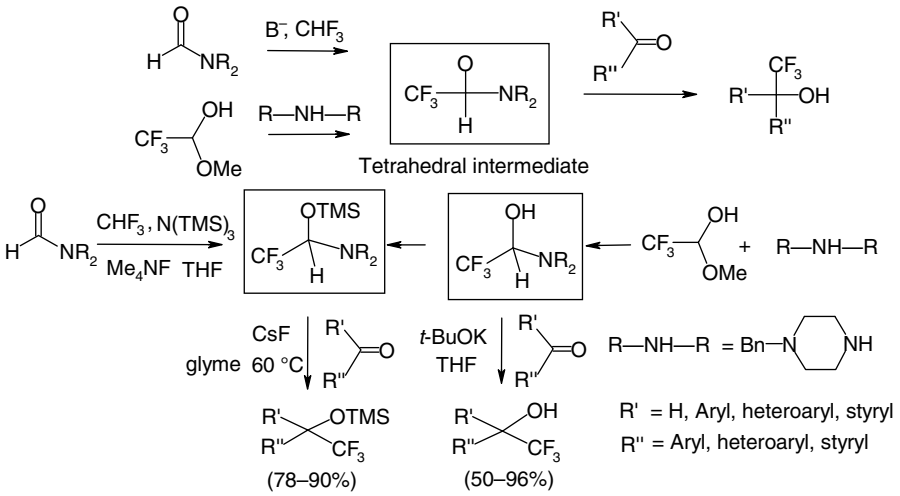

Figure 2.33 Nucleophilic trifluoromethylation with (*O*,*N*)-acetals of fluoral.[151, 152]

Trifluoromethyl phenylsulfone is accessible from fluoroform and diphenyldisulfide, and it has been proposed as a donor of CF_3. However, the reaction must be performed in basic medium (*t*-BuOK) and is then limited to nonenolizable aldehydes and ketones.[155] But it can also be used as a precursor of the Ruppert reagent. This latter is obtained with an excellent yield by treating the sulfone with magnesium in the presence of TMSCl (Figure 2.35).[136]

It should also be noted that a new reagent for trifluoroethylidenation, trifluoroethyldiphenylphosphine, can be used in Horner reactions under TBAF activation

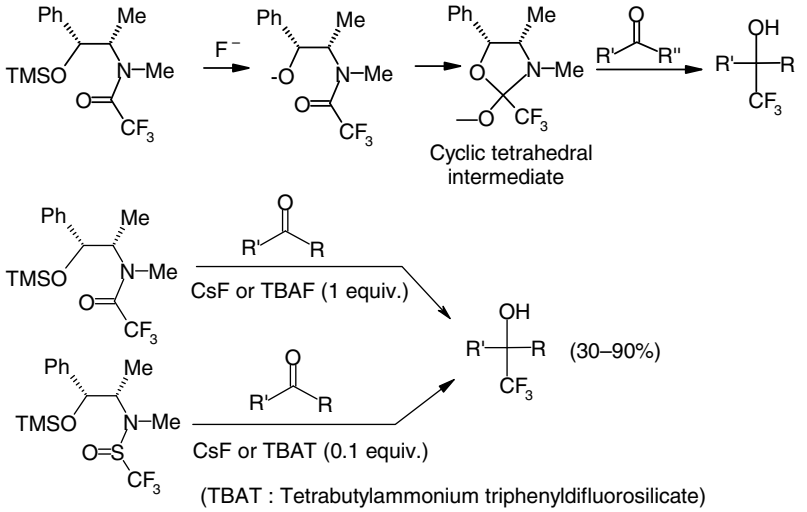

Figure 2.34 New approaches for trifluoromethylation.[155, 156]

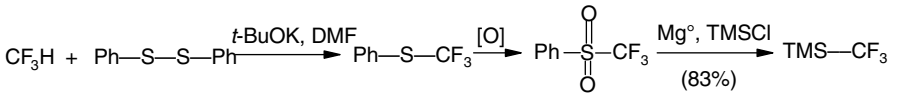

Figure 2.35 Preparation of CF_3TMS from fluoral.

and reacts with some enolizable aldehydes. However, the reaction is poorly stereoselective.[157]

2.3.2.3 Aromatic Trifluoromethylation Vinylic or aromatic nucleophilic trifluoromethylation often involves copper catalysis in the presence of an excess of fluoride ions.[127] Reactions generally take place in DMF at high temperature (100–120°C) and lead to the formation of an intermediate difluorocarbene generated from a presursor: for example, $ClCF_2CO_2Me$, $FO_2SF_2CO_2Me$, CF_3CO_2Na, or CF_3TMS (although in the last two cases, the formation of a difluorocarbene has not been formally demonstrated). Then the difluorocarbene undergoes the addition of fluoride ion and reacts with the copper salt to form an organocopper species. This latter reacts with an aromatic, vinylic, or allylic halide to afford the desired trifluoromethyl compound. The difluorocarbene is responsible for the presence of pentafluoroethylation side products, which are often detected when the aromatic halide is poorly reactive (Figure 2.36).[127, 133a] The aromatic substitution of a nitro group by the Ruppert reagent is also possible when the aromatic ring bears a second electron-withdrawing group.[133b]

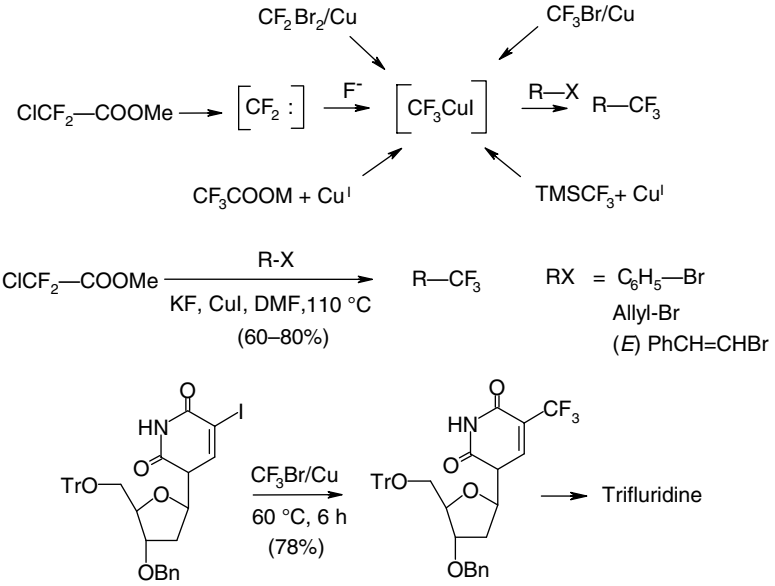

Figure 2.36 Copper-catalyzed trifluoromethylation.[127]

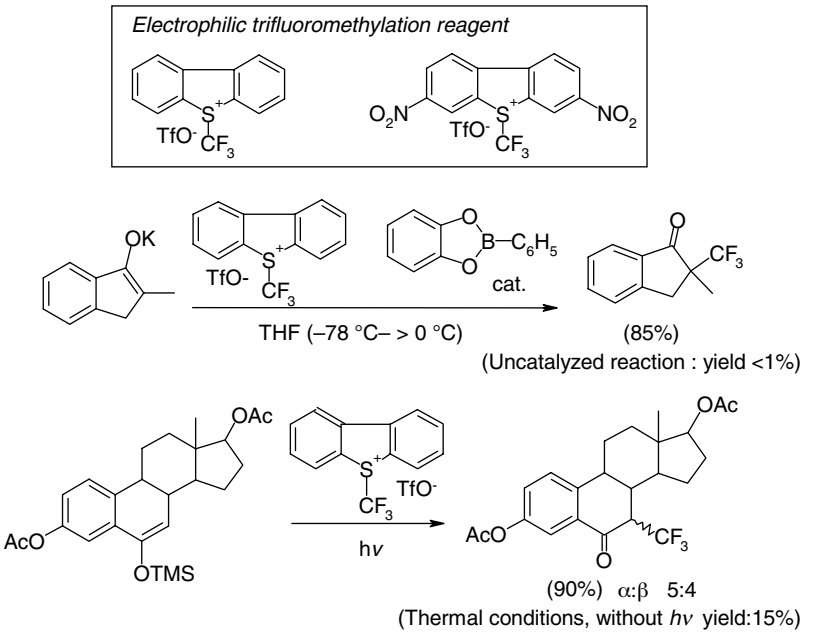

Figure 2.37 Electrophilic trifluoromethylation.[158, 159]

2.3.3 Electrophilic Trifluoromethylation

Electrophilic trifluoromethylation is still of minor importance in synthetic applications. The limited efficiency and the cost of the reagents able to transfer a CF_3^+ cation are important obstacles for the development of this approach. However, CF_3–S^+-type reagents can react with activated enolates under Lewis acid catalysis.[158] A recent and promising result shows that, when the reaction is performed under UV irradiation, yields significantly increase. This can lead to synthetic applications, as exemplified by the recent preparation of 7-CF_3 steroids (Figure 2.37).[159]

In the search for less expensive and more easily accessible reagents, a new hypervalent iodine(III)–CF_3 reagent has shown a promising reactivity in the mild and selective electrophilic trifluoromethylation of active methylene compounds and free thiols (Figure 2.38).[160] Synthesis of this reagent is easy and scalable.[160]

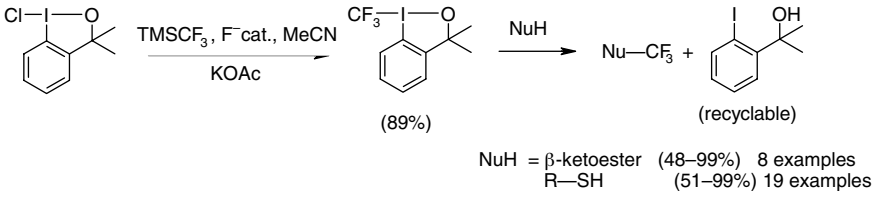

Figure 2.38 Electrophilic trifluoromethylation.[160]

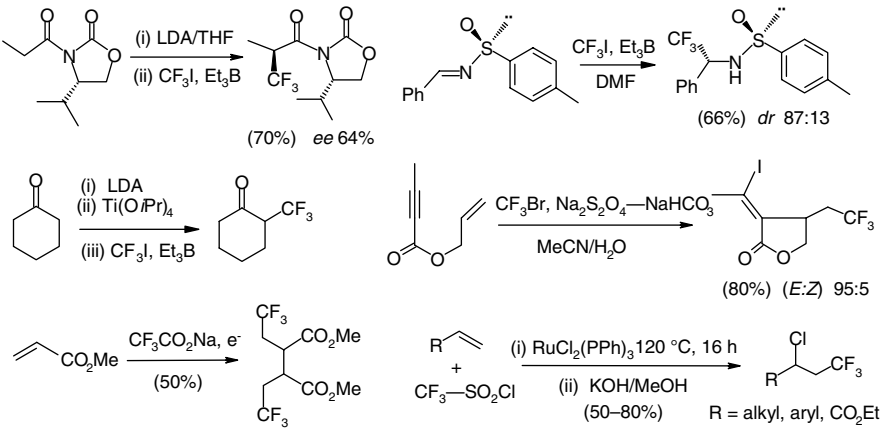

Figure 2.39 Examples of radical trifluoromethylation.[162–166,169]

2.3.4 Radical Trifluoromethylation

For a long time radical trifluoromethylation has been used in aromatic rather than in aliphatic series. Some examples of radical trifluoromethylation, with CF_3I under UV irradiation, of substrates with biological interest (e.g., nucleic bases, heterocycles, amino acids) are given in the following chapters. Although yields and selectivity are often low, this situation has recently reversed.[127, 161] It has been shown that these reactions can be more efficiently initiated by sodium dithionite or triethylborane. The addition of CF_3I onto enolates and chiral sulfinyl imines, initiated by Et_3B, is an efficient reaction. However, diastereoselectivity is only moderate (Figure 2.39).[162, 163] The radical trifluoromethylation of ketone titanium ate enolates also affords α-trifluoromethylketones in good yields.[164] Radical trifluoromethylation of ketone silyl enol ethers by activation with dialkylzinc has also be achieved.[161]

Other sources of radical CF_3, much less expensive than CF_3I, have been discovered. These are the anodic oxidation of sodium trifluoroacetate[165] (the decomposition being initated by a hydroperoxide or ruthenium catalyst)[166] and trifluoromethyl bromide (CF_3Br) using sodium dithionite as initiating agent.[167, 168]

The transfer of a trifluoromethyl group of xanthate R—O—(C=S)—S—CF_3 is a recent and powerful method for the trifluoromethylation of olefin.[170] An important and interesting point of this method is that the reaction product is a xanthate itself, able to undergo further radical reactions and permitting cascade reactions, as exemplified in Figure 2.40. The starting xanthates R—O—(C=S)—S—CF_3 are easily prepared from trifluoroacetic anhydride and sodium xanthate.[171]

2.3.5 Metal-Catalyzed Trifluoromethylation

It has recently been reported that rhodium catalysts ($Rh Cl(PPh_3)_3$) are able to mediate the addition of trifluoromethyl iodide, in the presence of Et_2Zn, onto the β position of

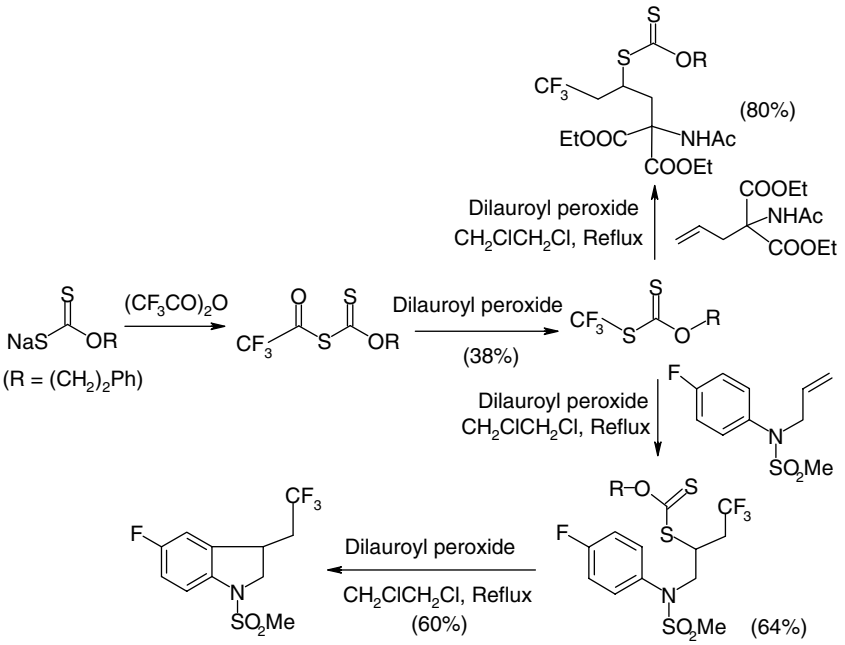

Figure 2.40 Trifluoromethylation with trifluoromethyl xanthate.[171]

enones in moderate to good yields. Hydrogen transfer of the ethyl group of Et_2Zn on the rhodium complex to the β position of the enone seems to play an important role in this new reaction (Figure 2.41).[172]

2.3.6 Formation of Carbon–Carbon Bonds from Trifluoromethyl Compounds

The main commercially available and/or easily accessible chemicals for the synthesis of trifluoromethyl-containing molecules are discussed in this section.

2.3.6.1 Starting from Trifluoroacetic Acid Derivatives Trifluoroacetic acid and its derivatives (e.g., esters, anhydride, fluoral, trifluoroethanol) are the major channel of the organic fluorine industry. They are relatively inexpensive and, compared to halons, they do not exhibit major environmental problems. They are the main source for the synthesis of trifluoromethylated compounds.

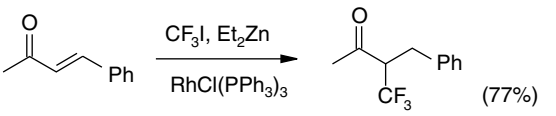

Figure 2.41 Transition-metal-catalyzed trifluoromethylation.

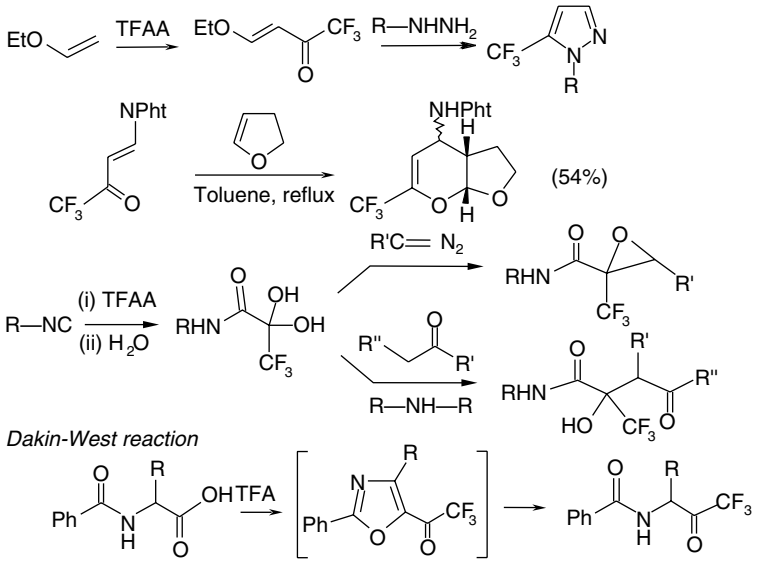

Figure 2.42 Synthesis from trifluoroacetic anhydride.

(a) Trifluoroacetic Anhydride Trifluoroacetic anhydride (TFAA) is a very reactive molecule (the corresponding trifluoroacetyl chloride is a gas that is rarely used). TFAA is able to acylate aromatic rings, via Friedel–Crafts reaction, into aromatic trifluoromethyl ketones. Electron-rich double bonds (e.g., enol ethers, isonitriles) are also acylated, affording β-substituted trifluoromethyl ketones. These latter ones are substrates in heterocyclization and cycloaddition reactions, giving rise to many heterocycles.[173–176] The trifluoroacetylation of amino acids yields α-amido trifluoromethyl ketones (Dakin–West reaction) that are key units in protease inhibitors (Figure 2.42).[177]

(b) Ethyl Trifluoroacetate Ethyl trifluoroacetate is a very important starting material to access trifluoromethyl compounds. With organolithium and organomagnesium reagents, the reaction stops at the ketone stage: due to the stability of the tetrahedral intermediate, the second addition of the organometallic species does not occur.[178, 179] When trifluoroacetates are condensed with functionalized carbanions, such as ester enolates,[180] glycine anions,[181] or anions in α of sulfones and sulfoxides,[182, 183] they afford β-diketones, β-keto esters, β-keto amino acids, and β-ketosulfones and sulfoxides, respectively. As an acylating reagent, it affords trifluoromethyl arylketones and β-ketonic compounds (Figure 2.43).[179]

The carbonyl of trifluoroacetates is reactive enough to react with phosphoranes and to yield trifluoromethyl enol ethers (the reaction must be conducted without lithium salts; i.e., the phosphorane must be generated without a nonlithiated base). In the same way, trifluoroacetamides and trifluorothioacetates afford, respectively, trifluoromethyl enamines and vinyl thioethers (Figure 2.44).[184, 185]

The compounds obtained in these reactions, especially enol ethers, are interesting building blocks: they can give rise to many other trifluoromethyl molecules. For

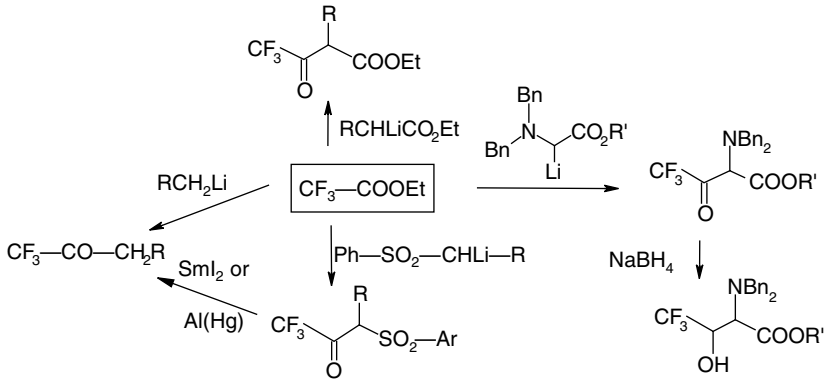

Figure 2.43 Acylation reactions with ethyl trifluoroacetate.

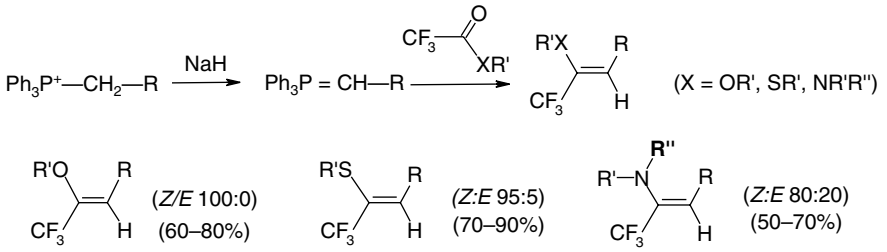

Figure 2.44 Preparation and reactivity of trifluoromethyl enol ethers.[184, 185]

example, the epoxidation reaction (eventually asymmetric) yields stable epoxy ethers. These latter ones have been utilized to prepare α-substituted trifluoromethyl ketones or can be selectively reduced to afford the corresponding amino alcohols (Figure 2.45).[186–189]

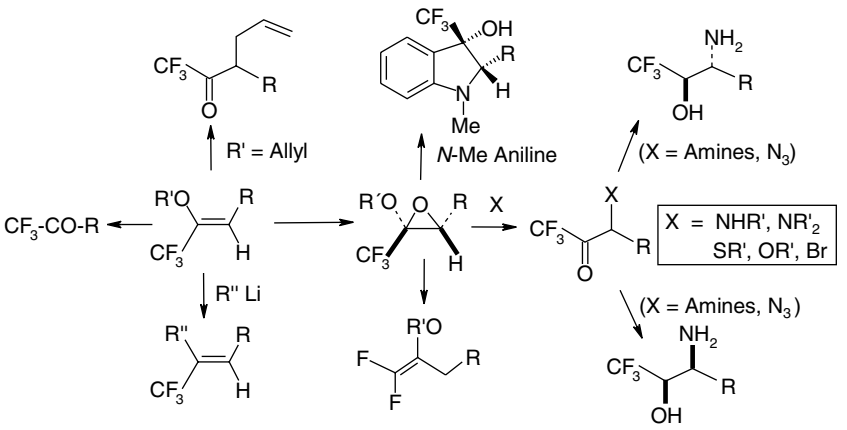

Figure 2.45 Reactivity of trifluoromethyl enol ethers.[186–189]

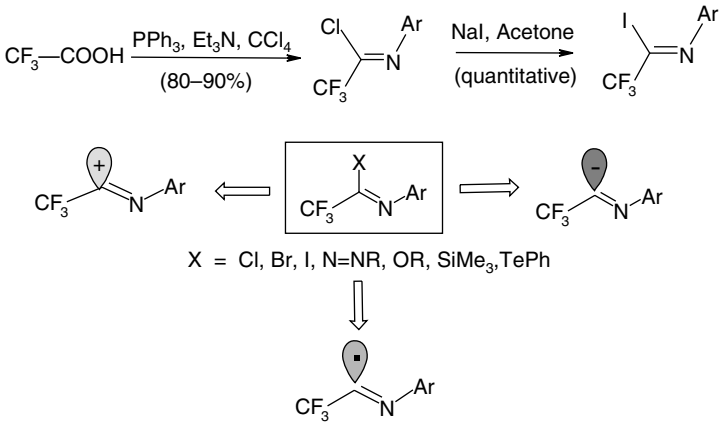

Figure 2.46 Trifluoroacetamidoyl halides.[190]

(c) Trifluoroacetamidoyl Halides Trifluoroacetamidoyl halides are not commercially available compounds, but they are easily prepared from trifluoroacetic acid. They have a broad spectrum of reactivity in electrophilic, nucleophilic, and radical processes (Figure 2.46). Consequently, the synthetic potential of these molecules is wide. Some examples of preparation of amines, amino alcohols, amino acids, and α-trifluoromethyl heterocycles are given in the Figure 2.47.[190]

2.3.6.2 Starting from Fluoral Fluoral (trifluoroacetaldehyde) is an unstable gas[192] that must be prepared before use by dehydration of the corresponding hydrate (commercially available). In spite of this limitation, fluoral itself has been used as a substrate in various reactions. Among the most recent examples, carbonyl-ene and hetero-Diels–Alder reactions deserve mention.[193, 194] The use of chiral Lewis acid catalysts allows asymmetric versions of carbonyl-ene[195] and Friedel–Crafts and Mukaiyama reactions[196, 197] (Figure 2.48).

Fluoral hydrate and hemiacetals are industrial products. They are stable liquids that are easy to handle, and they react as fluoral itself in many reactions. Thus, in the presence of Lewis acids, they react in Friedel–Crafts reactions.[198] They also react very well with organometallics[199, 200] (indium and zinc derivatives) and with silyl enol ethers.[201] Proline-catalyzed direct asymmetric aldol reaction of fluoral ethyl hemiacetal with ketones produced β-hydroxy-β-trifluoromethylated ketones with good to excellent diastereo- (up to 96% *de*) and enantioselectivities.[202] With imine reagents, the reaction proceeds without Lewis acid activation.[203] The use of chiral imines affords the corresponding β-hydroxy ketones with a 60–80% *de* (Figure 2.49).[204]

Chiral derivatives of hemiacetal from fluoral have been prepared by adding an alcohol to fluoral in the presence of (*R*)-BINOL—Ti(O—*i*Pr)$_2$ or by HPLC resolution of the racemate. The displacement of the sulfonate moiety from the tosyl derivative, by an alkyl lithium aluminate, affords the trifluoromethyl ether with inversion of configuration and an excellent chirality transfer (Figure 2.49).[205]

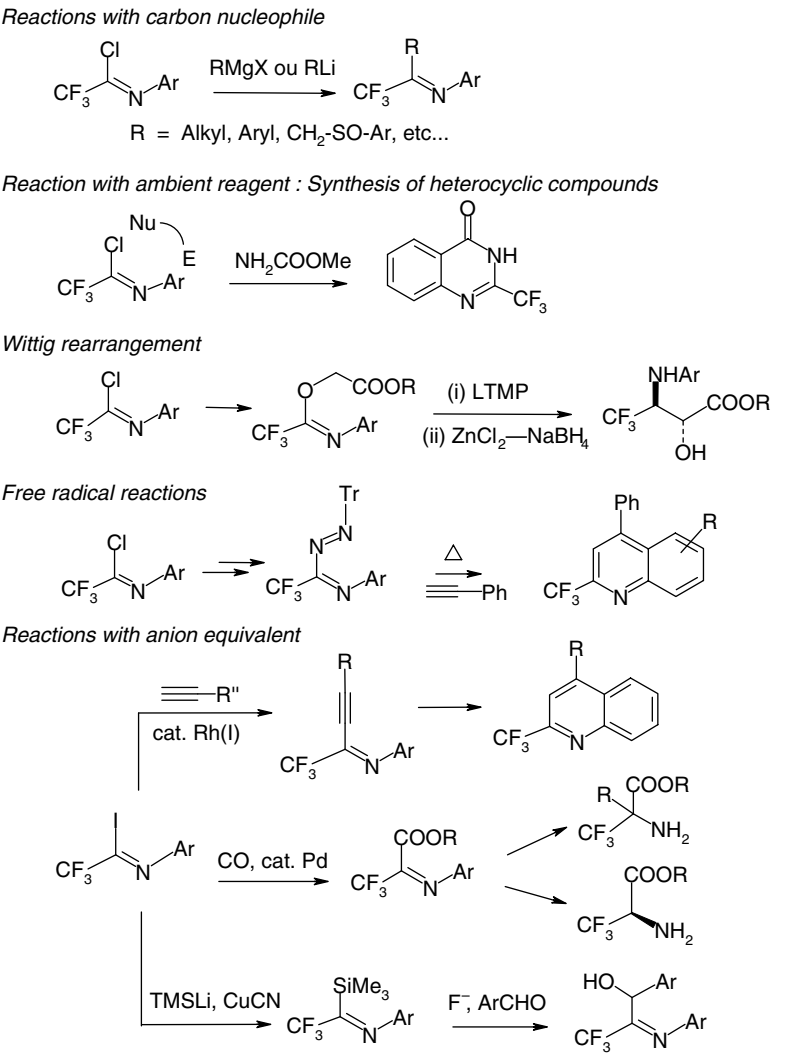

Figure 2.47 Examples of the reactivity of trifluoroacetamidoyl halides.[190, 191]

Imines and (*N*,*O*)-acetals from fluoral are useful precursors of trifluoromethyl nitrogen-containing molecules: amines, amino alcohols, amino acids, peptidomimetic units, heterocycles, and so on (Figure 2.50). These simple *N*-derivatives of fluoral are easily prepared from the hydrate or the hemiacetal. Imines of fluoral react in [2 + 1],[206] [2 + 2],[207] and [4 + 2][208] cycloaddition reactions affording aziridines, β-lactams, and heterocycles, respectively,[206–208] and in ene reactions.[209] The preparation of the imine is not always required as reactions can be performed as well on (*N*,*O*)-acetals of fluoral. These *N*-derivatives of fluoral react also with nucleophiles. Thus, various organometallics (organolithium, organomagnesium, and organozinc with aryl, alkyl, vinyl,

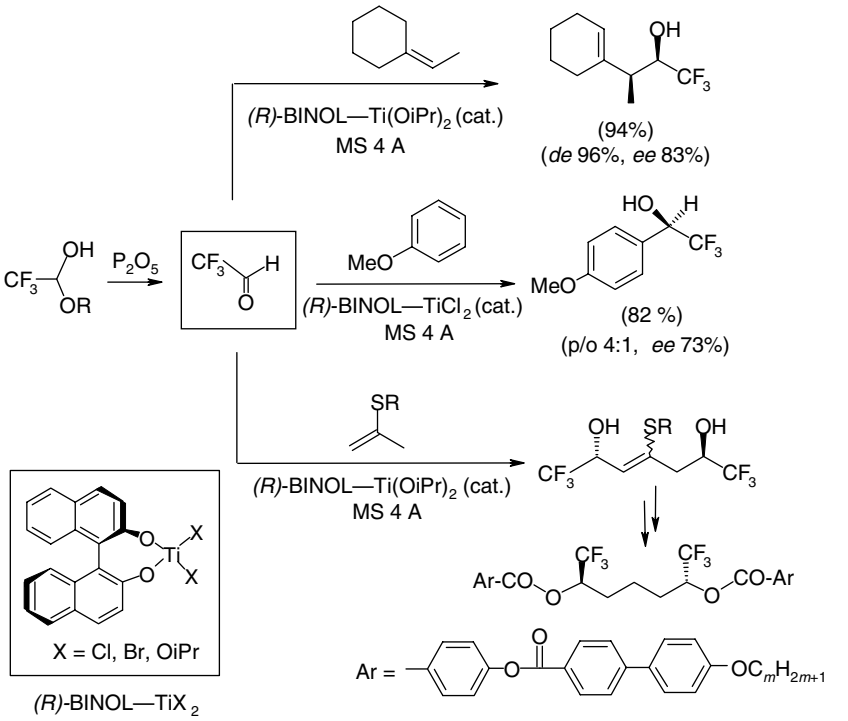

Figure 2.48 Lewis acid-catalyzed asymmetric reactions of fluoral.

allyl, or propargyl as organic moiety) add onto imines, hemiaminals, and aminals of fluoral.[210–212] The addition of TMSCN[213] (Strecker reaction) and allyl silane[214] have also been reported. Cycloaddition[215] and aldolization[216, 217] proceed also very well with fluoral (*N*,*O*)-acetals. In the last case, diasteroselective[210–213, 218, 219] and enantioselective[204] reactions give high *de* and *ee*.

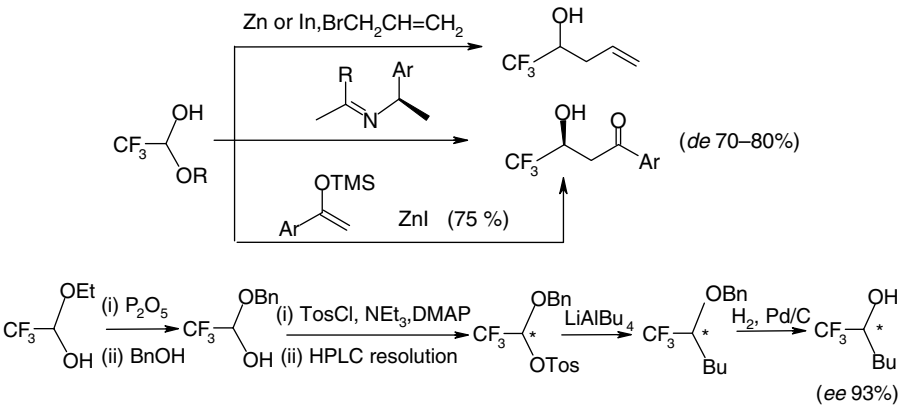

Figure 2.49 Examples of reaction with hemiacetal of fluoral.

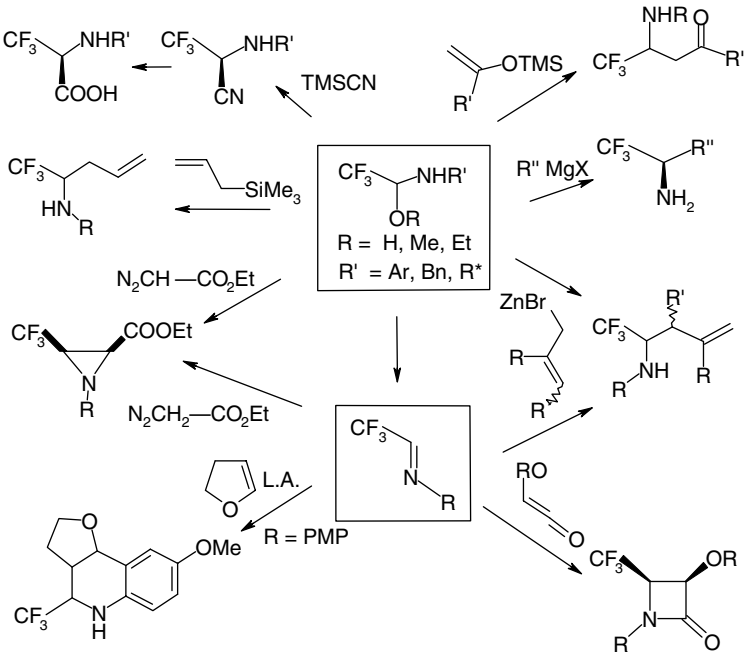

Figure 2.50 Synthetic application of simple nitrogen derivatives of fluoral.[211c]

Figure 2.51 reports some synthetic applications of α-allyl- and α-vinyltrifluoromethylamines.[211, 219, 220]

An innovative way to introduce trifluoroethanol and trifluoroethylamine moiety by the radical path has been described starting from xanthates of (*O*,*O*)- and (*O*, *N*)-hemiacetals of fluoral.[170] This powerful method allows cascade reactions, yielding elaborated molecules (Figure 2.52).[221, 222]

The higher homologue of fluoral, pentafluoropropionaldehyde, prepared by reduction of ethyl pentafluoropropionate, is a precursor of diethyl tetrafluoroketene dithioacetal, which is a versatile building block for the synthesis of trifluoromethyl-substituted functional compounds, such as trifluoromethyl lactones, lactams, and heterocyclics, as exemplified in the Figure 2.53.[223]

2.3.6.3 Other Trifluoromethyl Starting Materials To conclude this non-exhaustive overview, we report on other trifluoromethylated starting materials. Although they are less common, these compounds are commercially available, albeit generally more expensive than those previously cited.

(a) Ethyl Trifluoroacetoacetate This commercial compound is obtained by a Claisen condensation between ethyl trifluoroacetate and ethyl acetate. It is produced and used in industry in heterocyclization reactions, affording many trifluoromethyl heterocycles involved in agriculture and in pharmaceuticals.[180] It is also a precursor of

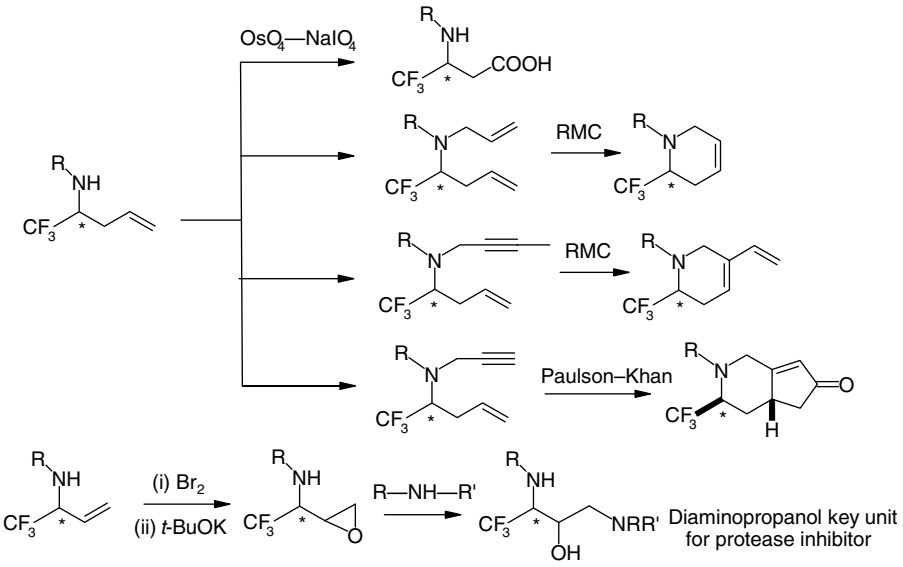

Figure 2.51 Synthetic applications of α-allyl- and α-vinyltrifluoromethylamines.[211c]

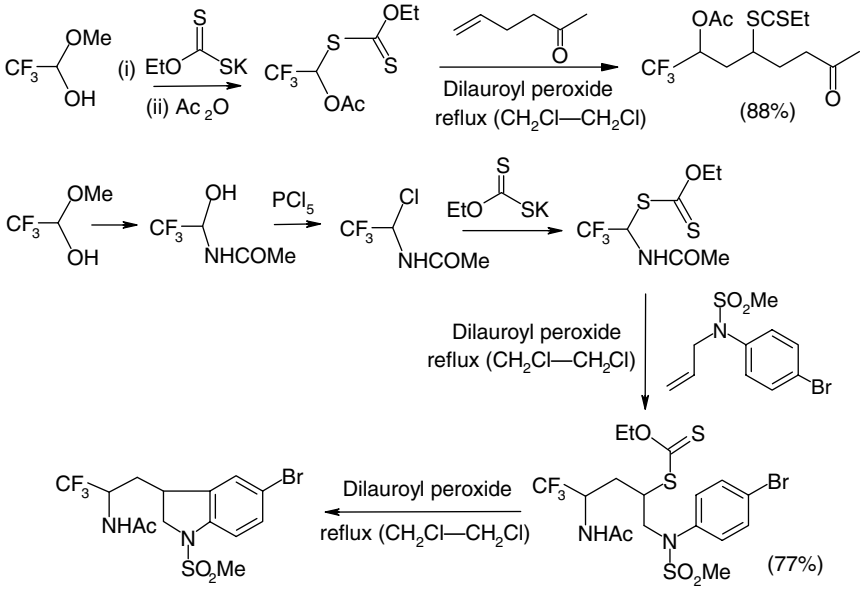

Figure 2.52 Radical introduction of trifluoroethanol and trifluoroethylamine moieties.

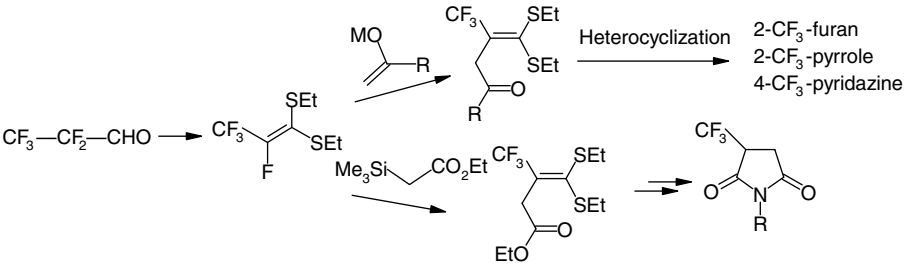

Figure 2.53 Synthesis with perfluoroketene dithioacetals.[223]

trifluoromethylketones via the Caroll reaction,[224] and of the fluorinated analogue of the Hagemann ester.[225] This latter compound is an interesting building block to access bicyclic compounds (Figure 2.54).[226]

(b) Ethyl Trifluoropyruvate Ethyl trifluoropyruvate is prepared on the industrial scale from hexafluoropropene oxide. The high electrophilicity of the carbonyl makes it highly reactive toward many nucleophiles. Among these reactions, carbonyl-ene (eventually asymmetric with chiral palladium complexes),[227] Friedel–Crafts (affording trifluoromethyl mandelic or indolacetic acids),[228] and aldolization reactions (affording butenolides) deserve mention.[229] Under solvent-free conditions, the enantioselective copper-catalyzed Friedel–Crafts alkylation of aromatic ethers with trifluoropyruvate occurs.[230] The reactivity of the corresponding imines and sulfinimines has captured much attention: these compounds allow access to α-trifluoromethyl amino acids (cf. Chapter 5).

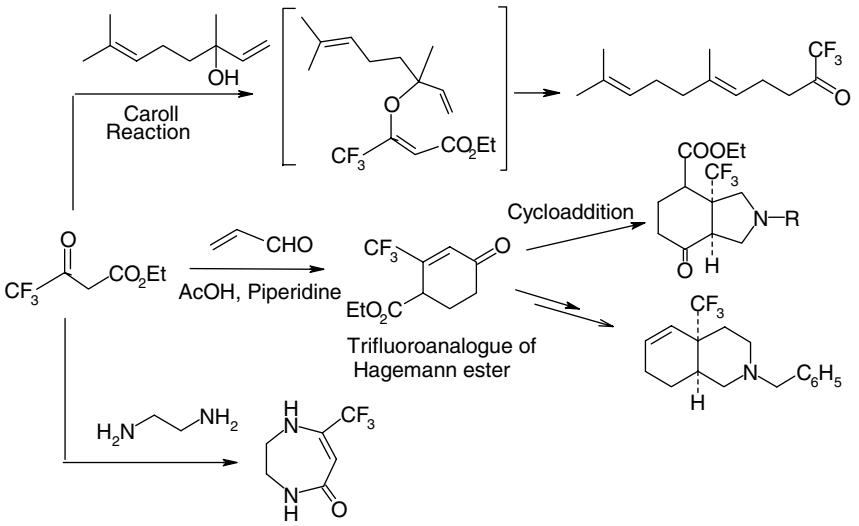

Figure 2.54 Synthesis from ethyl trifluoroacetoacetate.[180, 224, 226]

(c) Trifluoroacetone and Bromotrifluoroacetone *Trifluoroacetone* is a gaseous compound (bp 4°C) that is well known in the organic community as the precursor of trifluoromethyl dioxirane (TFMDO), a powerful epoxidation reagent.[231] It is also a building block for trifluoromethyl olefins through the Wittig or Wittig–Horner reaction[232] or via aldol condensation.[233, 234] It has been used to synthesize fluorinated analogues of fluoral (cf. Chapter 4).[233]

Bromotrifluoroacetone is a versatile source of synthons. It can be used to prepare α-substituted trifluoromethyl ketones, such as α-thioalkyl ketones. These latter compounds are esterase inhibitors and, consequently, many investigations are dedicated to their synthesis (cf. Chapter 7). At the industrial level, bromotrifluoroacetone is used to synthesize enantiopure trifluoroisopropylamines.[235] Bromotrifluoroacetone is also the precursor of the trifluoromethyl oxirane,[236] which can be prepared under enantiopure form when reduction of the carbonyl function is performed with a chiral boron reagent (DIP-Cl). Further base ring closing affords the epoxide with an excellent optical purity.[237] This latter method gives far better results than the industrial process (microbiological epoxidation of trifluoropropene), which provides the (*S*) enantiomer (*ee* = 75%). The opening reactions of this oxirane have been performed with various nucleophiles (O, S, N, C). Due to the effect of CF_3, the reaction occurs only on the terminal carbon and affords *β*-substituted trifluoromethyl alcohols.[236, 237] While the subsitution of the hydroxyl in α of CF_3 is difficult to perform, opening of the epoxide by an amine, followed by internal substitution, allows access to aziridines. Like ethyl trifluoropyruvate, trifluoropropene oxide is a precursor of trifluorolactic acids and aldehydes (Figure 2.55).[236] Interestingly, trifluoromethyl oxirane

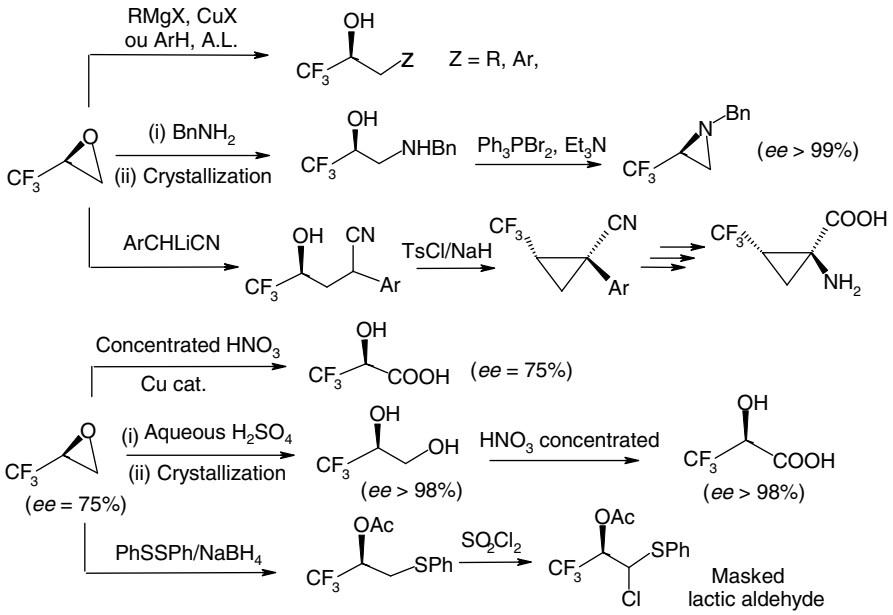

Figure 2.55 Synthetic applications of trifluoromethyl oxirane.[236, 238]

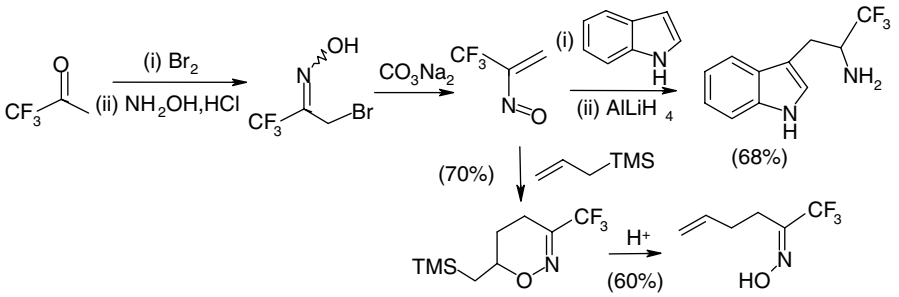

Figure 2.56 Reactions with trifluoro-2-nitrosopropene.[239]

and the corresponding aziridine can be deprotonated selectively and then reacted with electrophiles.[236b, 238]

As another application, treatment of bromotrifluoroacetone oxime with a base yields an interesting heterodiene. This molecule can be involved in hetero-Diels–Alder reactions with electron-rich olefins (Figure 2.56). In the presence of indole, it allows the introduction of the 2-aminotrifluoropropane motif (Figure 2.56).[239]

(d) Halogenofluoroethanes Halogenofluoroethanes can be used, for instance, to introduce a double bond bearing the *gem*-chloro-trifluoromethylethylene moiety, found in some perythrynoids (cf. Chapter 4). However, ecological considerations would make these compounds undesirable for future use.

In spite of this severe limitation, some valuable applications are reported herein. For example, zinc derivative of trifluorotrichloroethane (CF_3CCl_3, Freon 113) is stable and reacts with aldehydes to yield dichlorinated alcohols.[240] Dehydrohalogenation of these products affords olefins that are of high interest in the pyrethrynoid field.[241] Also, CF_3CCl_3 and CF_3CBr_3 add onto olefins and enol ethers through radical reaction.[242] Halothane, $CF_3CHClBr$, and CF_3CClBr_2 also react in the same manner.[243] As another example, CF_3CHCl_2 is a precursor of (*N*,*N*)-acetals of fluoral (Figure 2.57).[244] Other halogenofluoroethanes, such as CF_3CH_2F (HFC-134a), CF_3CH_2Cl, and $CF_3CHBrCl$, offer access to difluoroolefins (especially β,β-difluorostyrenes) via their zinc derivative.[245]

(e) 2-Bromotrifluoropropene This vinyl bromide can be involved in various metal-catalyzed cross-coupling: palladium-catalyzed reactions with boronic acids,[246] terminal alkynes, vinyl or aryl halides,[247] and acyl chlorides.[248] The zinc derivative of bromotrifluoropropene can also be used in transmetallation reactions (Figure 2.58).[249]

Bromotrifluoropropene is also an interesting precursor of the anion of trifluoromethylacetylene (Figure 2.58).[250–252]

(f) trans-Ethyl Trifluorocrotonate This ethylenic ester is a commercial product that can easily be prepared from ethyl trifluoroacetoacetate. It is an interesting substrate for the Michael reaction with ketone enolates, esters acyloxazolidines, and

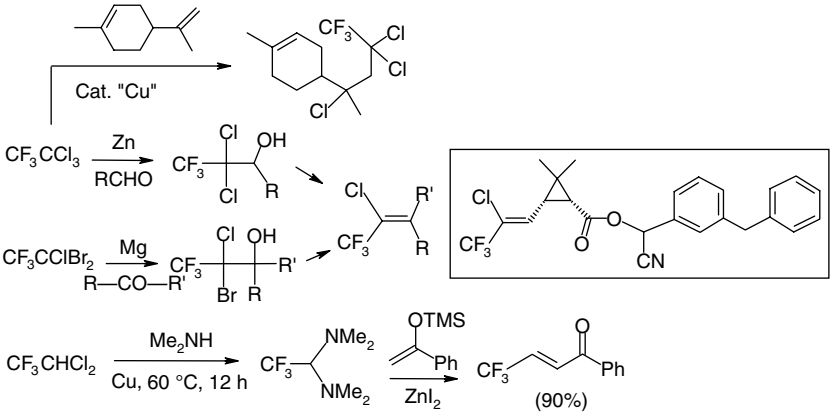

Figure 2.57 Synthesis with halogenofluoroethanes.[240–244]

so on and also for cycloadditions: [4 + 2] reactions[253] and 1,3-dipolar with nitrones and azomethine ylides.[254, 255]

2.4 SYNTHESIS OF PERFLUOROALKYL COMPOUNDS

These compounds are generally prepared by the same methods used to synthesize trifluoromethylated compounds. A significant number of reactions described in the CF_3 series are also applicable in higher series (C_2F_5, C_3F_7, C_4F_9). However, the synthesis of very highly fluorinated or perfluorinated compounds requires a more

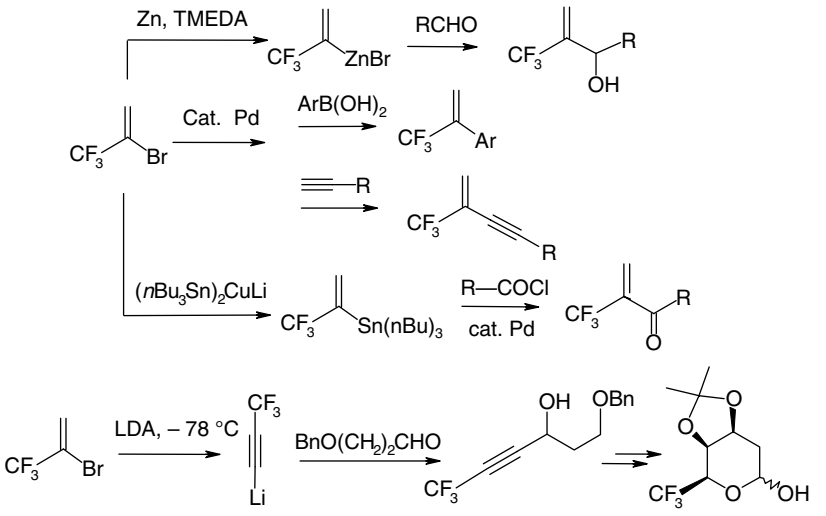

Figure 2.58 Synthetic applications of 2-bromotrifluoropropene.[246–252]

specific chemistry. Among the processes used, radical fluoroalkylation and the organometallic way are very popular. For this last method, Rf-metal compounds (with $Rf \geq C_2F_5$) are much more stable, and thus easier to utilize, than CF_3-metal reagents, in contrast to the Rf-TMS reagents, which are less reactive than CF_3-TMS.[132, 256] However, a limitation stems from the availability of the starting materials: outside perfluoroalkyl iodide, the range of reagents is very narrow. Synthesis of perfluoroalkyl compounds is almost not considered in this book. Indeed, except for perfluoroalkyl carbohydrates (cf. Chapter 5), there are very few applications of these compounds in bioorganic chemistry.

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3

EFFECTS OF FLUORINE SUBSTITUTION ON BIOLOGICAL PROPERTIES

The introduction of fluorine atoms into a molecule has an impact on its physical and chemical properties, with severe consequences on the biological activities. The absorption, distribution, recognition, and interaction processes with the biological target, as well as the metabolism and the elimination of this molecule, are affected. The possibility to modify or modulate the pharmacological profile of a molecule by inserting fluorine atoms clearly explains why the bioorganic and medicinal chemistry of fluorine has become so important, and why many drugs and pesticides are fluorinated compounds.

A lightly fluorinated analogue of a natural substance, or of a biologically active molecule, is generally recognized by the same biological macromolecule target (enzyme or receptor, nucleic acid). However, the specific physicochemical properties of fluorine, especially its strong electronegativity and its own reactivity that is different from that of other halogens, modify interactions between the molecule and the constituents of the biological medium.

First, a drug must reach its biological target. This latter is located in a cell itself located inside a tissue or an organ. Next, the exogenous molecule has to be absorbed, has to overcome multiple barriers depending on the administration protocol (PO, IV, topical, rectal) and has to avoid to detoxication enzymes without being cleared before reaching its target. The presence of fluorine atoms may influence each of these steps: absorption, transport, and metabolism. The second step is the interaction with the target. As will be shown, the presence of fluorine atoms may have a great influence on the molecular recognition and affinity.

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

Fluorinated groups (e.g., F, CF_2) are isosteric or isopolar of various functional groups, and they can mimic them in the association processes with biological macromolecules. They can also interact afterwards with the target, because of the specific reactivity of the fluorinated molecule. This explains the important role played by the incorporation of fluorine atoms in the design of receptor ligands and enzyme inhibitors: substrate analogues, transition state analogues, and mechanism-based inhibitors.

Despite the progress achieved during the last few years, understanding the effects of fluorine is still limited. While some of these effects are relatively straightforward to interpret, predicting effects of the overall behavior of a fluoro compound is often uncertain and this point will often be underlined in this book.[1–4] Nevertheless, in this chapter, we attempt to clarify and rationalize fluorination effects on the biological behavior of a molecule, with their consequences on the affinity, absorption, and metabolism properties. We also explain how the electronic properties of a fluorinated substituent (through changes in polarity, in the reactivity of neighboring functional groups, and in the stability of reaction intermediates) allow the design of enzyme inhibitors. These different aspects are illustrated with recent examples taken from the literature. More detailed examples developed in the following chapters dedicated to fluorinated analogues of natural products, including amino acids and sugars, enzyme inhibitors, and fluorine-containing drugs.

3.1 AFFINITY FOR THE MACROMOLECULE TARGET

The affinity of a substrate with its biological target is first connected to its complementarity with this macromolecule target. The molecular recognition and affinity depend on all the favorable interactions that exist in the supramolecular assembly formed between the substrate and the macromolecule. If the presence of fluorine atoms enhances the strength or the number of these favorable interactions, the affinity of the fluorinated substrate will be higher than that of the parent compound. The main parameters involved are the steric and conformational effects, the dipolar/hydrophobic interactions, and the hydrogen bonds.

3.1.1 Steric Effects

The van der Waals radius of a fluorine atom (1.47 Å) is between that of hydrogen (1.20 Å) and oxygen (1.52 Å). Many experimental data show that when a hydrogen atom is substituted by a fluorine atom, only weak steric disturbances are induced, despite the difference in size. Conversely, the steric volume of CF_2 or CF_3 is much larger than that of methylene or a methyl group, respectively.[5] Generally, fluoroalkyl groups are much bulkier than alkyl groups (cf. Chapter 1). It is generally considered that the size of a CF_3 group is close to that of an isopropyl group.[4b,c] The steric hindrance induced by the presence of fluorine atoms may destabilize the supramolecular structure formed between the macromolecule and the fluoro analogue of the substrate, or even prevent its formation.

Comparison of the olfactory properties of the trifluoro analogue of citronellol is a significant example (Figure 3.1).[6, 7] While the mono-fluorinated analogues exhibit only

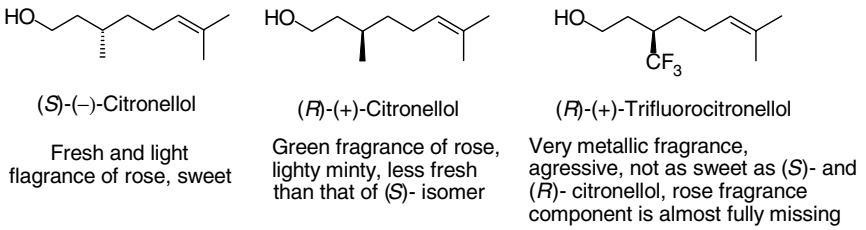


Figure 3.1 Comparison of the olfactory properties of citronellols and of trifluorocitronellol.[7]

minor differences in olfactory properties, this is quite different for trifluorocitronellol.[6] In the absence of other factors, the great differences observed between citronellol and trifluorocitronellol are very likely due to a different recognition by the olfactory receptors, related to the bigger size of the CF_3 group with respect to the CH_3.[7]

The rather considerable size of the CF_3 group allows it to efficiently mimic the side chain of several amino acids involved in ligands or in enzyme inhibitors (e.g., valine, leucine, phenyl alanine, phenyl glycine). Moreover, the hydrophobic character of the CF_3 group (or Rf) (*vide infra*) favors complementarity with the lipophilic pockets of the proteins that are dedicated to receive the side chains of lipophilic amino acids.[16a] Interestingly, the ability of a trifluoromethyl group to mimic a big lipophilic substituent (e.g., isobutyl, benzyl) can be accompanied by a change of the agonist/antagonist character of the ligand, when the binding activity remains unchanged.[8]

3.1.2 Conformational Changes

Due to the different sizes of a hydrogen and fluorine atoms, the substitution of hydrogen atoms by one or several fluorine atoms may modify the conformation of a molecule. Thus, dihedral angles of lipid chains of fluorinated analogues of tristearine are notably modified by the presence of fluorine atoms, with repercussions on physical properties.[9] The influence of geometry and conformational stability on the affinity of a substrate for its target is wellknown. However, few studies have been dedicated to the influence of conformational changes, induced by the presence of fluorine atoms, on biological properties. Nevertheless, a significant example with fluorinated derivatives of taxol is reported in Chapter 4.

The gauche effect — which has the same electronic origin as that of the anomeric effect — is able to stabilize a conformation that should, *a priori*, be disfavored by steric factors. Thus, the gauche effect prevents the *trans* antiperiplanar conformation of two electronegative substituents borne by two vicinal carbon atoms (Figure 3.2).[10, 11]

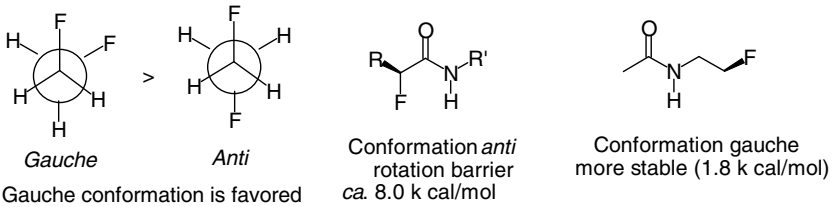


Figure 3.2 Gauche effect of fluorinated compounds.

Ab initio calculations and crystallographic data show that α-fluoroamides and α-fluoroesters prefer adopting *trans* periplanar conformation, with the C—F bond *anti* with respect to the carbonyl (Figure 3.2).[12] In a similar way, the structure of the *N*-fluoroethyl acetamide in the crystalline state shows that the conformation stabilized by a gauche effect is the most stable (Figure 3.2).[12] This gauche effect has been used to favor the active conformation of the ribofuranose cycle of the sangivamycine analogue, a nucleoside that inhibits protein kinase C.[13] This effect could also be used to modify the conformation of peptidic chains.

3.1.3 Dipolar Interactions and Electric Field

The complementarity of the electric fields of the substrate and of its binding site is an important factor for the affinity, especially because biological macromolecules contain many polar units in their binding site. At an electrostatic level, the energy involved in the interaction between dipoles is even more stabilizing when the product of the electric charges is high. The strong electronegativity of the fluorine atom, and thus the strong dipole of the C—F bond, favors dipole–dipole interactions in the binding site. For this reason, a fluorine atom can replace another halogen, and even an oxygen atom (or a hydroxyl group). In the same line, an aromatic ring bearing a fluorine atom may mimic a nitrogen-containing heterocycle (pyridine, 2.2 debyes; fluorobenzene, 1.7 debyes). However, the electrons from the lone pairs are strongly retained around the fluorine atom: they are poorly polarizable and thus not able to induce electric fields. This is also true for the electrons of the C—F bond. As a consequence of this low polarizability, the presence of fluorine atoms reduces the ability of a molecule to respond to electric fields.[1,15,16a]

3.1.4 Hydrogen Bonds and Other Weak Interactions

Hydrogen bonds play a major role in the interactions of a substrate with its biological target. This latter is generally a protein, which bears many possible sites for potential hydrogen bonds.

(a) From the Fluorine Atom Itself Obviously, unlike a hydroxyl group, fluorine cannot be a hydrogen bond donor (cf. Chapter 1) (Figure 3.3). On the other hand, it is a poor acceptor of hydrogen bonds despite its strong electronegativity and its lone pairs of electrons ($\beta_2^H = 0.1$ for fluorobenzene, while it is 0.09 for iodobenzene and 0.14 for benzene). This is mainly due to the low polarizability

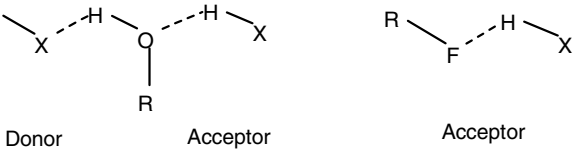


Figure 3.3 Comparison of the potential hydrogen bonds between hydroxyl and fluorine.

of the electron pairs of the fluorine atom, which thus contribute only weakly to the electron transfer $n \rightarrow \sigma^*$.[1, 14–16a]

Theoretical calculations have shown that the strength of a F···H bond could be estimated as between 2.0 and 3.2 kcal/mol, while that of an O···H bond is between 5 and 10 kcal/mol. Examination of the crystalline structures of protein–ligand complexes taken from databases (Cambridge Crystallographic Data Centre) shows only few examples where fluorine is really involved in close contact with hydrogen atoms, revealing the presence of hydrogen bonds.[1, 14–18] Moreover, these close contacts can often be interpreted as the result of a geometry imposed by other types of hydrogen bonds, and do not necessarily stem from a dynamic interaction connected to the fluorine atom.[19–21]

Nevertheless, some crystalline structures can be found where the stability seems to stem from the C—F···H—C hydrogen bond type, and not from C—O···H bonds. For instance, in deoxo-4-fluorophenyl-ribofuranose crystals, the distance between the fluorine atom and the ortho hydrogen atom of a second molecule is 2.3 Å,—shorter than the sum of the van der Waals radii of the two atoms considered. These F···H interactions should be one of the stabilizing forces of oligoribonucleotide duplexes formed from these fluorinated nucleotides (Figure 3.4).[22a] However, this example shows aromatic fluorine and hydrogen atoms, where hydrogen bonds are strengthened through electron delocalisation.[10, 22b] A short C—H···F—C distance has also been observed in the crystalline structure of a cyclopropane derivative (2.194 Å) (Figure 3.4).[23]

Other noncovalent interactions such as the C=O···F—C type, between a fluorine atom and the carbonyl of an amino acid, may take place in the stabilization of enzyme–inhibitor supramolecular structures.[22b, 24] This is why the 4-fluorophenyl group is an important motif for the binding pocket, as shown by the one order-of-magnitude enhancement of the affinity by introducing a fluorine on the thrombin inhibitor (Figure 3.5).[24b]

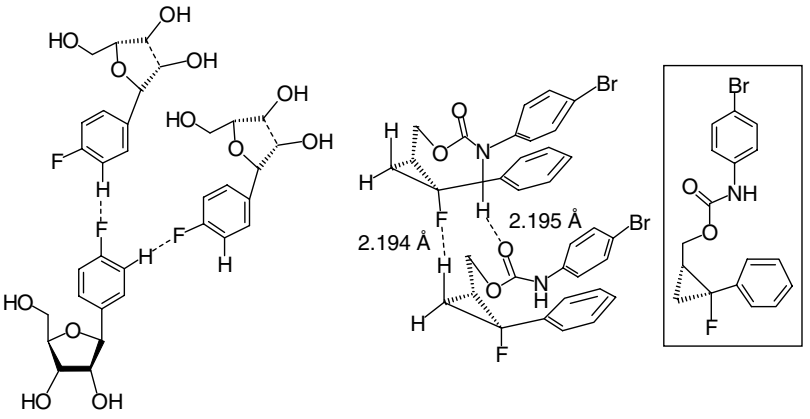
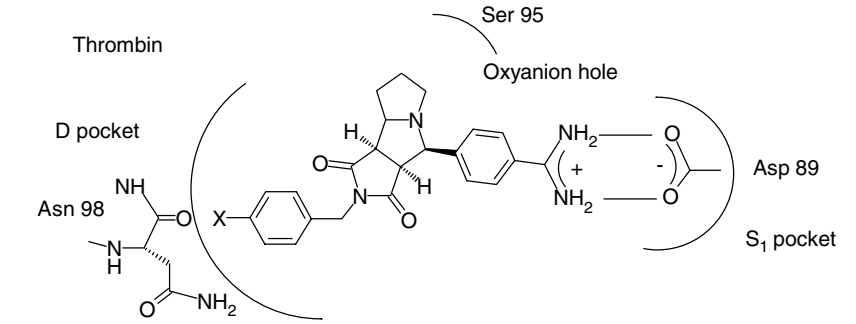
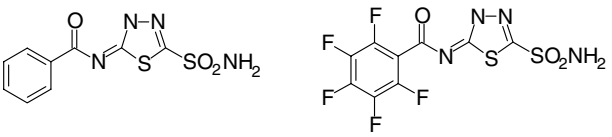


Figure 3.4 Hydrogen bonds C—F···H—C.[22, 23]



	K_i [μM]	Selectivity :($K_{i(trypsin)}/K_{i(thrombin)}$)
X = H	0.31	15
X = F	0.057	67



Affinity to Carbonic Anhydric Hydrolase II K_i = 17 nM K_i = 1.5 nM

Figure 3.5 C—F···O=C interactions of fluorophenyl and pentafluorophenyl group.[22b, 24, 25]

Moreover, fluorine substitution reduces polarizability, increases the hydrophobic surface, and provides an enhanced driving force for desolvation (estimated driving force 0.2–0.5 kcal/mol).[16]

Pentafluorination diminishes the π electron density of phenyl, making it more suitable for participation in stacking or charge transfer with the phenyl groups of other aromatic amino acids of the active site. Moreover, the greater acidity of fluorine in pentafluorophenyl allows weak H bonds that favor affinity. As an example, the inhibitory power of carbonic anhydrase by the pentafluoro analogue of methazolamide is increased tenfold (Figure 3.5).[25]

(b) From Neighbouring Functions Fluorination has an important indirect impact on hydrogen bonds *via* neighboring functions (hydroxyl, amine, carbonyl, hydrogen). The electron-withdrawing effect of the fluorine atom and of fluoroalkyl groups (CF_2, CF_3,. . .) modifies the pK_a of neighboring functions, and hence their character of hydrogen bond donor or acceptor (Table 3.1).

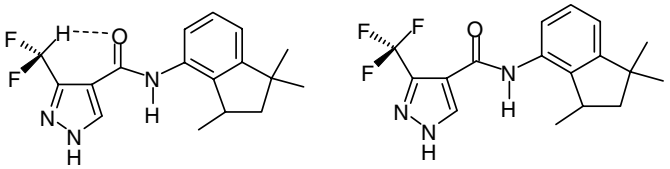
Values of the α_2^H parameter, which represents the ability of a substituent to be a donor of hydrogen bonds, show that the presence of fluorine atoms notably enhances the hydrogen bond donor ability of a hydroxyl group. Conversely, values of β_2^H, which represents the ability to accept hydrogen bonds, are lowered by the presence of fluorine atoms.

Table 3.1 pK_a, α_2^H, and β_2^H values of fluorinated compounds in CCl_4

Compound	pK_a	α_2^H	β_2^H
CH_3CH_2—NH_2	10.7	0	0.70
CF_3CH_2—NH_2	5.9		0.36
$MeCONEt_2$			0.71
CF_3—$CONEt_2$			0.47
CH_3CH_2—OH	15.9	0.33	0.44
FCH_2CH_2—OH		0.40	0.36
CF_3CH_2OH	12.4	0.57	0.18
CF_3—CHOH—CF_3	9.3	0.77	0.03
C_6H_5—OH	10.0	0.60	0.22
C_6F_5—OH	5.5	0.76	0.02
CH_3—CO—CH_3			0.48
CF_3—CO—CF_3			0.20

The acidic character of fluorinated alcohols, and consequently the excellent ability to donate hydrogen bonds, justifies their use as central peptidomimetic units in inhibitors of serine and aspartyl proteases.[26] An enhancement of α_2^H of the OH-11β of 9-fluorocorticoids has also been invoked to explain their pharmacological properties.

The acidity of the hydrogen of the difluoromethyl group (CF_2H) allows stabilizing interactions with electron-withdrawing groups such as a carbonyl. For instance, it has been suggested that the better fungicide activity of a difluoromethyl amidopyrazole, with respect to the trifluoromethyl parent compound, is due to the stabilization of the conformation, which makes possible a hydrogen bond C=O···H—CF_2 (Figure 3.6). This hypothesis is based on semiempirical calculations of energy showing a 5 kcal/mol



Compound	Dose (ppm)	% of fungicide activity [a]
CF_2H	100	92
	20	73
CF_3	100	62
	20	57

[a] Fungicide activity toward *Alternaria solani* (tomato parasite).

Figure 3.6 Hydrogen bonds of CF_2H compounds.[27]

Table 3.2 pK_a and α_2^H values of gaseous general anesthetics

Anesthetic	pK_a	α_2^H
$CF_3CHClBr$	23.8	0.22
$CHCl_3$	24.1	0.20
$CH_3OCF_2CHCl_2$	26.1	0.17
CHF_2OCF_2CHFCl	26.7	0.19

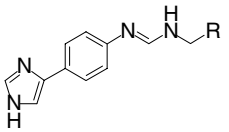
stabilization of this conformation, with a C—H···O=C bond distance of 2.16 Å. The existence of this hydrogen bond has also been confirmed by experimental NMR studies.[27]

A hydrogen bond, involving an acidic hydrogen atom borne by a fluorine-substituted or halogen-substituted carbon, seems to contribute to the activity and selectivity of volatile fluorinated anesthetics (Table 3.2). These molecules, although nonfunctional, can bind stereoselectively with protein targets of the central nervous system.[28, 29] Different biological behaviors have been reported for both enantiomers of isoflurane (cf. Chapter 8).[30]

3.1.5 pK_a of Amines

Lowering of the pK_a induced by the presence of fluorine atoms makes protonation of an amine function more difficult. This decreased basicity may alter the affinity for a receptor, depending on whether the ligand acts as a neutral or protonated form. For example, Figure 3.7 shows the impact of fluorination on the potency of the H_2 antagonist mifentidine (an analogue of cimetidine), which acts on the neutral form.[31] Conversely, when the ligand interacts as a protonated form, affinity is decreased.

In a similar way, this lowering may facilitate an enzymatic reaction when the nonprotonated species is a better substrate for an enzyme than the protonated one. The rate of methylation of β,β-difluoroethylamine by N-methyltransferase of rabbit lung is increased by a factor of 4.[32]



R	pK_a		Protonated at pH 7.4 (mol%)		H_2 Antagonist (pM) (Guinea Pig Atrium)
	Imidazole	Amidine	Monocation	Neutral	
CH_3 (mifentidine)	5.57	8.65	93.2	5.3	177
CH_2F	5.55	8.12	82.6	16	61
CF_2H	4.54	6.60	13.5	86.3	21
CF_3	4.45	6.14	5.1	94.8	7.6

Figure 3.7 Activity of H_2 antagonist of fluoro analogue of mifentidine.[31]

3.1.6 Fluorous Interactions

Perfluoroaromatic rings are of special interest, because of C_6F_6—C_6H_5X stacking interactions[33] and of their binding properties.[34]

Fluorous effects in the active site of DNA polymerase have been observed when highly fluorinated nucleotides are present in the DNA template or are supplied as nucleoside triphosphates. When supplied opposite the nonnatural bases in the template strand, the hydrophobic fluorinated nucleoside triphosphates have been incorporated by up to two orders of magnitude more than the natural nucleoside triphosphates.[35] These results suggest the importance of hydrophobicity, stacking, and steric interaction in the polymerase-mediated replication of DNA base pairs that lack hydrogen bonds. These findings and other research suggest that the enhanced hydrophobicity of highly fluorinated bases could be useful in various applications, for instance, in the design of chips for DNA or RNA in genomic technologies.

This fluorous effect can also be effective for the stabilization of proteins. For example, the selective pairing of peptides that contain perfluorinated chains has been demonstrated, and perfluorinated amino acid side chains have been shown to stabilize the hydrophobic-driven folding of proteins.[36, 37]

3.2 ABSORPTION

Biological membranes are constituted of lipid bilayers, which form major obstacles for the distribution of a drug to its target. In the case of oral administration, the drug must go from the intestine to the blood (intestinal barrier), then from the blood to an organ, where barriers also exist (e.g., the brain–blood barrier). Finally, the molecule must generally go into the cell of the diseased organ or of the pathogenic microorganism by passing through several cell barriers. These steps of transportation and absorption are dependent on various factors, such as lipophilicity, pK_a, solubility, and the molecular weight of the drug. The presence of fluorine atoms may have an influence on these parameters.[38a] However, this effect is rarely clarified.

3.2.1 Lipophilicity

The lipophilicity of a substance is often evaluated by using its $\log P_{\text{octanol}}$ value, which is the logarithm of its octanol/water partition coefficient. This value is quite representative of the ability of a molecule to pass through a lipidic membrane. However, a high $\log P$ means a strong lipophilicity as well as a strong hydrophobicity. In the case of fluorinated molecules, conversely to hydrocarbon compounds, there is no correlation between lipophilicity and hydrophobicity because fluorinated molecules are both hydrophobic and nonlipophilic (cf. Chapter 1). The unique feature of the carbon–fluorine bond stems from the association of the hydrophobic character with a high dipolar hydrophobicity (polar hydrophobicity). This latter property results from a high electronegativity and the small size of the fluorine atom and the very low polarizability of the C—F bond.[16a]

In aromatic series, when hydrogen atoms are replaced by fluorine atoms or by fluoroalkyl groups, an enhancement of $\log P$ occurs.[16a] The CF_3, CF_3O, and CF_3S

Table 3.3 log *P* of fluorinated and nonfluorinated compounds

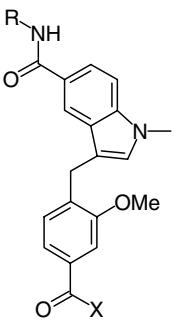
Compound	log *P*
C_6H_6	2.1
C_6H_5—F	2.3
C_6H_5—CH_3	2.1
C_6H_5—CF_3	3.0

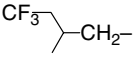
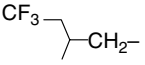
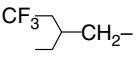
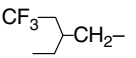
groups are the most hydrophobic substituents known (cf. Chapter 1); they are widely used in crop science[39] (See Table 3.3).

In contrast, there are less experimental data available for aliphatic series. Fluorination lowers lipophilicity and enhances the hydrophobicity. However, other factors, like strong hydrogen bonds or the enhancement of the dipolar moment, may lower the hydrophobicity and render the molecule more soluble or make its penetration easier.

For experimental facilities, calculated values of log *P* (Clog *P*) are often used. These latter values are calculated by means of commercially available software. Nevertheless, relatively important gaps are often observed between calculated and measured values. They depend on parameters and increments used by the software, and caution is required when using Clog *P* values, even inside homogeneous series. For instance, the examination of the Clog *P* values in a series of leukotriene antagonists shows that the substitution by fluorine atoms seems to lower the log *P* value and then the lipophilicity.[38b] Actually, measurement of the log *P* value indicates that calculated values are systematically overestimated (from 0.6 to 1.2 log units) in the case of non-fluorinated compounds, while the correlation fits for fluorinated molecules (Table 3.4). In this

Table 3.4 Measured and calculated log *P* values (Clog *P*) of leukotriene antagonists

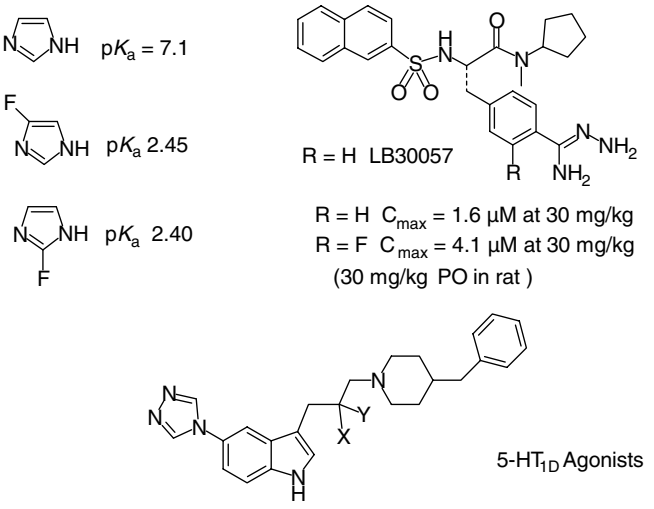


R	X	log *P* (calc)	log *P* (measured)	Difference
	*o*-SO_2Tol	6.97	5.85	1.12
	*o*-SO_2Tol	6.38	6.18	0.20
	OH	5.58	4.86	0.72
	OH	4.99	5.12	−0.13
	*o*-SO_2Tol	7.50	6.29	1.21
	*o*-SO_2Tol	6.91	6.45	0.46
	OH	6.11	5.42	0.69
	OH	5.52	5.53	−0.01

example, fluorinated compounds are slightly more lipophilic than the nonfluorinated analogues.[38b] However, some other examples illustrate an opposite situation: bad correlation for the fluorinated compounds and good correlation for the nonfluorinated ones. These data highlight that log *P* values have to be used with great caution.

3.2.2 pK_a and Solubility

The effect of fluorine atoms on the pK_a of neighboring ionizable functions is to modify the absorption properties of a molecule. The absorption process of an ionizable drug depends on the respective proportions and lipophilicity of charged and neutral species. The introduction of fluorine atoms may allow one to modulate the ionization of the molecule at physiological pH (pH = 7.4). Thus, the lowering of pK_a of amines and nitrogen-containing heterocycles, by means of fluorinated substituents, can be a very important factor to facilitate absorption, especially for oral administration of drugs.[42b] β-Trifluoromethyl amines are not protonated at physiological pH, and ortho fluorination lowers (by one unit) the pK_a of phenols, anilines, and benzoic acids. The effect on heterocyclic bases, such as an imidazole, is even more important (Figure 3.8).[10] This diminution of the basicity is one of the arguments given to explain the better cellular absorption of antibacterial 6-fluoroquinolones with respect to their nonfluorinated analogues (cf. Chapter 8).[41]



X	Y	log *P*	log *D*(pH 7)	pK_a	IC_{50}	EC_{50}
H	H	4.97	2.34	9.7	0.3 nM	0.6 nM *very low bioavailability*
F	H	4.63	3.25	8.7	0.9 nM	0.9 nM *moderate bioavailability*
F	F	4.89	4.80	6.7	78 nM	*affinity decreased due to lowering of pK_a*

Figure 3.8 Influence of fluorine atoms on the pK_a and the absorption.[40, 42]

An interesting example concerns the enhancement of absorption of orally active thrombine inhibitors: taking into account the fact that oral absorption can be increased by lowering the basicity of the functions of the P_1 substituent, a fluorine atom has been introduced in the ortho position of the amidrazone function. This has led to an enhancement in the blood maximal concentration peak after oral administration of the compound in a rat (Figure 3.8).[42a]

Lowering of the pK_a provoked by the presence of fluorine atoms renders the protonation of an amine function more difficult. The diminution of the basicity may lower the affinity for a receptor, as in the case of serotonin 5-HT_{1D} receptor agonists (Figure 3.8).[42c] This change in pK_a has strong repercussions on the solubility of the amine in water, depending on the pH of the medium, as highlighted by log *D* values at pH 7, when the effect on log *P* values is negligible (Figure 3.8).[39, 41, 42c]

Although not directly connected to the influence of the pK_a, a very interesting example shows the complexity of the absorption problems and consequently of the bioavailability. It concerns some peptidyl fluoroketones, inhibitors of human neutrophilic elastase (HNE) (Figure 3.9). While tripeptidyl α-trifluoromethyl ketone is an excellent inhibitor of HNE, it is inactive when given oraly. In contrast, the pentafluoroethyl analogue, although slightly less active *in vitro*, is active under oral administration. NMR studies performed in buffer solution have shown that the hydratation degrees of these CF_3 and C_2F_5 peptidyl ketones are different: the CF_3 ketone only exists in its hydrate form, while hydrate and ketone forms are in equilibrium for the C_2F_5 compound. In the latter case, the hydrate form is probably disfavored by the important steric hindrance of the C_2F_5 group (*vide supra*) as well as by its bigger hydrophobicity. This example shows that the nature of the fluoroalkyl group strongly affects the absorption and/or the elimination of the drug via the effect on the equilibrium between ketone and hydrate forms (Figure 3.9).[43]

It is sometimes observed that compounds bearing few fluorinated atoms are more soluble in water than their nonfluorinated analogues.[7] An example in Figure 3.10 illustrates this effect.[44] Moreover, in this case, it matches with Clog *P* values. However, generalizing this effect would be unwise.

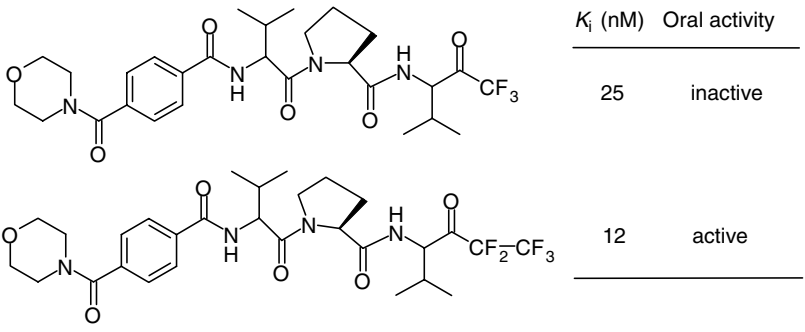


Figure 3.9 Influence of a fluoroalkyl group on the inhibition of HNE and the activity of peptidyl fluoroalkyl ketones.[43]

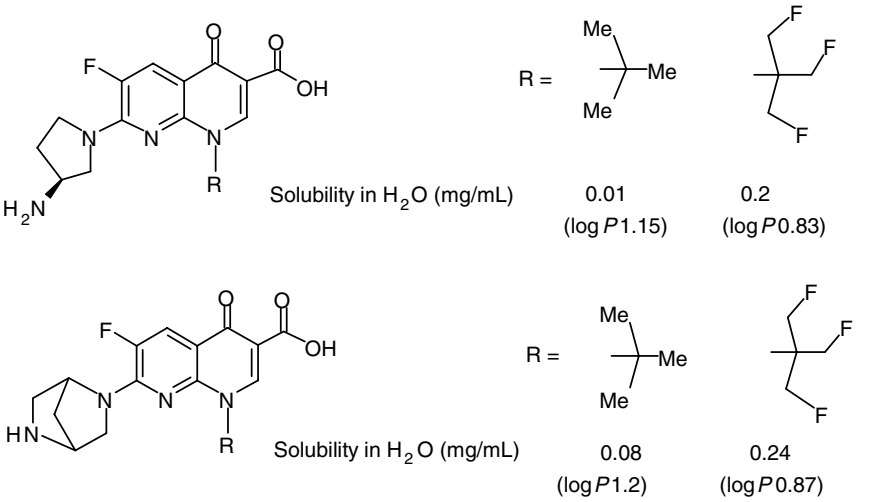


Figure 3.10 Solubility of antibacterial fluoroquinolones (fluoronaphthyridins).[44]

3.3 METABOLISM

The introduction of fluorine atoms in a molecule can be used to modify the processes and the rates of metabolism of the drug, in order to extend the plasma half-life or avoid the formation of toxic metabolites. Due to the properties of the fluorine atom, in particular its electronic effects, it may interact differently during the biotransformation steps, according to the type of processes involved (oxidative, reductive, hydrolytic, etc), which allow the clearance of the exogen molecule (i.e., the elimination of the active substance from the organism).

3.3.1 Oxidative Metabolism

Slowing down of the oxidative metabolism process is one of the most frequent reasons for introducing one or several fluorine atoms in to a lead compound, in order to transform it into a drug candidate. This approach has largely stood the test of time in many therapeutic classes, and it is usually used "to block" oxidation sites of aromatic rings. Indeed, the hydroxylation of an aromatic ring is often the first step in the detoxication of an exogen compound in liver (phase I) (Figure 3.11).

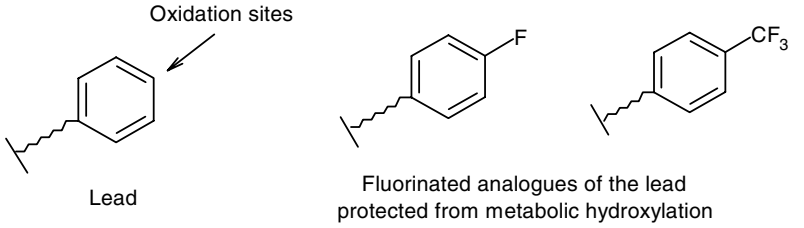


Figure 3.11 Biological oxidation of an aryl ring.

While other electron-withdrawing substituents may play the same role, fluorine (or a CF_3 group) has the advantage of other beneficial effects without engendering too strong disturbances (*vide supra*).

The numerous neuroleptic (butyrophenones and diphenylbutylamines) are classical examples of this strategy (cf. Chapter 8).[40]

The stability toward oxidative processes is generally attributed to the strength of the C—F bond, which is more important than that of the C—H bond (cf. Chapter 1). However, biological oxidations do not involve the homolysis of a C— or C—H bond, and so, they cannot be directly associated with the bond strength. It seems more judicious to invoke the difficult formation of the O—F bond to explain the protection against the hydroxylation of the *ipso* carbon.[1] The fluoroalkyl groups such as CF_2, CF_3, and C_2F_5 exhibit an almost complete inertia toward oxidation. Consequently, they can advantageously replace an alkyl group to avoid the oxidative metabolism. Generally, metabolism of the molecule does not occur in the neighborhood of the fluorine atom, and goes through alternative mechanisms in other positions (Figure 3.12).[45]

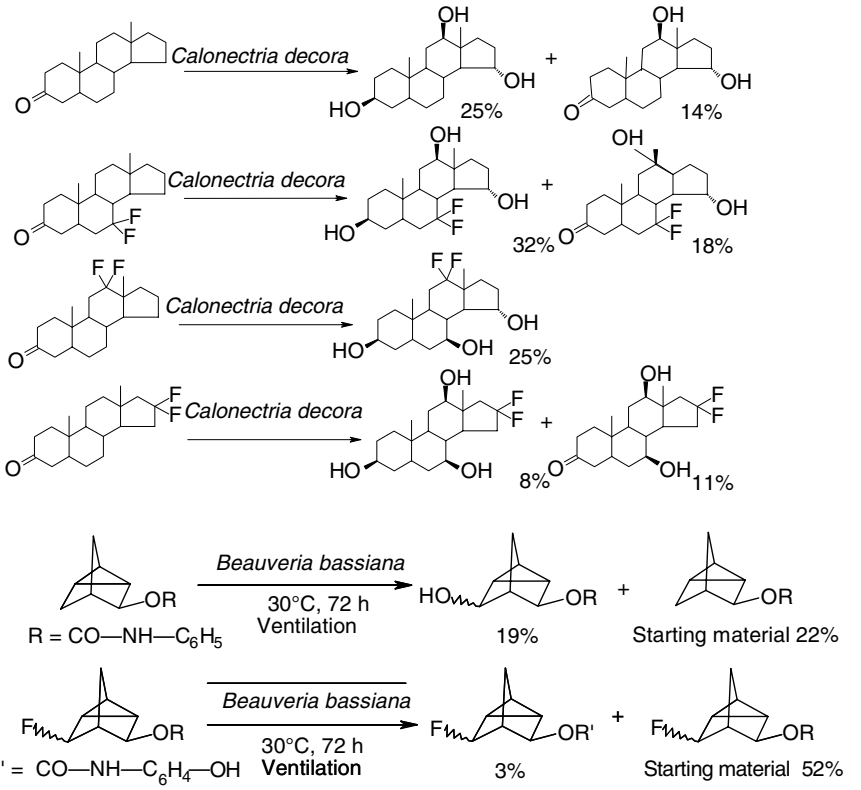


Figure 3.12 Influence of the presence of fluorine atoms on microbiological hydroxylation.[45b,c]

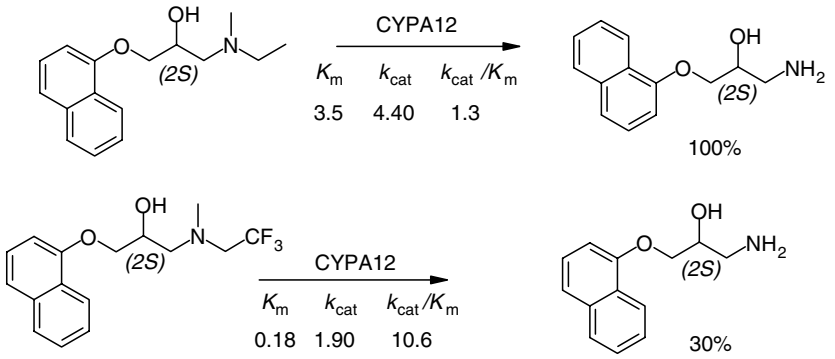
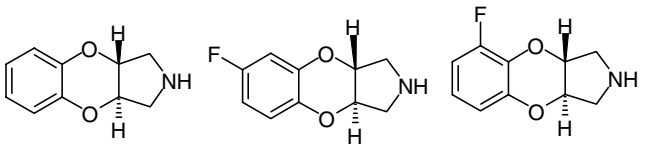


Figure 3.13 Metabolism of fluorinated analogues of propanolol by recombinant CYP1A2.[46]

Kinetic parameters of metabolism of fluorinated analogues of propanolol by cytochrome enzyme (recombinant CYP1A2) have been determined. They clearly indicate that the *N*-dealkylation process was 10-fold lower for the N—CH_2CF_3 compound with respect to propanolol itself. Hydroxylation of the naphthalene ring process is not observed in the case of propanolol but it becomes the major process with the fluoro analogue (Figure 3.13).[46] The same decreased metabolism trend has also been observed with lower pK_a values for CYP2D6 cytochrome enzyme.[46]

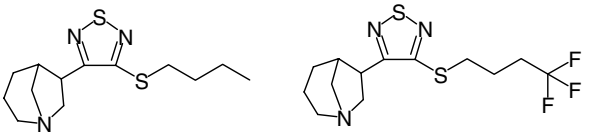
Fluoroalkyl groups also protect the contiguous carbon atoms, and sometimes also the hydrogen atoms borne by a β-carbon (Figure 3.12). Most of the oxidations of the sp^3 C—H bonds involve cytochrome P450 enzymes, which generate radical-cation intermediates. The electron-withdrawing effect of the fluoroalkyl group interferes with the electronic deficiency connected to the development of the C···H···O—Fe^{IV}.[1] Moreover, the difficult accessibility to the active site also participates to the contributes effect of the fluoroalkyl groups.[45a]

Substitution in position 2 by a fluorine atom protects position 3 of fluparoxan (an α_2 antagonist) from metabolic hydroxylation. Moreover, it restores a good affinity with the receptor, which is lost in the case of a fluorination in position 1 (Figure 3.14).[40]



In vitro ($K_i\,\alpha_2$)	8×10^{-9}	1.25×10^{-7}	1.25×10^{-8}
In vivo (ED_{50} mg/kg PO)	1.5	13.8	0.68

Figure 3.14 *In vitro* and *in vivo* activity of the antagonist α_2 fluparoxan.[40]



(5S,6S)exo *(5S,6S)exo* (LY316108)

Analgesic activity (Affinity for M receptor and analgesic activity *in vivo* (mice)		
K_i (nM)	0.45	0.40
ED_{50} (mg/kg	0.19	0.10
Plasma concentration (ng/Kg) (after 1 h, 30 mg/kg orally)	21	805

Figure 3.15 Enhancement of the plasma concentration by the slowing down of the oxidative metabolism of a muscarinic analgesic.[47]

The presence of the CF_3 group in the compound reported in the Figure 3.15 protects the side chain from metabolic oxidation during the first hepatic bypass. In another respect, plasma concentration of this compound is strongly increased. Moreover, the pharmacological activity on the gastrointestinal tract is more selective with the CF_3 compound.[47]

Oxidative metabolism leads to the formation of reactive species (e.g., epoxides, quinone-imines), which can be a source of toxicity. Thus, slowing down or limiting these oxidations is an important second target in medicinal chemistry. The metabolism of halothan (the first modern general anesthetic) provides hepatotoxic metabolites, inducing hepatitis: the oxidation of the non-fluorinated carbon generates trifluoroacetyl chloride. This latter can react with proteins and lead to immunotoxic adducts (cf. Chapter 8, Figure 8.87).[48, 49] Replacement of bromine or chlorine atoms by additional fluorine atoms has led to new families of compounds, preferentially excreted by the pulmonary route. These molecules have a very low metabolism rate (1–3%) (cf. Chapter 8).[49, 50]

Metabolism of the antimalarial amodiaquine provides quinone-imine, which is an electrophilic metabolite responsible for hepatotoxicity and agranulocytosis. These side effects have severely restricted the clinical use of amodiaquine. Replacement of the phenolic hydroxyl by a fluorine prevents the oxidation process. Then *N*-dealkylation becomes the major process. This has led to further refinements, with the preparation of the *N*-*t*butyl analogue, a compound that resists metabolic side chain cleavage and has an excellent *in vitro* and *in vivo* profile (Figure 3.16).[51]

3.3.2 Hydrolytic Metabolism

The presence of fluorine atoms protects a molecule not only from oxidative metabolism but also from proteolysis by disfavoring the formation of cationic intermediates involved in the proteolysis process. This is particularly important for

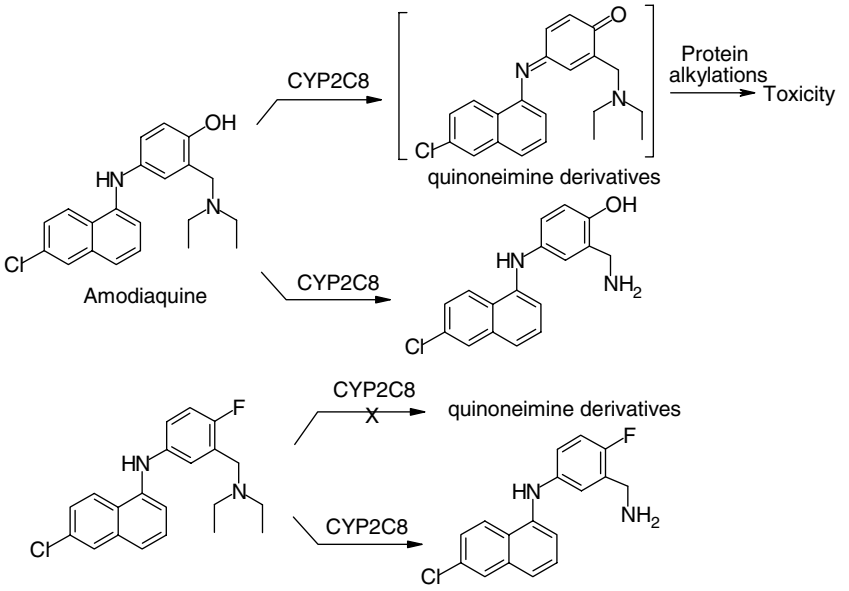
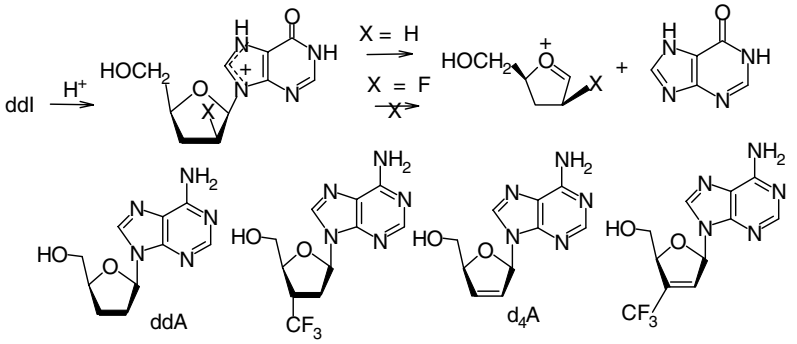


Figure 3.16 Amodiaquine and fluoroamodiaquine metabolism.

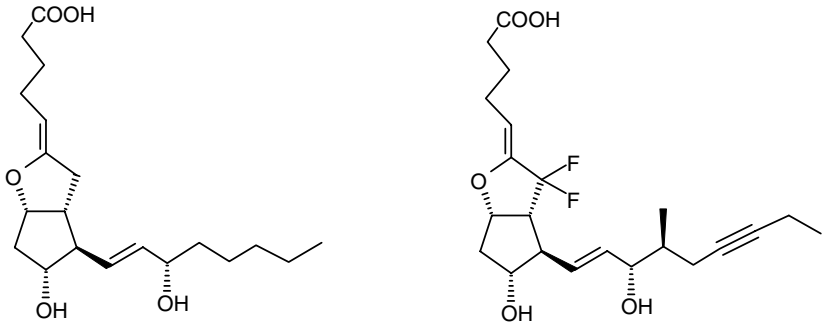
oral administration of drugs that are sensitive to acidic media because of the very acidic pH in the stomach.

As an example, ddI (2,3-dideoxyinosine), an inhibitor of the HIV reverse transcriptase (RT-HIV), has only a 30 s half-life at pH 1 (at 37 °C). Some formulations allow circumventing the problem of the consequent inefficient oral administration. A chemical alternative consists of the introduction of a fluorine atom in 2β to retard the generation of the oxonium ion involved in proteolysis (Figure 3.17).[52] Indeed, the



pH 2 $t_{1/2}$	20 min	89 h	< 1 min	8,9 h
pH 7 $t_{1/2}$	stable	stable	53 h	stable

Figure 3.17 Effect of fluorination on the stability of derivatives of ddI and of ddA toward acids[1, 52a].



Prostacyclin (PGI_2) (AFP-07)

Figure 3.18 Enhancement of the hydrolytic stability of prostaglandin derivatives by fluorination.[53]

fluorinated analogue is stable in acidic medium while retaining the *in vitro* antiviral activity. However, some other problems seem to prevent clinical development.[1, 52a]

A second example concerns the instability of prostacyclin in physiological mediam, which is connected to the presence of the enol ether function ($t_{1/2} = 5$–10 min at pH = 7.4 and at 37°C). Hydrolysis is so fast that its use as a vasodilator and as an inhibitor of platelet adhesion cannot be exploited. The introduction of fluorine atoms in β of the enol double bond led to compounds with good metabolic stability while retaining the strong activity as an inhibitor of platelet adhesion (Figure 3.18) (cf. Chapter 4).[53] Proteolysis is slowed down as the oxonium, resulting from the protonation of the enol ether, is destabilized by the CF_2 group.[54]

A third example of this approach concerns artemisinin derivatives, and it will be developed in Chapter 4.

To summarize, the presence of fluorine atoms in a molecule globally enhances its capacity to resist metabolism and prevents the generation of toxic electrophilic metabolites. The reduced toxicity of the fluorinated drug with respect to its non-fluorinated analogue is a frequent consequence of fluorine introduction, as illustrated by the representative case of the volatile general anesthetics. This effect negates the frequent attitude that associates fluorine and toxicity (e.g., monofluoroacetic acid, a violent poison). In point of fact, fluorine atoms present in a drug are generally excreted at the ultimate phase as alkaline fluorides or trifluoroacetate salts.

3.4 MODIFICATION OF CHEMICAL REACTIVITY: ENZYME INHIBITORS

Modifications of the chemical reactivity generated by the presence of fluorine atoms in a molecule are connected to three main factors: the strength of the C—F bond, the electron-withdrawing character of the fluorinated substituents, and the possible loss of a fluoride ion or of HF in the processes of β-elimination. On these bases and taking into account the ability of fluoro-substituents to sterically or electronically mimic other

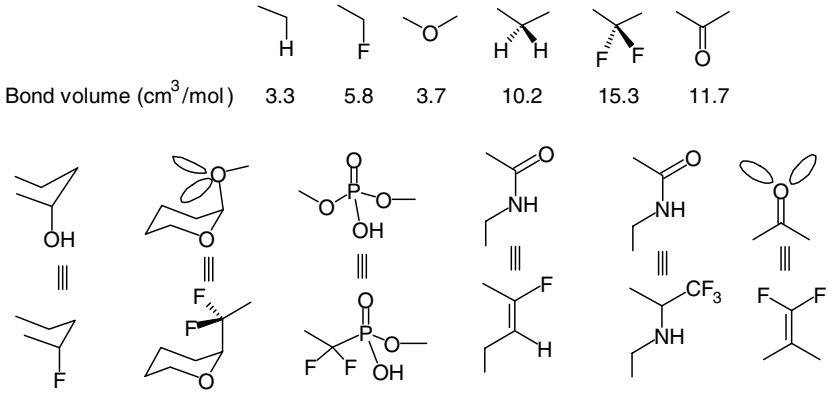


Figure 3.19 Fluorinated mimics and bond volume of some functional groups.

chemical functions, various strategies have been developed for designing enzyme inhibitors. The guiding principles for the design of enzyme inhibitors based on the properties of fluorine are introduced here. The inhibition of enzymes by fluorinated compounds is detailed in Chapter 7.

3.4.1 Analogue of Substrates as Inhibitors

A fluorine atom can sterically mimic a hydrogen atom and stereoelectronically mimic a hydroxyl group. This provides quite similar favorable interactions for the affinity for the active site of the enzyme: dipole–dipole interaction and strengthening of the hydrogen bonds (*vide supra*). Some other fluorinated groups are used or proposed to mimic other functions as illustrated in Figure 3.19.

Thus, the monofluoroalkene moiety is a nonhydrolyzable isostere of the peptidic bond, which could be used as a peptidomimetic unit in the design of protease inhibitors.[55, 56] This type of rigid isosteres of the peptidic bond can facilitate the *cis*/*trans* conformational control of the replaced peptidic fragment. Due to the double bond, the bond length and the angles of the peptidic bond are suitably mimicked, and the fluorine atom complements the analogy for the electronic properties. This approach has been developed in the case of prolylamide fragments, in order to mimic the *trans*-like conformation of the peptidic bond (cf. Chapter 5). A monofluoroalkene moiety can also replace the peptide bond in peptide nucleic acids (PNA). These latter mimic DNA and are able to complementarily bind oligonucleotides with high affinity and sequence specificity.[57]

Trifluoroethylamines can also be considered as metabolically stable amide isosteres. A CF_3 group can replace the C=O of an amide and generate a stable, nonbasic amine that maintains excellent hydrogen bonding. This concept has been developed in the design of protease inhibitors (cathepsin K) (Figure 3.20).[58]

Fluorophosphonates, fluoro-*C*-glycosides, and difluorodisaccharides can be used as nonhydrolyzable and stable mimics of phosphates, sulfates, and disaccharides, where the anomeric oxygen is replaced by a CHF or a CF_2 group.

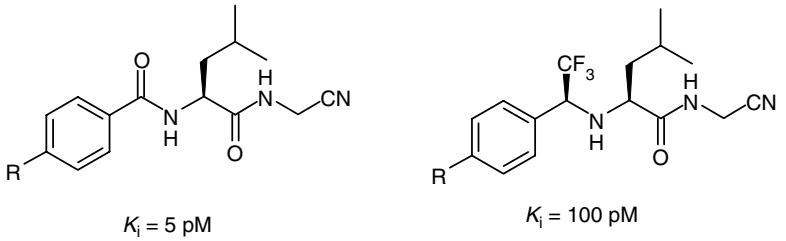


Figure 3.20 Inhibitors of human cathepsin K.[58]

The difluorophosphonates have been the subject of a great number of studies due to their potential application in the inhibition of numerous phosphatases and kinases.[59, 60] Thanks to the fluorine atoms, the electronegativity lost by the replacement of the oxygen atom by a CH_2 is recovered (Figure 3.21).

Considering the acidity, monofluorophosphonate is the closest compound to the parent phosphate (Figure 3.21). The improved inhibition obtained with monofluorophosphonates with regard to difluorophosphonates can thus be explained (Figure 3.21). However, the replacement of the oxygen by the CF_2 group has a steric impact. Indeed, the fluorine atoms are localized in the space usually occupied by the lone pairs of oxygen.

The replacement of the anomeric oxygen of *C*-glycosides and *C*-disaccharides by a CF_2 leads to difluoro-*C*-glycosides, difluoro-*C*-disaccharides, and difluoro-*C*-glycopeptides. These hydrolytically stable compounds have been synthesized, but their use as inhibitors does not seem to have been biologically validated.[61–65]

3.4.2 Inhibition by Stabilization or Destabilization of Intermediates of Biological Processes

3.4.2.1 Stabilization of the Tetrahedral Forms of Fluoroalkyl Ketones

The presence of a fluoroalkyl group in α of a carbonyl strongly enhances the electrophilicity and then the reactivity toward nucleophiles. The anionic tetrahedral intermediates are stabilized by the electron-withdrawing group Rf.[66, 67] This

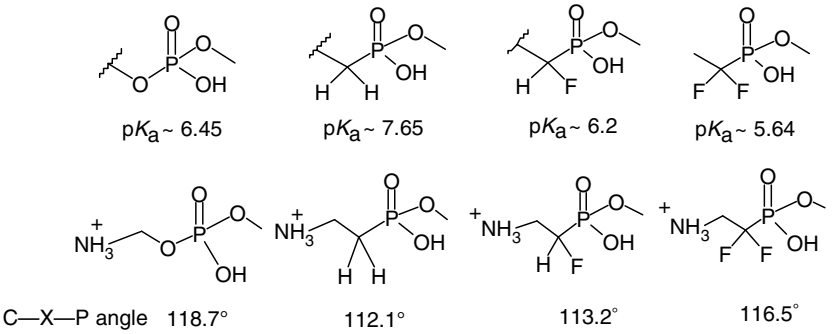


Figure 3.21 Acidity of phosphates/phosphonates, and C—X—P angles.[9]

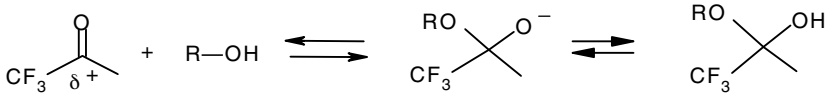


Figure 3.22 Stability of tetrahedral hemiketalic forms of trifluoromethyl ketones.

phenomena is illustrated by the ability of fluoroketones to afford stable hydrates in aqueous medium (Figure 3.22).

These hemiketalic adducts are very good mimics of the tetrahedral transition state involved in the enzymatic hydrolysis of the ester bond or of the peptidic bond.[68, 69] The nucleophilic entity of the active site of the enzyme (e.g., hydroxyl of hydrolytic serine enzymes) can easily add on the activated carbonyl of the fluoroketone, leading to a very stable tetrahedral intermediate. Consequently, the equilibrium cannot be displaced—the enzyme is not regenerated and is thus inhibited (Figure 3.23).[71]

Di- and trifluoromethyl ketones inhibit a great number of esterases and proteases with often very high inhibition constants (cf. Chapter 7). Although the fluorinated ketone is covalently bonded to the nucleophilic residue of the enzyme, the inhibition is reversible, as the inhibitor could be displaced by another nucleophile. The covalent nature of the interactions as well as the tetrahedral structure of the adducts have been demonstrated by kinetic studies, by NMR experiments, and by the X-ray diffraction of the enzyme–substrate complexes.[69–71]

Hydrogen bonds of the amidic NH from the cavity of the active site with the oxyanion enhance the pK_a of this oxyanion from several units.[69] This contributes to the great stability of this adduct (Figure 3.24). These various reasons account for the very strong inhibition constants observed with this type of reversible inhibitor.

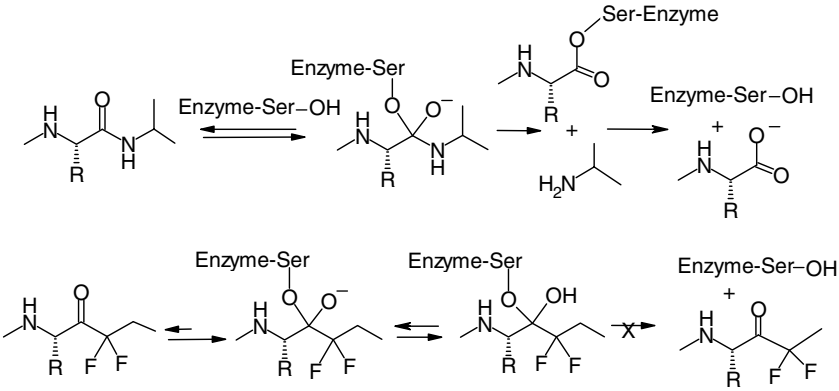


Figure 3.23 Inhibition of a serine protease by an amidodifluoromethylene ketone.

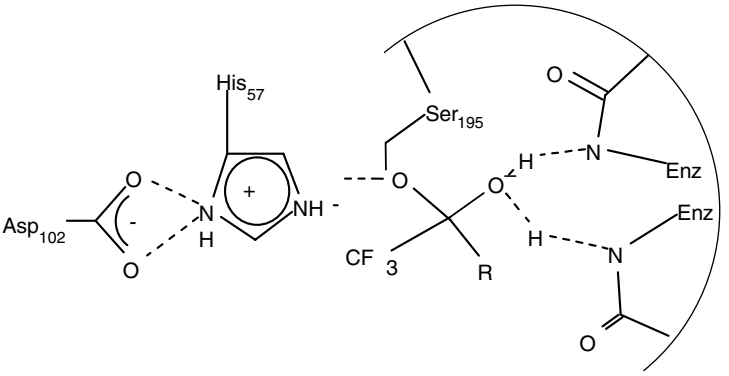


Figure 3.24 Fluorinated ketones, transition state analogue inhibitor of chymotrypsin.[69]

3.4.2.2 Destabilization of Cationic Intermediates The electronegative character of a fluorinated substituent can be used to inhibit the development of the positive charge in a biological process when this latter involves a positively charged transition state. This approach has been used to perform mechanistic studies on the enzymatic farnesyl transfer involved in the synthesis of isoprenoids. The presence of fluorine atoms significantly decreases the transfer rates of the isopentenyl pyrophosphate catalyzed by the diphosphate farnesyltransferase (FPPase) or by the farnesyltransferase protein (FTPase).[72]

Some irreversible inhibitors of the glycosyltransferases have been designed on the basis of the destabilization by a fluorinated substituent of the alkoxycarbenium ion intermediate. The presence of fluorine atoms renders the formation of the incipient alkoxycarbenium ion too difficult from an energetic point of view. As a consequence, the elimination of the leaving group, which normally provides this alkoxycarbenium ion, becomes difficult (cf. Chapter 7).[73]

3.4.3 Irreversible Inhibition with Mechanism-Based Inhibitors (Suicide Substrates)

The elimination reaction ($E1_{CB}$) of a leaving group in β of an anionic center is a well-known reaction in organic chemistry and is commonly called β-elimination. The easy formation of α,β-ethylenic ketones starting from β-chloroketones is a good illustration. Most often, the presence of a negative charge is not necessary—a simple development of a charge being sufficient to initiate the reaction. Although the fluoride anion is not a good leaving group (due to the great strength of the C—F bond), β-fluoroketones, imines, and esters easily afford this β-elimination reaction (Figure 3.25). The β-elimination process remains efficient for CF_2 and CF_3 compounds, while the C—F bond is stronger. Indeed, the fluorine atom renders the α proton more acidic, which makes easier the formation of the anion, which is the driving force of the reaction.

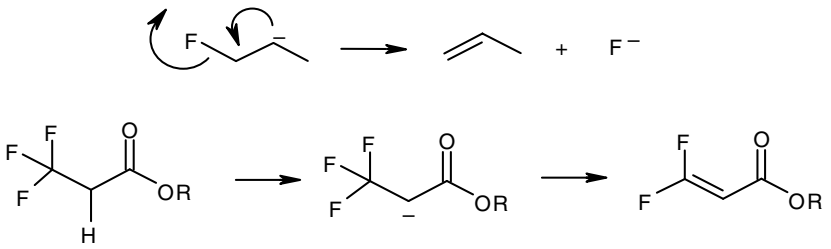


Figure 3.25 Fluorine in β-elimination reactions.

These transformations are efficient under biological conditions only if another activating group is present (e.g., carbonyl, aryl).[74] Such an activating group is important, since the elimination product (resulting from the loss of a fluoride ion) is a Michael acceptor. Moreover, if one or several fluorine atoms are present on the newly formed double bond, this latter will be even more reactive (Figure 3.25). Thus, elimination of a fluoride ion, promoted by an enzyme, from a β-fluoro amino acid leads to a very reactive Michael acceptor. The latter can undergo an irreversible addition of a nucleophile residue of the enzyme active site, and then inhibit it (Figure 3.26).[75,76] The mechanisms of inhibition, often more complex, are detailed in Chapter 7.

Due to the great strength of the C—F bond with respect to that of other halogens, fluorine is a poorer leaving group than chlorine or bromine. This gives fluorinated compounds great advantage and justifies this choice in designing such mechanism-based inhibitors: alkyl fluorides are bad alkylating reagents and are stable in aqueous or nucleophilic medium. Thus, a fluorinated derivative is stable under physiological conditions and does not interact with the numerous nucleophiles of the medium. Consequently, a fluoro compound does not alkykate nucleophilic sites of the enzyme in a nonspecific manner, conversely to chlorinated analogues, which are generally nonspecific affinity labelers.

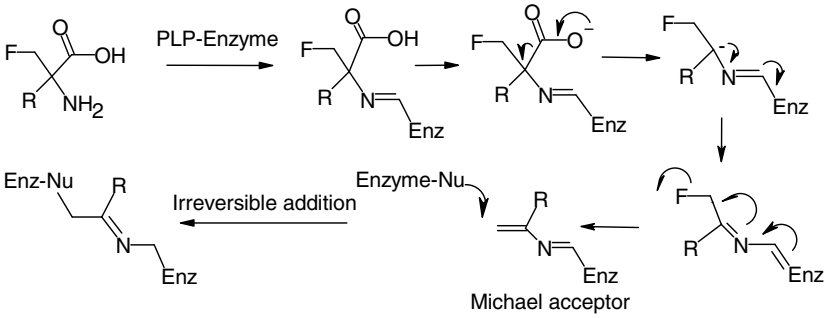


Figure 3.26 Principle of the inhibition of an enzyme based on the elimination of a fluoride ion and formation of a Michael acceptor.

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4

FLUORINATED ANALOGUES OF NATURAL PRODUCTS

This chapter deals with fluorinated analogues and derivatives of natural products. We report on examples of fluoro analogues taken from the main families of natural compounds. This chapter is not exhaustive, and mainly focuses on biological applications and medicinal chemistry. Fluoropeptides, fluoroamino acids, and fluorocarbohydrates are the topics of Chapters 5 and 6, respectively.

In contrast with numerous fluorinated drugs, where fluorine atoms are borne by aromatic rings (cf. Chapter 8), in analogues of natural products the fluorine atoms are generally present on an aliphatic moiety. The syntheses of such compounds are much more difficult, and specific new methods are required. These synthetic improvements have led to remarkable results in medicinal applications.

4.1 FLUORINATED PRODUCTS IN NATURE

Fluorine is found in nature as mineral fluorides, and it is the most abundant halogen in the Earth's crust. Thus, it is rather surprising that less than 15 fluorinated organic molecules have been isolated from plants. They are all secondary metabolites of fluoroacetate. Among these compounds, all monofluorinated, half are composed of ω-fluorinated homologues of fatty acids.[1]

Conversely to most of the plants, some from Africa, South America, and Australia are able to biosynthesize fluoroacetate from mineral fluorides and stock it at relatively high concentrations. Indeed, fluoroacetate is a powerful inhibitor of the Krebs cycle

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

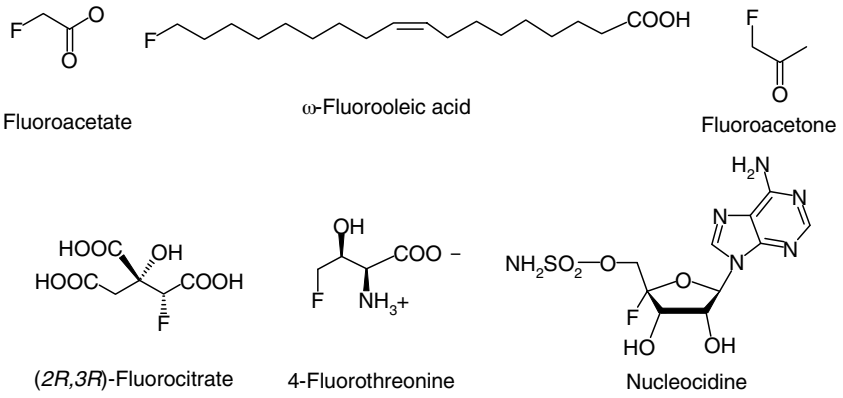


Figure 4.1 Fluorinated natural products.

and is very toxic for numerous living systems. However, some animal species, living in regions where those plants are endemic, have developed a resistance to fluoroacetate. These animals can be 50–150 times more tolerant to this compound than animals who live in nonendemic areas.[2] The biochemical bases of this resistance still remain elusive. Fluoroacetate can also be biosynthesized by bacterial cultures (*Streptomyces cattleya*) in the presence of fluoride ions.[3]

Among fluorinated secondary metabolites, the following examples can be examined (Figure 4.1). *Fluorocitrate* comes from the *in vivo* conversion of fluoroacetate and is responsible for the toxicity of this latter compound (cf. Chapter 7). Condensation of fluoroacetyl-CoA with oxaloacetate is catalyzed by citrate synthetase (this enzyme usually incorporates Ac-CoA in the cycle of the citric acid).[1,4]

ω-Fluorinated fatty acids with long chains (e.g., ω-fluorooleic acid) can be found in some African plants. They stem from a common precursor—fluoroacetyl-CoA. This would be utilized, instead of acetyl-CoA, in the first step of the synthesis of fatty acids, which involves the transport protein acyl malonyl (malonyl-ACP).

Nucleocidine is a nucleoside that has been isolated from cultures of *Streptomyces clavus*, a bacteria found in the ground of India. This nucleoside has an intriguing structure: it bears a fluorine atom in the 4′ position of the ribose cycle.[5] This fact seems to exclude the possibility of its biosynthesis from a fluoroacyl fragment.

4-Fluorothreonine has been isolated in cultures of the bacteria *Streptomyces cattleya* in the presence of fluoride ions.[3] Studies done with labeled precursors (glycerol, serine, glycine) show that there are high rates of incorporation in the 4-F-threonine as well as in the fluoroacetate. The postulated biosynthetic pathway (Figure 4.2) suggests the key role of a common precursor, fluoroacetaldehyde, which would be formed by the glycolytic pathway. Accumulation of fluoroacetaldehyde in cell extracts of bacteria, and its conversion into 4-F-threonine and fluoroacetate, have been demonstrated (Figure 4.2).[6,7]

For the first time, an enzyme able to "create" a carbon–fluorine bond has been isolated from *Streptomyces cattleya*. This enzyme has been characterized and then named *fluorinase*. In the presence of fluoride ions, this enzyme catalyzes the conversion of *S*-adenosyl methionine into 5′-fluoro-5′desoxyadenosine (Figure 4.3).[8]

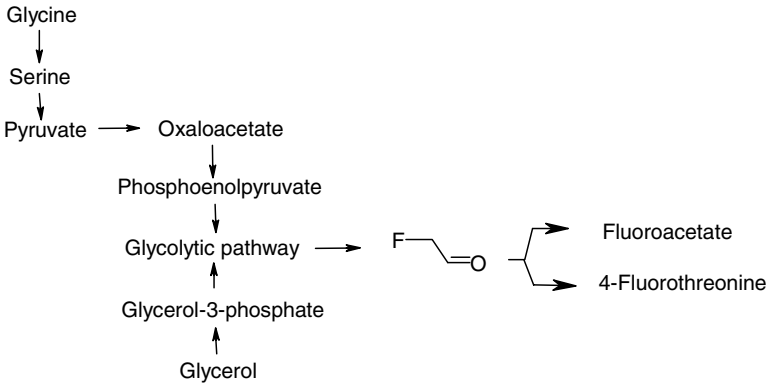


Figure 4.2 Biosynthetic scheme of 4-fluorothreonine in *S. cattleya*.[6,7]

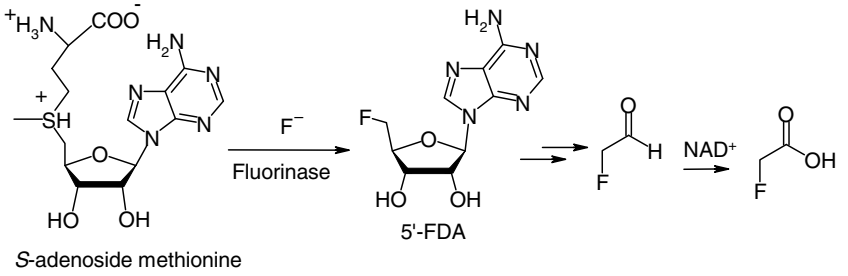


Figure 4.3 Creation of a carbon–fluorine bond by the fluorinase in *S. cattleya* and biosynthesis of fluoroacetate.[8]

4.2 STEROIDS

4.2.1 Corticosteroids

The first example of the influence of a fluorine atom on the biological properties of a molecule was for a family of corticosteroids.[9] This discovery has very important applications on a medicinal level: the use of fluorinated compounds to modify biological properties for therapeutic applications.

As soon as corticosteroids, such as cortisone, were used in the treatment of rheumatoid arthritis (glucocorticoid activity), important undesirable side effects appeared (sodium retention). In order to reduce sodium retention, while increasing the anti-inflammatory activity, Fried performed various chemical modifications. He observed that introducing a fluorine atom in the 9α position of hydrocortisone acetate highly enhanced (11 times) the glucocorticoid activity, while the undesired sodium retention was lowered.[9]

The original synthesis of 9-fluorocorticoid by Fried involves opening 9,11-epoxy hydrocortisone acetate by HF. This oxirane is prepared in two steps from hydrocortisone acetate. This synthesis remains the only method to prepare 9-fluorocorticoids (Figure 4.4).[9] To date, there is no alternative known method for this purpose.[10]

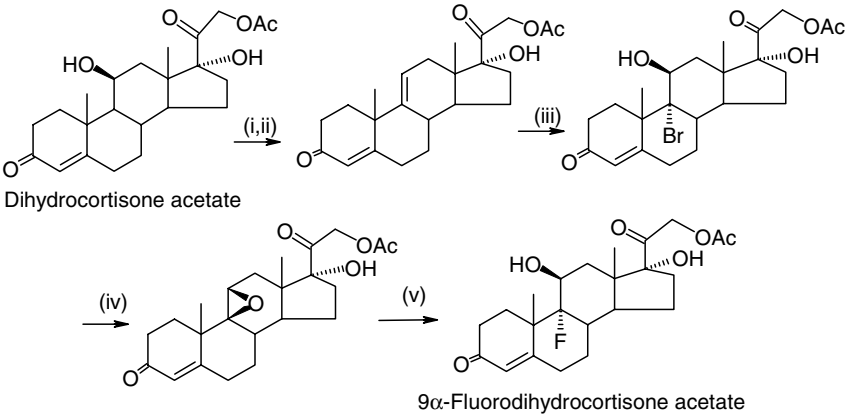


Figure 4.4 Synthesis of 9α-fluorohydrocortisone.[9]

Other modifications of the molecule (e.g., introduction of a double bond or a substituent in position 1) have given rise to very powerful anti-inflammatory and anti-arthritic drugs that are used in dermatology (*triamcinolone, betamethasone, dexamethasone;* cf. Chapter 8) (Figure 4.5). These compounds have greatly reduced residual mineralocorticoid activity.

More recently, compounds bearing a second fluorine atom in position 6 (generally with α configuration) have been developed (*fluprednisolone*). The introduction of this second fluorine atom can be performed by different pathways: opening of 5,6-oxirane by HF,[11] or electrophilic fluorination of dienol derivatives (cf. Figure 8.33, Chapter 8).[12–14] The fluorine in position 9 is introduced by means of the Fried method. These derivatives, substituted in both positions 6 and 9, are used in the treatment of asthma and allergy (*fluocinolone, diflorasone, fluticasone;* cf. Chapter 8).

Why fluorine atoms at C-6 and C-9 positions have effects on the pharmacological profile (in particular, on the enhancement of the glucocorticoid activity and its dissociation of the mineralocorticoid activity) is not always very clear. Three hypothesis coexist:

1. Enhancement of the acidity of the 11β-hydroxyl can increase the affinity of the molecule for the receptor, which is responsible for the glucocorticoid activity.

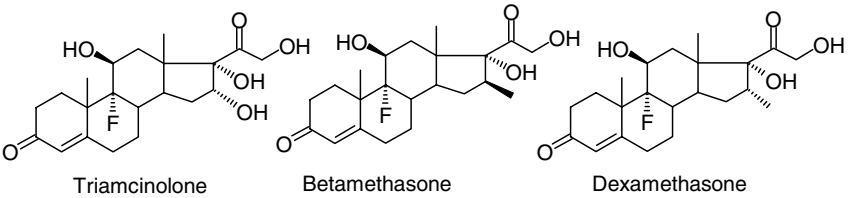


Figure 4.5 Examples of anti-inflammatory fluorocorticoids.

2. The slight conformational modification of the A ring (revealed by X-ray diffraction), which probably comes from an interaction between the fluorine on C-9 and the axial OH on C-1, could contribute to the differences of affinity.[15] However, X-ray structure of the cocrystallized form of fluorocortisol with the glucocorticoid receptor does not explain the impact of fluorine on the increase in affinity (cortisol $K_i = 0.67\ \mu M$ versus 9α-fluorocortisol $K_i = 0.027\ \mu M$).[16]
3. The fluorine at C-9 can reduce the oxidative metabolism of hydroxyl-11. Oxidation of OH-11 into ketone is fast for the cortisol and is accompanied by the loss of biological activity.[17,18] However, this hypothesis would imply metabolites to contribute to the mineralocorticoid activity.

4.2.2 Steroids with Trifluoromethyl Groups in Angular Position

4.2.2.1 19,19,19-Trifluorosteroids Synthesis of 4-, 6-, or 7-trifluoromethyl steroids (some of which are inhibitors of 5α-reductase; cf. Chapter 8) can be performed by means of the classical methods of trifluoromethylation or fluorination. Conversely, synthesis of steroids that bear a trifluoromethyl group in the 18 or 19 angular position has been an important and challenging goal; original approaches have been required for their synthesis. The difficulties of the synthesis are specifically due to the CF_3 group, since the CF_2H compounds can be prepared by fluorination of the aldehyde (e.g., the 19-carboxaldehyde) with the DAST reagent.[19] 19,19-Difluoroandrosten-3,7-dione is an irreversible inhibitor of the estrone synthase (aromatase). Although the mechanism has not been demonstrated, inactivation is probably due to the transformation of the substrate into acyl fluoride, which further acylates a residue of the active site of the enzyme.[19]

The key intermediate in the synthesis of the derivatives of 19-F_3-androstane is the trifluoro analogue of the Wieland–Miescher ketone. Its preparation involves a Diels–Alder reaction between a trifluoromethyl ketone and a siloxy diene. Another original step is the regioselective reduction of a diketone: only the ketone function in β of CF_3 (probably activated by this substituent) is reduced (Figure 4.6).[20b,21] Then, a succession of classical reactions leads to derivatives of androstane from the trifluoro analogue of the Wieland–Miescher ketone (Figure 4.7).[22]

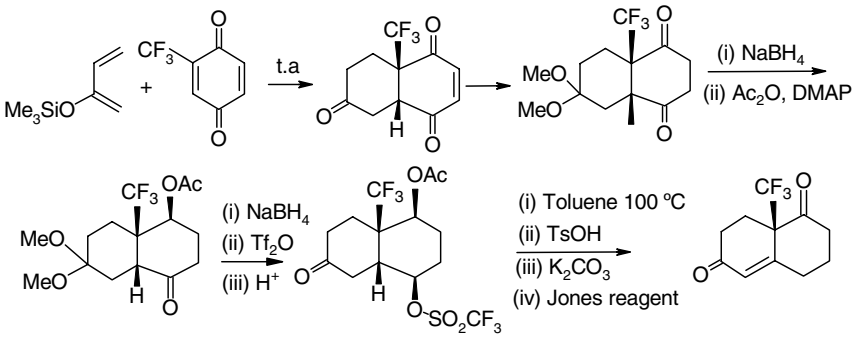


Figure 4.6 Synthesis of the trifluoro analogue of the Wieland–Miescher ketone.[19,21]

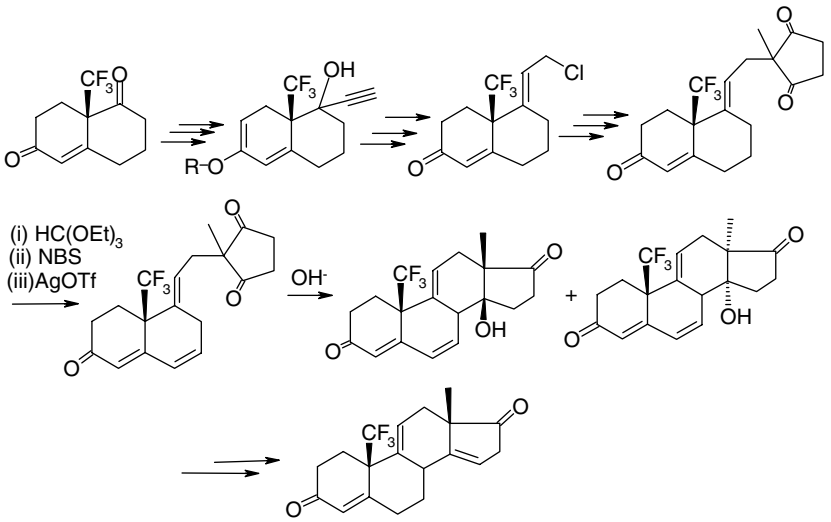


Figure 4.7 Synthesis of derivatives of 19-trifluoroandrostane.[22]

Some syntheses of decanones and octalones, angularly substituted by a CF_3 group, have also been performed by means of radical cyclization or by intramolecular Michael addition. These precursors have allowed access to other steroid derivatives with a trifluoromethyl group in the 19 position (Figure 4.8).[23]

4.2.2.2 18,18,18-Trifluorosteroids The first synthesis of 18,18,18-trifluoroestradiol was performed in 1983. The key step is the alkylation of trifluoromethylcyclopentanedione with an allyl alcohol. Due to the very easy dehydrofluorination of the fluorinated diketone, even in an extremely low basic medium, reaction is tricky. The final

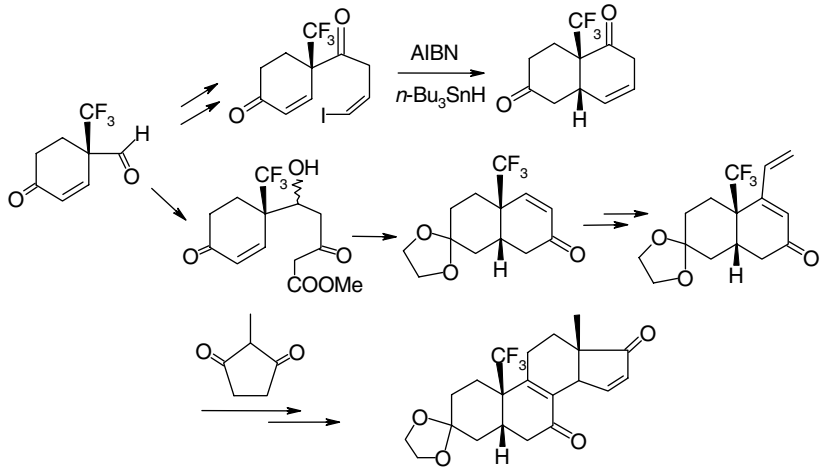


Figure 4.8 Synthesis of 19,19,19-trifluoroandrastane derivatives.[23]

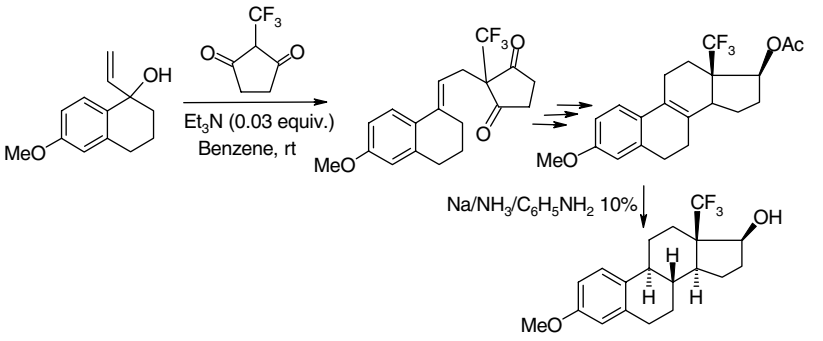


Figure 4.9 Synthesis of 18,18,18-trifluoroestradiol.[24, 25]

reduction of the double bond Δ8–9, by sodium in liquid ammonia, affords 3-methoxy-18,18,18-trifluoroestradiol with the natural relative configurations (Figure 4.9).[24, 25]

Another stereoselective synthesis of 18,18,18-trifluoroestradiol was described more recently. An intramolecular [4 + 2] cycloaddition allows the formation of cycles B, C, and D. Cycle A is further built after reduction of the aromatic B ring (Figure 4.10).[26, 27] The androgenic or inhibitor properties of aromatases of 18,18,18-trifluorosteroids are rather low.

4.2.3 Fluorinated Analogues of Metabolites of Vitamin D_3

Vitamin D_3 is transported toward the liver where it undergoes hydroxylation at C-25 to 1α,25-dihydroxyvitamin D_3 (calcitriol; Figure 4.11). In the kidney, it undergoes

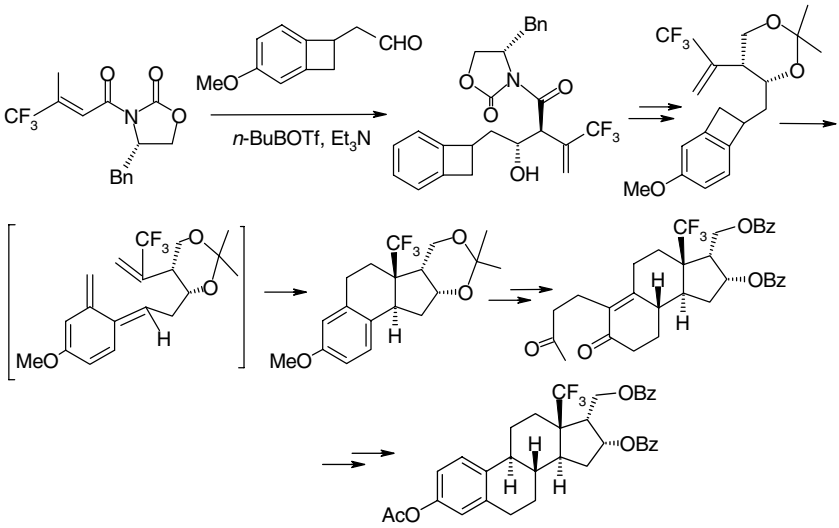


Figure 4.10 Stereoselective synthesis of 18,18,18-trifluorosteroids.[26, 27]

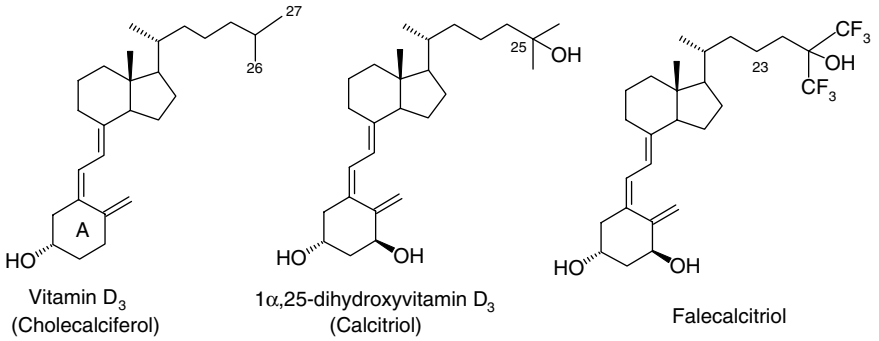


Figure 4.11 Vitamine D_3 and falecalcitriol.

further hydroxylations at different sites, depending on the Ca^{2+} serum concentration. The most biologically active metabolite of vitamin D_3 is calcitriol, which plays important roles in the regulation of calcium and phosphor metabolism. It is used for treating bone diseases but is also involved in cell proliferation and inducement of cellular differentiation.[28, 29] Since fluorination of vitamin D_3 may have an impact on its metabolism pathway—and so may dissociate these two activities—many fluorinated analogues have been synthesized with the aim of limiting the calcemic activity (hypercalcemia) and increasing the anticancer activity.

Fluorination of the vitamin D_3 side chain was anticipated to have an impact on its metabolism pathway. 26,27-Hexafluorocalcitriol, *falecalcitriol*, was found to be several times more potent than calcitriol in the regulation of Ca^{2+} metabolism and of the immune system.[30] The reason for this higher biological activity has been attributed to several mechanisms: a higher activity of its 23(*S*)-hydroxylated metabolite [26,27-hexafluoro-1,23(*S*),25$(OH)_3D_3$], a lower affinity of falecalcitriol for the vitamin D binding protein (VDR),[30, 31, 34c] and a higher affinity of falecalcitriol–receptor complexes for DNA. Falecalcitriol (Hornel®) is prescribed as a hypercalcemiant to treat some bone diseases (hypocalcemia, rickets, and osteomalacia) and hyperparathyroidism (Figures 4.11) (cf. Chapter 8). The synthesis of falecalcitriol is described in Figure 8.79 (Chapter 8).

From this success, further efforts have been focused on dissociating the calcemic activity from the antiproliferative activity, with the aim of limiting the former (hypercalcemia) and increasing the anticancer activity. Accordingly, many fluorinated analogues have been synthesized. In particular, starting with falecalcitriol, fluorine atoms have been introduced onto positions 22, 23, and 24 of the side chain and onto positions 1 and 2 of the A ring.[32,33,39] Numerous other structural modifications have also been achieved on the fluorinated side chain (e.g., introduction of unsaturation, sulfone, oxetan), as exemplified in Figure 4.12.[33, 34] Some of the resulting compounds, in particular 22(*S*)-hydroxy-falecalcitriol, exhibit an excellent selectivity, with a very high activity on human carcinoma lines (HT-29) and no calcemic effect, as assessed *in vivo* in rats.[34c] Fluorinated analogues of vitamin D_3 metabolites have also been used as probes in ^{19}F NMR to perform studies on the conformation of the complex between vitamin D_3 and its receptor.[34b]

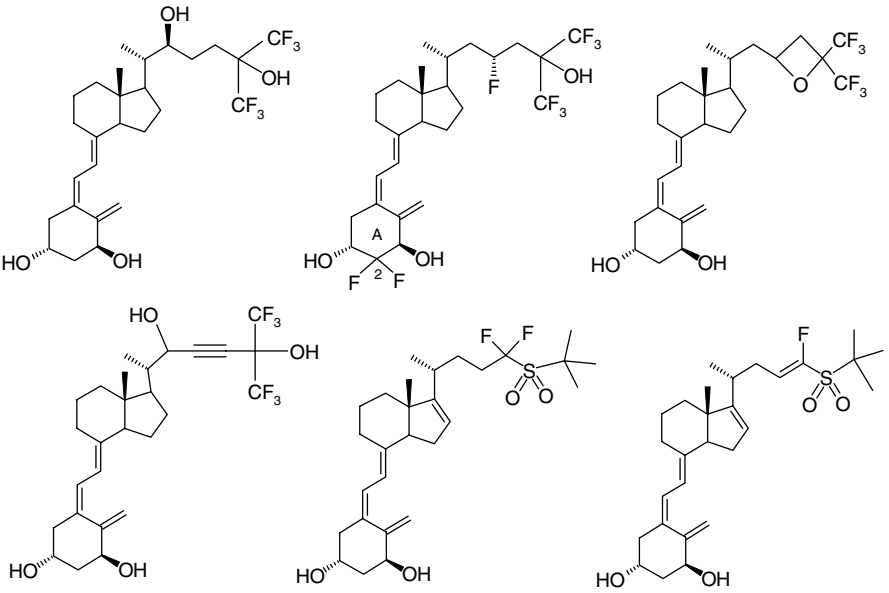


Figure 4.12 Fluorinated analogues of dihydroxycalciferol.

Introduction of a fluorine atom on the A ring of vitamin D_3 metabolite has also been realized. Surprisingly, the introduction of fluorine at C-2 increases the calcemic activity (higher than calcitriol), while the affinity for the calcitriol receptor is strongly decreased (10 % of calcitriol affinity).[35, 36] The 1-hydroxyl has also been replaced by a fluorine atom (Figure 4.13). Fluorination could also be stereoselectively performed through an electrophilic fluorodesilylation (Figure 65).[37, 38] This compound *BXL-628* (now *Ro-26-9228*) inhibits the growth factors involved in benign prostatic hyperplasia (BPH), without direct androgenic effects. It is currently in Phase II of clinical development.[39, 40]

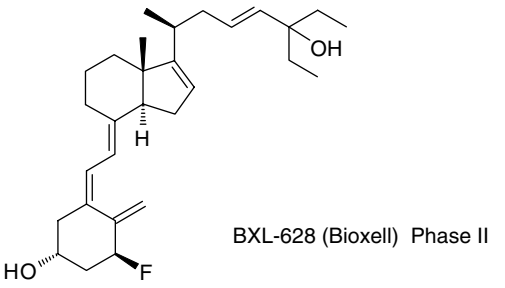


Figure 4.13 Fluorinated vitamin D_3 metabolite used in BPH treatment.

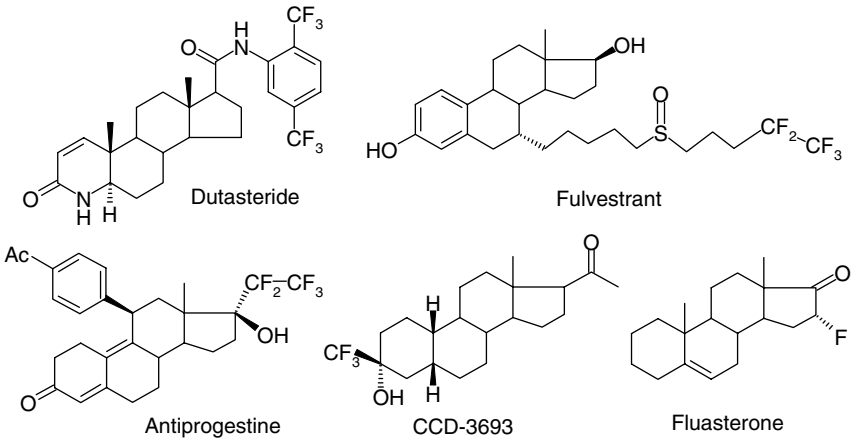


Figure 4.14 Recent fluorinated steroids with therapeutic interest.

4.2.4 Other Fluorinated Steroids

Some compounds fluoroalkylated in position 7α of estradiol have also been prepared by electrophilic fluoroalkylation of corresponding enol derivatives (cf. Figure 2.37 in Chapter 2, and Figure 8.74 in Chapter 8).[20a]

After a decrease in the importance of steroids in the field of drug research during the last 20 years, a renewal is now being observed. Recently, some fluorinated and fluoroalkylated steroids have been launched or are in advanced phases of clinical development, such as the *dutasteride* (5α-reductase inhibitor), *CCD-3693* (GABA agonist), *fulvestrant* and *antiprogestine* (antihormone), and *fluasterone* (diabetes) (Figure 4.14). Details on the synthesis on these compounds can be found in Chapter 8.

4.3 TERPENES

4.3.1 Artemisinin

Artemisinin is a natural endoperoxide-containing sesquiterpene, isolated from a plant used in traditional Chinese medicine. Acetalic artemisinin derivatives (artemether, artesunate) are very active against chemoresistant forms of *Plasmodium falciparum*, and are clinically used for treatment (Figure 4.14).[41] However, they suffer from an unfavorable pharmacological profile. They are quickly metabolized by fast oxidative metabolism, hydrolytic cleavage, and glucuronidation.

Dihydroartemisinin (DHA) is the active metabolite of acetalic derivatives of artemisinin (artemether, artesunate). Oxidation by cytochrome P450 enzymes or/and hydrolysis provides DHA, which is itself poorly stable *in vivo*. Indeed, the corresponding oxonium ion, a precursor of inactive metabolites by ring opening or by glucuronidation, can easily be formed (Figure 4.15).

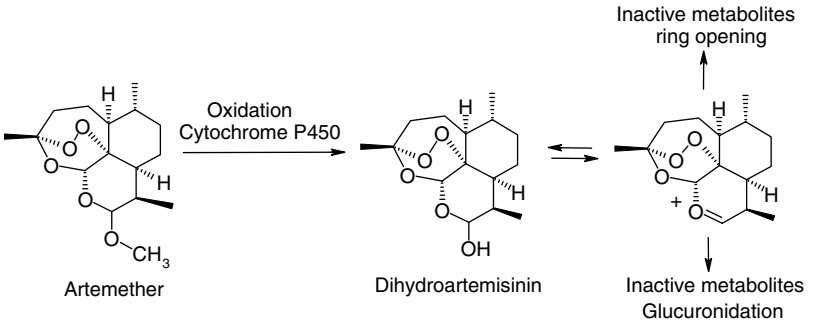
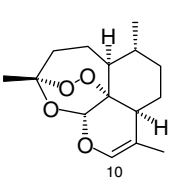


Figure 4.15 Metabolism of artemisinin derivatives.

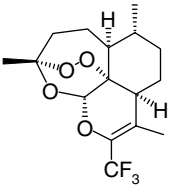
Extensive research has been carried out in efforts to increase the duration of action of artemisinin derivatives.[42] An approach to design more metabolically stable artemisinins has been developed by introducing a trifluoromethyl group at C-10.[43–45] Due to its electron-withdrawing character, this substituent was expected to efficiently protect artemisinins from oxidative and hydrolytic cleavage, and from glucuronidation when a hydroxyl is present at C-10. The hypothesis has clearly been validated by a comparison of the *in vitro* and *in vivo* antimalarial activities of fluorinated and non-fluorinated 10-deoxoartemisinins (Figure 4.16). 10-Desoxoartemisinin is active *in vitro* in *Plasmodium falciparum* strains ($IC_{50} = 20$ nM), but it is completely inactive *in vivo*. The introduction of a trifluoromethyl group on the carbon 10 maintains the *in vitro* activity ($IC_{50} = 6$ nM) and restores the *in vivo* activity and remarkably protects mice *in vivo*.[45, 46] The electron-withdrawing effect of the CF_3 group inhibits protonation of the double bond leading to the oxonium ion, which is responsible for the very fast decomposition of desoxoartemisinin into



Deoxoartemisinin

In vitro IC_{50} 20 nM

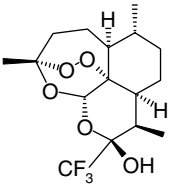
In vivo (Peters' test) Survival 0%



CF_3-deoxoartemisinin

In vitro IC_{50} 6.3 nM

In vivo (Peters' test) Survival 90%



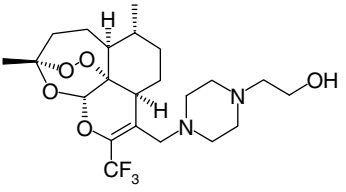


Figure 4.16 *In vitro* and *in vivo* antimalarial activities of glycols derived from artemisinin.

inactive metabolites (Figure 4.16).[46–48] Based on these results, 10-CF_3-analogues of DHA, artemether, arteether, and artesunate have been prepared. They also exhibit very interesting *in vivo* antimalarial properties and better stability under stomach acid conditions. A prolonged plasma half-life was demonstrated for some of them.[45, 48] This approach has led to the preclinical development of orally active 10-trifluoromethyl dihydroartemisinin and 10-trifluoromethyl deoxoartemisinin (Figure 4.16).[43, 45, 46, 48]

4.3.2 Taxol

Paclitaxel (Taxol®) and *docetaxel* (Taxotere®) are important drugs in chemotherapy for the treatment of several cancers. These antimitotic drugs act on the microtubules: they inhibit the depolymerization of microtubules while at the same time favoring the polymerization of tubuline into microtubules. However, the geometry of the binding site of taxoids on tubules is still unknown. Taxol and Taxotere are composed of a phenylisoserine side chain fixed on baccatine III, a diterpenic taxane framework. They are prepared by hemisynthesis from these two compounds. Fluorinated derivatives of Taxol and Taxotere have been prepared by introduction of fluorine atoms on the phenyl of the side chain and/or on the phenyl of the benzoate group of baccatine (Figure 4.17).[49]

The fluorine atoms of F-paclitaxel and F-docetaxel have been used as probes for NMR studies to determine the stable conformations of the taxoids in solution according to the nature of the medium (hydrophilic or hydrophobic) and have been compared to the X-ray crystal structure, in the solid state, to get information on the conformation of the isoserine chain in the binding site with the microtubules.[50, 51]

CF_3-acetyl docetaxel is an analogue of docetaxel in which the phenyl group of the isoserine chain has been replaced by a trifluoromethyl group. For its preparation, a

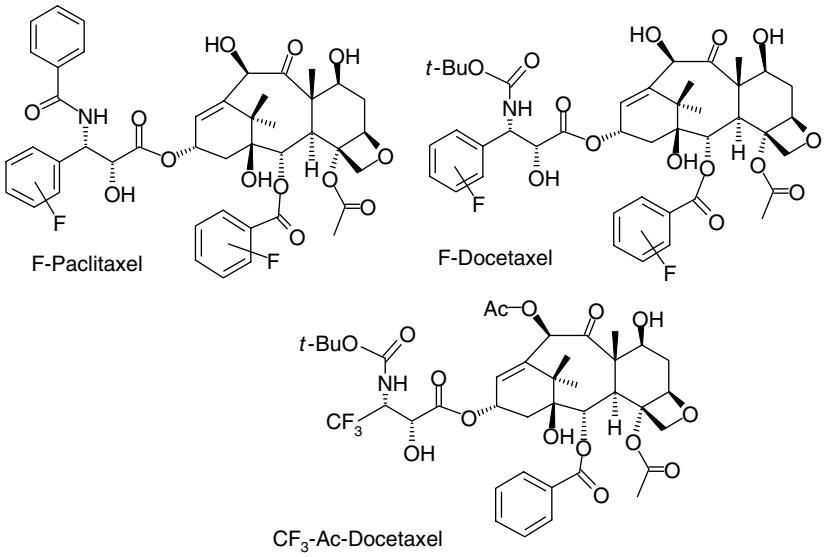


Figure 4.17 Fluorotaxoids.

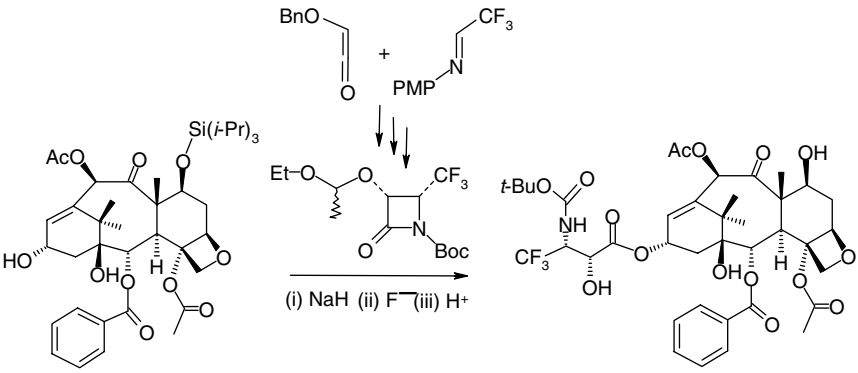


Figure 4.18 Synthesis of CF_3-acetyldocetaxel.[52, 53]

	A-121 (Ovarian)	A-549 (NSCLC)	HT-29 (Colon)	MCF-7 (Breast)	MCRF-7-R (Breast)
Paclitaxel (Taxol®)	6.3	3.6	3.6	1.7	300
Docetaxel (Taxotere®)	1.2	1.0	1.2	1.0	235
CF_3-Acetyldocetaxel	0.3	0.2	0.4	0.2	17

Figure 4.19 Antitumoral activity of paclitaxel (Taxol), docetaxel (Taxotere), and CF_3-acetyldocetaxel.[50, 53]

racemic trifluoromethyl β-lactam[52] has been coupled with acetyl baccatine III. During the reaction, a high level kinetic resolution of the racemic β-lactam occurred and led to the taxoid with desired configurations at the C-2′ and C-3′ positions (2′*R*,3′*R*) (Figure 4.18).[53] Evaluation of the biological activity of CF_3-acetyldocetaxel showed that this one had a tremendously higher *in vitro* cytotoxicity toward human cell lines than docetaxel or paclitaxel, in particular, toward resistant cell lines MCF7-R (Figure 4.19).

Molecular dynamic and NMR studies have shown that only the "extended" conformation of CF_3-acetyldocetaxel (i.e., in which the isoserine side chain is distant from the baccatine moiety) is independent of the hydrophilic or hydrophobic nature of the medium. In the other derivatives of Taxol, the globular conformation is largely favored by a protic medium.[54] Thus, it would be interesting to perform studies of complexes with tubulines in the solid phase to determine if the cytotoxic activity is connected with the conformation.

4.4 PIGMENTS AND VITAMINS

4.4.1 Retinoids

Retinoid acid is a transcription factor. Retinoids play significant roles in dermatology, in the prevention of some cancers, and in the chemistry of vision. Consequently, many works have been dedicated to fluorinated analogues of retinoids.

Retinal and carotenoids are pigments that act as photon traps. Retinal is the chromophore of rhodopsin. This latter is one of the photoreceptor proteins that are involved in the vision mechanism of superior organisms. 11-*cis*-Retinal binds with opsine through an iminium ion formed with a lysine residue. Then, in the presence of light, it undergoes a photochemical isomerization into *trans*-retinal and, consequently, it induces a conformational change of the protein. Thus, interactions of the protein with its environment are modified. This geometrical change leads to the deprotonation of the iminium ion and an enzymatic cascade occurs. The photochemical cycle finally ends with the return of the protein to its initial conformation with, as global balance, the pumping of a proton through the membrane (Figure 4.20).[55]

By introducing fluorine atoms to the polyenic system of retinal, the geometry, electronic properties, hydrophobicity, and absorption properties of the molecule will be modified. Thus, fluoro derivatives of retinal are useful tools to understand the interactions between retinal and opsin, especially on the level of charge and hydrophobic effects at the protein site. Moreover, fluorine atoms are probes in ^{19}F NMR and allow studies on model molecules of visual pigments.[55] Consequently, syntheses of mono-, di-, and trifluoro derivatives of retinal have been the subject of many investigations.

Monofluorinated derivatives of retinal are generally prepared from a monofluorophosphonate by using a Horner–Wadsworth–Emmons type–reaction.[56–58] Difluorinated compounds are prepared through a different approach: alkylation of a sulfone in C-15 with 2,3-difluoro allyl bromide. This sulfone is prepared from β-ionone.[59] The monofluorinated retinoids in positions 8, 10, 11, 12, and 14, as well as the retinoids where methyls 19 or 20 have been replaced by a single fluorine atom, all form artificial pigments with bacterio rhodopsin, a protein that is used as a model (Figure 4.21).[56, 58] Variation of the absorption wavelength of these artificial pigments, with respect to the wavelength of the native rhodopsin, depends on the position of the fluorine atom.[58] Spectrophotometric studies with 11-*cis*-12-fluororetinal and with opsin have allowed distinction between the intermediates of the photochemical cycle. These intermediates are close to the natural pigments, conversely to those formed from10-fluororetinal.[56]

Replacement of each methyl group of retinal (16, 17, 18, 19, 20) on the cycle ring as well as on the side chain by a trifluoromethyl group has also been performed for the

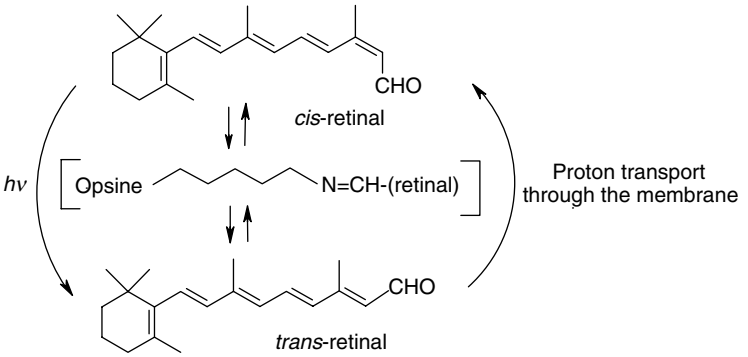


Figure 4.20 Photochemical isomerization of retinal.

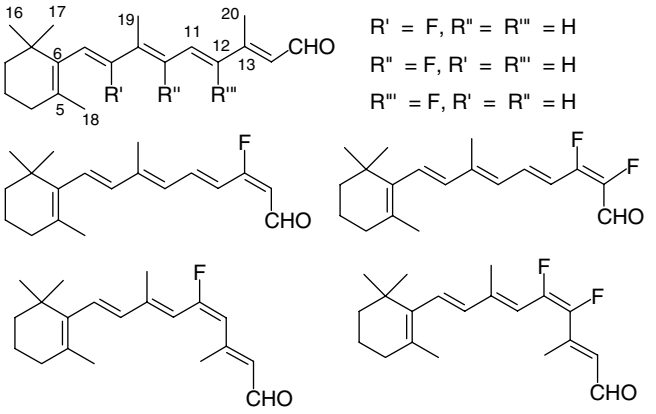


Figure 4.21 Mono- and difluoro analogues of retinal.

same kind of studies. For the preparation of these compounds, proper synthetic paths have been established for each position of the CF_3.[60–64]

As for the monofluoro compounds, syntheses of 19,19,19- and 20,20,20-trifluororetinals are generally based on Wittig–Horner type approaches. These syntheses often permit access to the various *cis*- and *trans*-trifluororetinal stereomers (Figure 4.22). The key aldehyde used for the synthesis of 19,19,

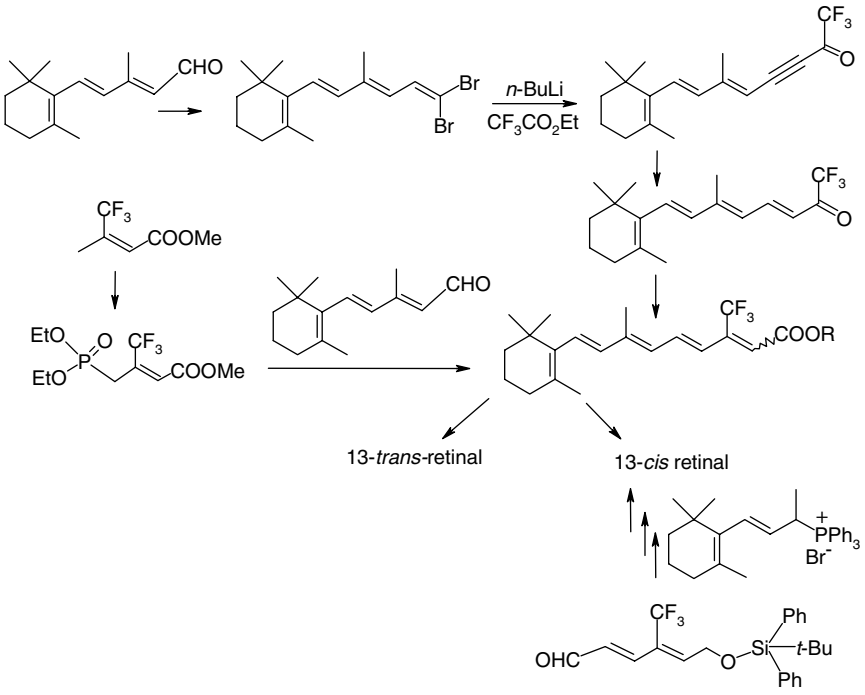


Figure 4.22 Synthesis of 20,20,20-trifluororetinal.[60, 62, 63]

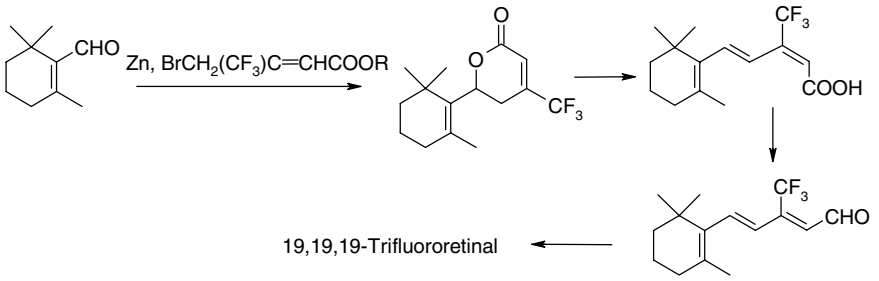


Figure 4.23 Synthesis of 19,19,19-trifluororetinal.[65]

19-trifluororetinals is prepared by means of a Reformatsky reagent from β-fluorocitral (Figure 4.23).[65]

Another general method for the preparation of 19,19,19- and 20,20,20-trifluororetinals involves the aldol condensation of trifluoroacetone with an ethylenic aldehyde. When performed in the presence of acetic acid and piperidine, it affords an α,β-unsaturated ketone. Applied to cyclocitral and its homologues, the method leads to polyenic trifluoromethyl ketones. From these ketones, the various trifluorinated retinoids are prepared by known methods (Figure 4.24).[61]

Preparation of 18,18,18-trifluororetinal required synthesis of trifluorocyclocitral as precursor. For this purpose, the 1,4-addition of a cuprate (prepared from an ω-bromo-trifluoromethylcarbinol) onto a vinylidene phosphonate was performed. The alcohol moiety is then deprotected and oxidized into ketone. A further intramolecular Wittig–Horner reaction, followed by reduction, led to trifluorocyclocitral. 18,18,18-Trifluororetinal is then easily obtained from this compound (Figure 4.25).[63c]

Synthesis of 16,16,16-trifluororetinal requires the construction of a quaternary center bearing a CF_3 group. For this, a Diels–Alder cycloaddition (cf. trifluoromethyl steroids) between a trifluoromethacrylate and a functionalized diene has been conducted. The obtained adduct has been transformed further into the trifluoromethyl analogue of β-cyclocitral (Figure 4.26).[64, 65]

The presence of a CF_3 group in 16,16,16-trifluororetinal provokes an hypsochrom effect, probably due to the torsion between the polyenic chain and the cycle.[64] However, this effect is not necessarily accompanied by the translocation of a proton.[66] Conversely, a CF_3 group in the 13 position (20,20,20-F) maintains the proton pump

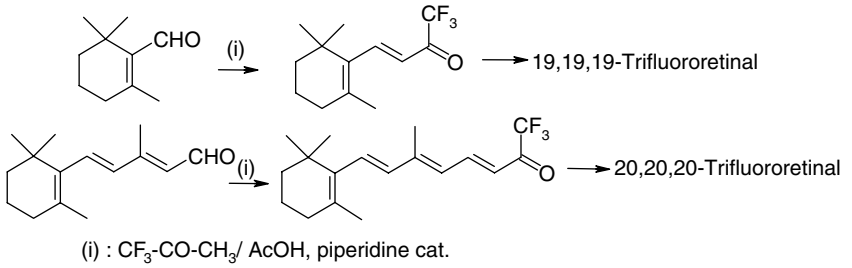


Figure 4.24 Synthesis of 19,19,19- and 20,20,20-trifluororetinals.[61]

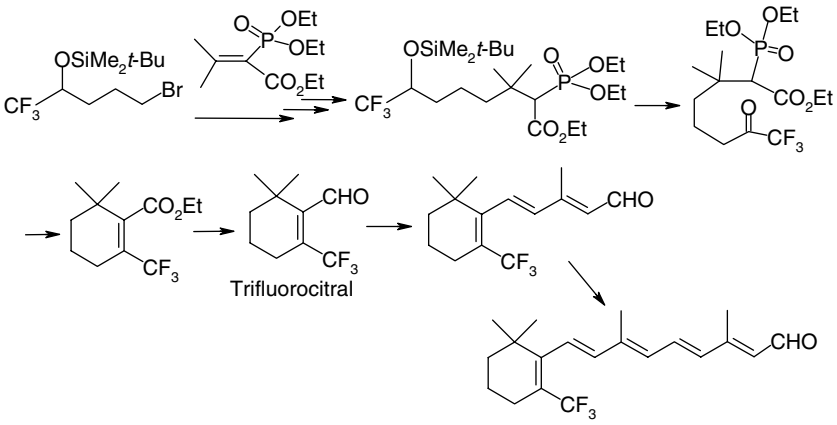


Figure 4.25 Preparation of 18,18,18-trifluororetinal.[63c]

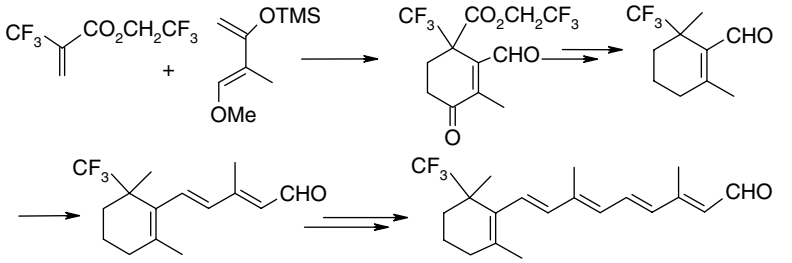


Figure 4.26 Synthesis of 16,16,16-trifluororetinal.[64]

activity of the pigment while the absorption properties are modified, due to the modification of the electronic repartition.

The antitumor activities of mono-, di-, and trifluorinated analogues of retinoic acids on the polyenic chain, and also of some aromatic analogues, have been evaluated on mice papillomas. Some of these compounds exhibit superior activities to nonfluorinated analogues.[67]

4.4.2 Carotenoids

Carotenoids constitute an important family of natural pigments, closely connected to retinoids. Fluorinated carotenoids have caught far less attention than retinoids. However, some mono- and difluoro analogues of colored natural pigments, such as astaxanthins have been prepared (Figure 4.27).[68, 69] The syntheses of 9-CF_3 and 13-CF_3-β-carotenes, as well as the preparation of trifluoromethylated canthaxanthins, have been performed by a C20 + C20 approach starting from 13-CF_3-retinal through a Wittig reaction. The di-CF_3 compounds have been prepared by means of McMurry couplings from CF_3-retinal. Presence of the CF_3 group often enhances oxidation potentials.[70]

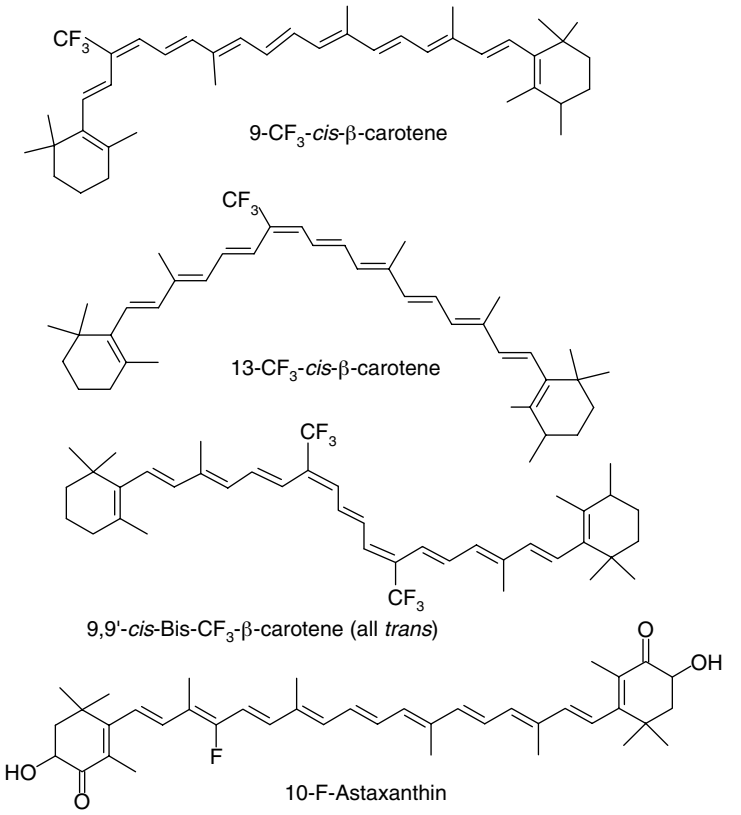


Figure 4.27 Examples of fluorinated carotenoids.

4.4.3 Vitamins D

Fluorinated analogues of vitamin D_3 have already been covered in Section 4.2.3; vitamin D is generally considered a steroid hormone.

4.4.4 Vitamins E and K

Methyl groups of the aromatic ring of vitamins E and K have been replaced by trifluoromethyl.[71,72] Replacement of the three methyls of the side chain by one or several trifluoromethyls (Wittig-like approach from *ad hoc* trifluoromethyl ketones) as well as the difluorination at C-4 (synthesized from bromodifluoroacetate) in vitamin E (tocopherol) have also been realized (Figure 4.28).[73,74] The relaxation times T_2 of the various CF_3 groups have been measured in suspensions of liposomic bilayers and compared to those obtained in solution. The goal of these studies was to determine the mobility and the molecular orientation of the vitamin in a lipidic bilayer, to establish its role in the stabilization of membranes.[75]

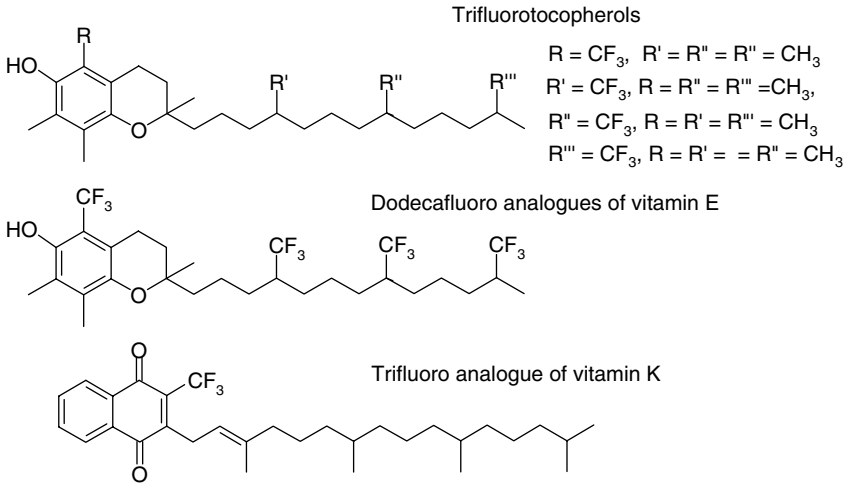


Figure 4.28 Trifluoromethylated analogues of vitamins E and K.

4.4.5 Porphyrins

Like retinoids, porphyrins can be considered as essential prosthetic groups for vital biological processes. The polyvalent roles of porphyrinic molecules in the transmembrane processes of charge separation, electron transport, and signal transduction have motivated many studies with synthetic porphyrins. This interest has recently been reinforced by the emergence of photodynamic therapy (PDT) for the treatment of cancer. This involves the use of porphyrins as photosensitizing agents. These compounds accumulate in cancer cells, which are further irradiated (visible light, laser). The energy transfer to molecular oxygen releases the singlet oxygen, which is the cytotoxic agent.

The presence of fluorinated groups on porphyrins exerts a strong influence on the hydrophobicity, the stability of metalloporphyrins, the electronic density of pyrrole rings, the absorption wavelengths, and the redox properties of the photosensitizing agents. Moreover, it also allows studies by ^{19}F NMR and the *in vivo* monitoring of PDT. Consequently, synthesis of fluorinated porphyrins have captured significant attention.

The synthetic paths of fluorinated porphyrins (fluorine atoms or fluoroalkyl chains) are numerous and depend on the fluorination site (periphery or *meso* position). These syntheses are performed through the use of fluoroalkylated pyrroles, through DAST fluorination, or through direct perfluoroalkylation. Some examples are given next.

The oldest methods for synthesis involve the condensation–cyclization of trifluoromethyl or fluoroalkyl pyrroles in the presence of a metal salt. These reactions afford tetrakis(fluoroalkyl) porphyrins.[76] The electrophilic trifluoromethylation of porphyrins is selective and leads to β-CF_3 and *meso*-CF_3 porphyrins.[77] While condensation of *meso*-trifluoromethyl-dipyrromethane with an aldehyde in acidic medium is rather difficult, it proceeds with better yields and permits a selective introduction of trifluoromethyl groups in *meso*.[78] The Ruppert reagent (CF_3TMS) has been used to

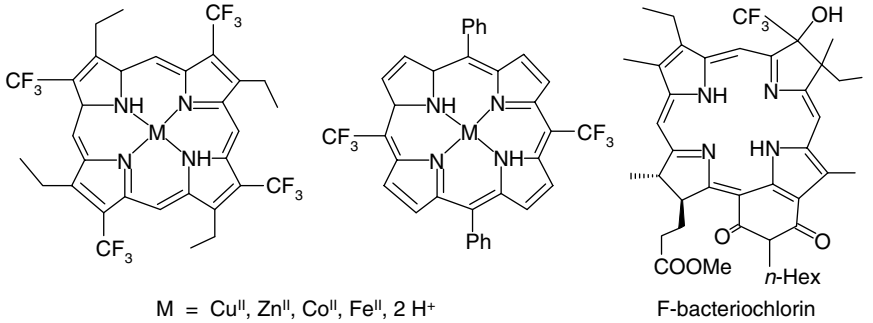


Figure 4.29 Examples of trifluoromethyl porphyrins.

prepare various trifluoromethyl analogues of porphyrins, chlorins, and bacteriochlorins starting from the corresponding carbonyl derivatives (Figure 4.29).[79]

A fluorinated analogue of *meso*-bilirubin, a biliary pigment, has been prepared from a pyrrole bearing a propionic chain on which the fluorine has been introduced with DAST reagent by reaction with hydroxyl of the lactic lateral chain. The presence of fluorine modifies the spectral properties and the solubility (Figure 4.30).[80]

A broad array of fluoro analogues of natural porphyrins have been synthesized to unearth efficient and selective photosensitizing agents. Thus, di- and trifluorinated analogues of protoporphyrin (a component of hemoglobin and of other important enzymes) have been prepared through hemisynthesis from deuteroporphyrin (Figure 4.31). Some of these products show remarkable specificities for some tumor cell lines. Moreover, these products may allow detection by NMR imaging.[81,82] Photofrin II is derived from hematoporphyrin (HpD) and has been developed for the diagnosis and treatment of tumors (PDT).[83] ^{19}F NMR studies on trifluoromethylmyoglobin have also been used for quantitative characterization of dynamic processes occurring at the heme active site in myoglobin, an oxygen storage hemoprotein.[84]

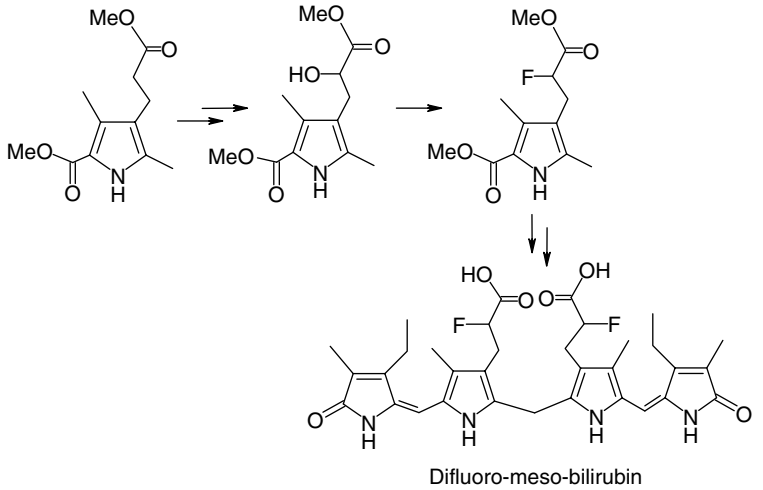


Figure 4.30 Synthesis of F-*meso*-bilirubin.

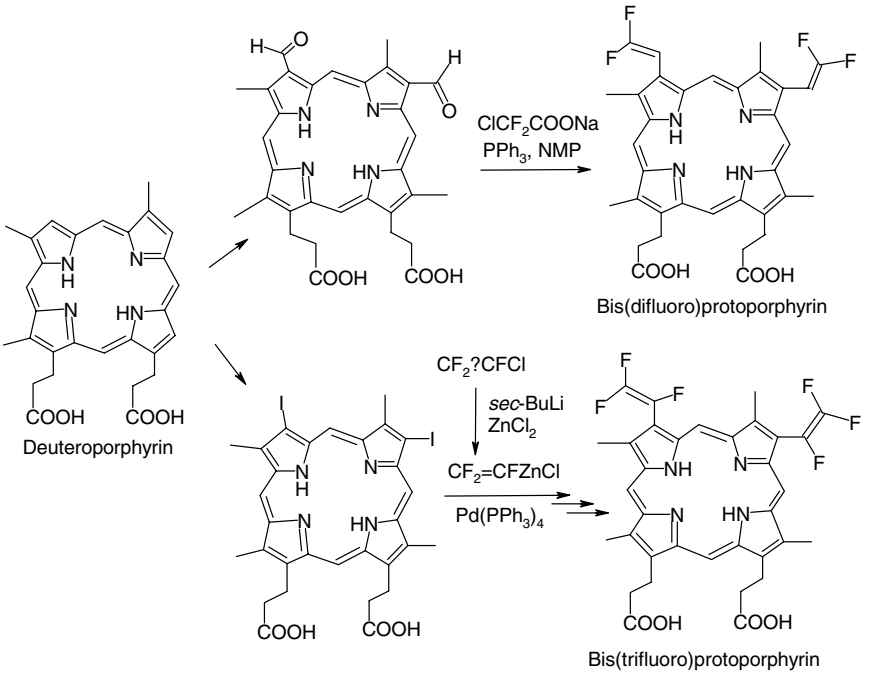


Figure 4.31 Fluorinated derivatives of protoporphyrin.

Enantiopure fluorinated analogues of hematoporphyrins have also been prepared through total syntheses. These preparations involve cyclocondensations with chiral derivatives of pyrroles (Figure 4.32).[85]

4.5 LIPIDS AND PROSTANOIDS

Due to the importance of the arachidonic cascade on a broad range of biological activities, intensive studies have been devoted to the synthesis of prostanoids and arachidonic metabolites. One objective was to acquire a better knowledge of their very puzzling roles in signal transduction, and to elucidate the diverse functions of receptors. Another important objective was to find more stable analogues, for development as potentially valuable drugs. Fluorination of prostanoids was particularly well adapted to these aims, and numerous fluorinated derivatives have been synthesized.[86] Among them, some drug candidates have emerged and are undergoing clinical development or are marketed drugs (cf. Chapter 8).

Mono-, di-, and trifluoro derivatives of fatty acids have been prepared in regio- and stereoselective manners, in order to evaluate the gauche effect induced by fluorine atoms on the conformation of hydrocarbon chains and for enzymatic studies.[86a, 87]

Arachidonic acid is the biosynthetic precursor of metabolites (such as prostaglandins) that play a basic role in cell signal processes. Fluorine atoms have been introduced on the strategic oxidation sites of arachidonic acid in order to study the

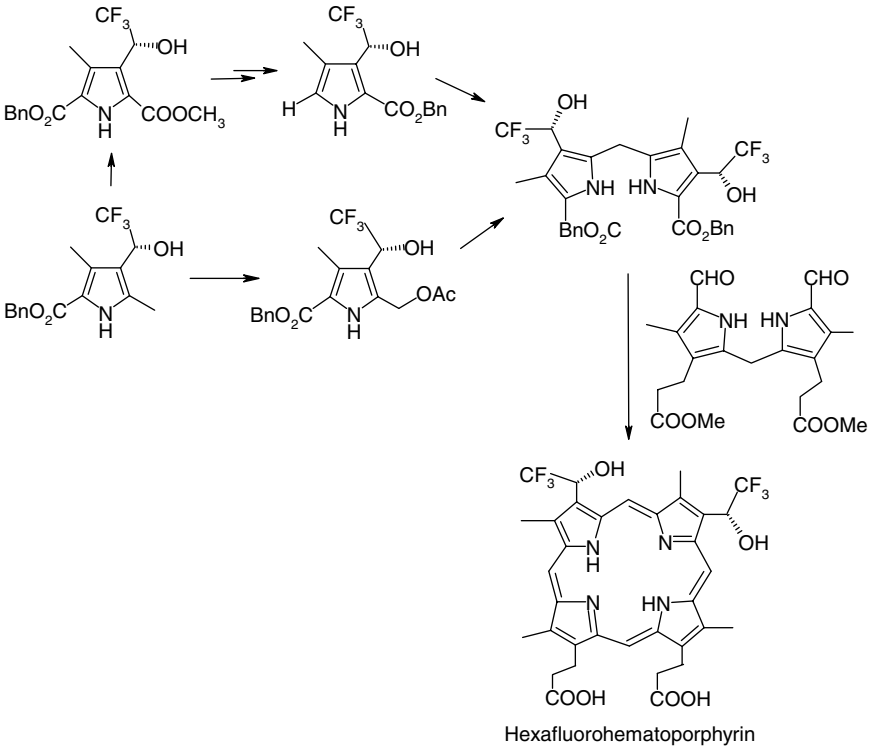


Figure 4.32 Synthesis of fluorinated analogues of hematoporphyrin.

biosynthetic mechanisms of metabolites, to obtain inhibitors of the enzymes involved in the arachidonic cascade, and to develop to potential drugs (Figure 4.33).

Fluorine atoms have been introduced mainly at the vinylic positions 5, 6, 8, and 9, the allylic positons 7, 10, and 13, and the terminal positions 2, 19, and 20.[86] Only a few significant examples of these numerous works are discussed here:

1. A polyvalent and stereocontrolled synthesis of 5- and 6-fluoroarachidonic acids.[88, 89]
2. A convergent synthetic approach developed for 10,10-, 13,13-, and 20,20-difluoroarachidonic acids, based on the reactivity of disymmetric difluorodiynes, which are accessible from propargyl alcohol (Figure 4.34).[90]
3. A preparation of 20,20,20-trifluoroarachidonic acid (Figure 4.35).[91] This molecule is much more stable than the natural compound. This is probably due to blocking of the oxidation in the ω position by the terminal CF_3 group.[92] This latter group does not interfere in the metabolic transformation into F-leukotriene B_4 during incubation with human neutrophiles. 5,5-Difluoroleukotrienes B_3 and B_4 have also been synthesized.[86a, 93]

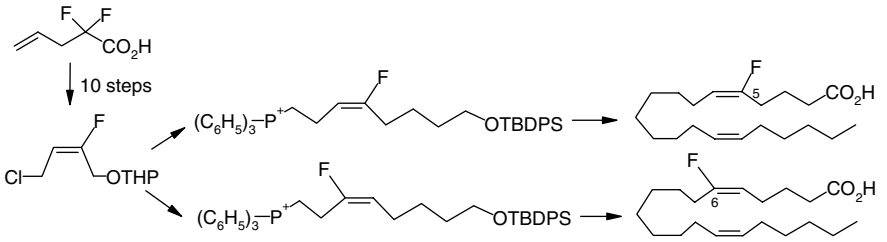


Figure 4.33 Synthesis of the 5- and 6-fluoroarachidonic acids.

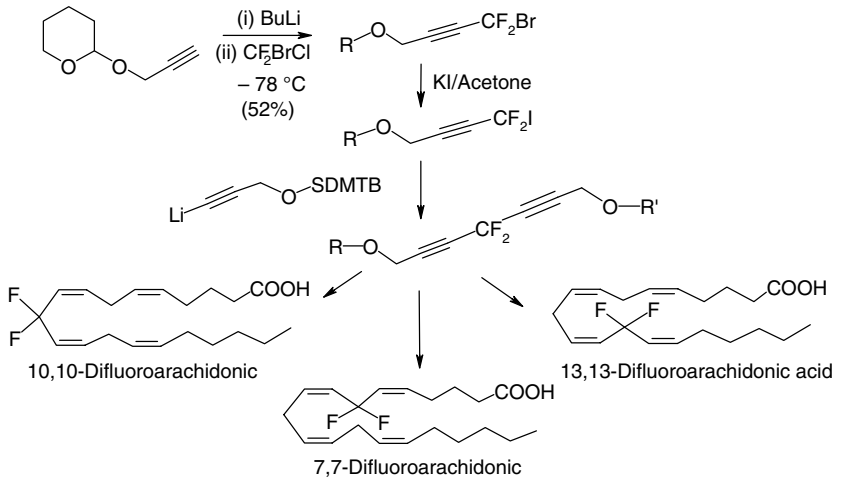


Figure 4.34 Synthesis of 10,10-, 13,13-, and 20,20-difluoroarachidonic acids.[90]

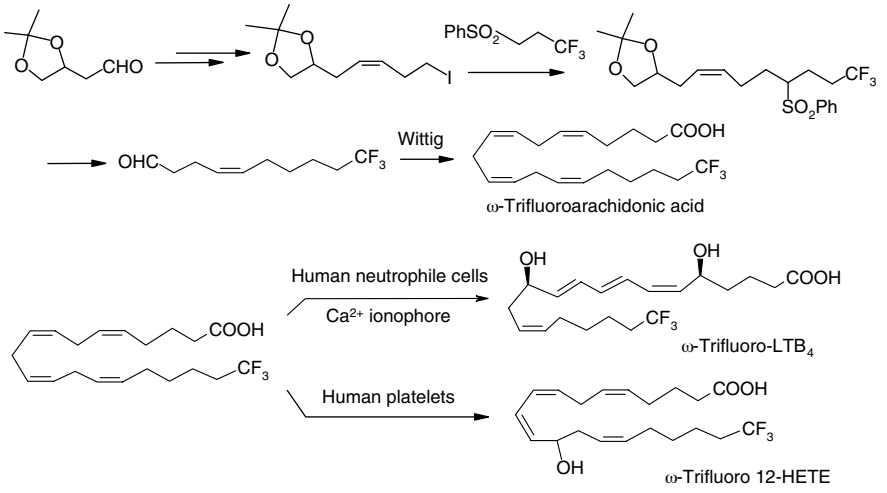


Figure 4.35 Synthesis of 20,20,20-trifluoroarachidonic acid and its transformation into 20,20,20-trifluoroleukotriene B_4 (LTB_4) and trifluoro-12-HETE.

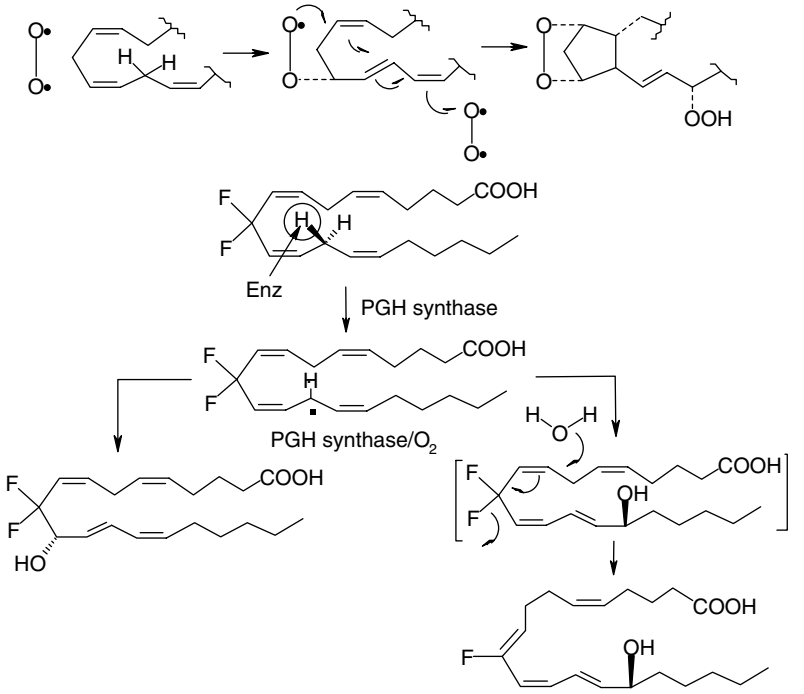


Figure 4.36 Conversion of 10,10-difluoroarachidonic acid by PGH synthase.

The enzymatic conversion of 10,10-difluoroarachidonic acid by lipoxygenases and PGH synthases is highly interesting. Indeed, among the positions that undergo enzymatic oxidation, two are in β of the fluorine atoms. Fluorination hinders neither recognition by the enzyme nor – remarkably – enzymatic oxidation in α (C-11) (Figure 4.36). However, in contrast with arachidonic acid, oxidation in C-11 is not the major process, but oxidation at C-15 occurs. The presence of fluorine inhibits the formation of the expected 9,11-endoperoxide, and no cyclization product (prostaglandin-type) has been detected.[94]

Fluoroanalogues of prostanoids (PGI_1, PGI_2, and $PGF_{2\alpha}$) have been synthesized in order to enhance the stability of these products, which undergo a very fast metabolization (Figure 4.37). These syntheses involve electrophilic fluorination,[95,96] the Reformatsky reagent of ethyl dibromofluoroacetate,[97] or a difluorophosphonate in a Wittig–Horner reaction[98] (Figure 4.38). Analogues of PGI_2, of PGI_{2a}, and of *Travoprost* (a compound in clinical trials for the treatment of glaucoma) (cf. Chapter 8), in which the hydroxyl in 15 has been replaced by a fluorine atom, have also been prepared.[99]

The instability of PGI_2 under physiological conditions ($t_{1/2} = 5$–10 min at pH = 7.4 and at 37°C) is connected with both the rapid oxidation of the lateral chain and the presence of the enol ether function. It is so unstable that its function as a vasodilator and

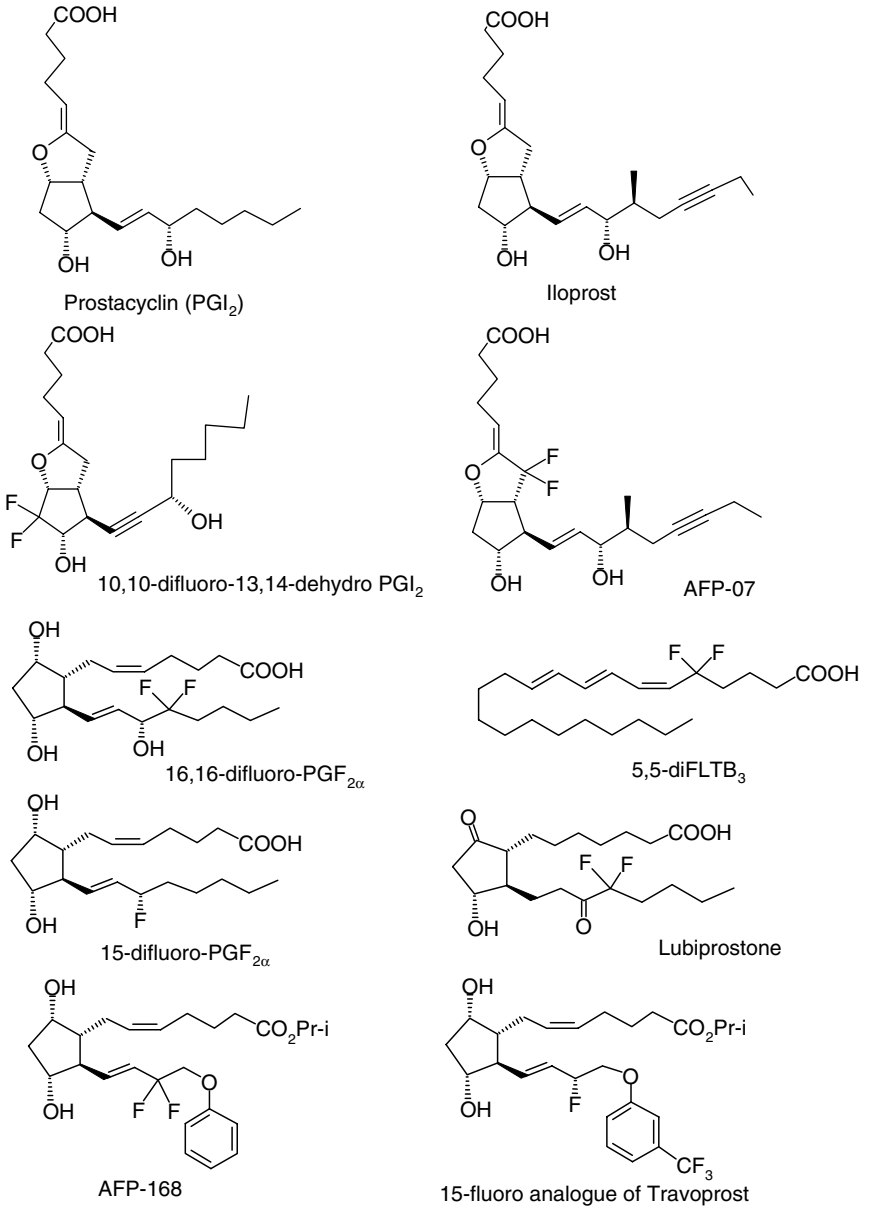


Figure 4.37 Examples of fluorinated prostacyclins and leukotrienes.

inhibitor of platelet adhesion cannot be clinically exploited (cf. Chapter 3). Fluorine atoms have been introduced on the position β to the enolic double bond of *Iloprost,* a more stable derivative of PgI_2 (Figure 4.37). The proteolysis is dramatically slowed since protonation of the enol ether to give an oxonium ion is inhibited by the presence of fluorine atoms.[100] Thus, the drug candidate *AFP-07*

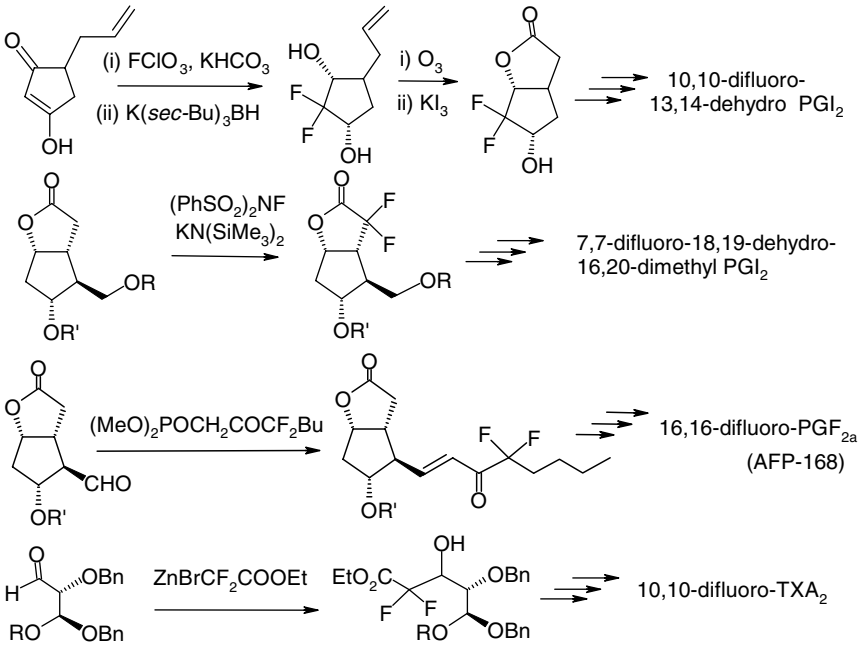


Figure 4.38 Preparation of fluorinated intermediates for the synthesis of fluorinated prostacyclins.[96–98]

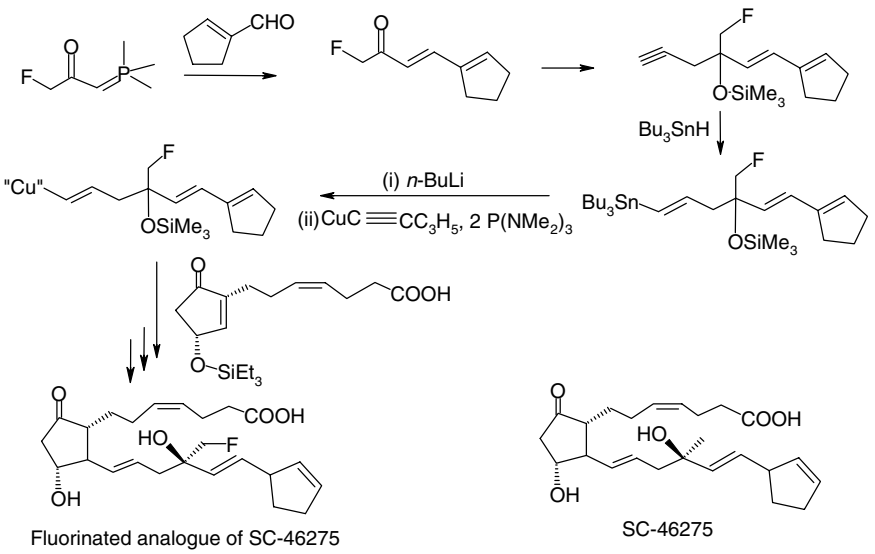


Figure 4.39 Synthesis of the fluorinated analogue of SC-46275.[103]

possesses a good metabolic stability while retaining a strong activity as an inhibitor of platelet adhesion (Figure 67).[86b, 96]

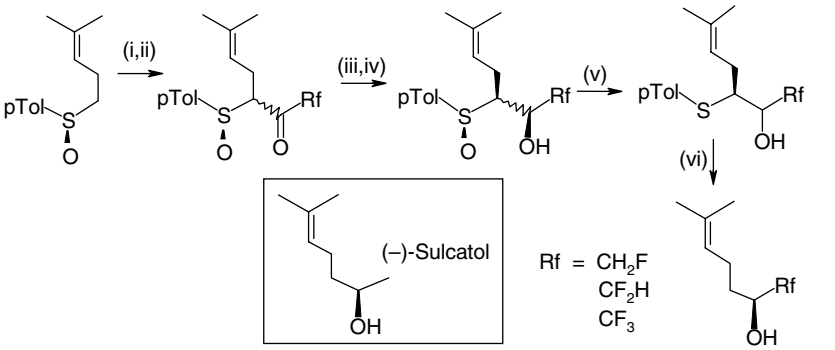
Lubiprostone, a 16,16-difluoro-15-ketoprostaglandin, an agonist of chloride channels, and *AFP-168*, a deoxy-15,15-difluoro PF_{2a}, are currently under clinical development (Figure 4.37) (cf. Chapter 8).[101, 102]

The beneficial effect of fluorine atoms on hydrolytic stability has been demonstrated with synthetic prostaglandin (SC-46275). This compound possesses an antisecretory activity that protects the stomach mucous membrane. However, its clinical development was too problematic because of the instability of the tertiary allyl alcohol function in acidic media (epimerization, dehydration, etc). A fluorine atom has been introduced on the C-16 methyl to inhibit the formation of the allylic carbocation (Figure 4.39). The fluoroanalogue possesses the same biological activity but does not undergo any degradation or rearrangement, and it epimerizes only slowly.

4.6 PHEROMONES AND TOXINS

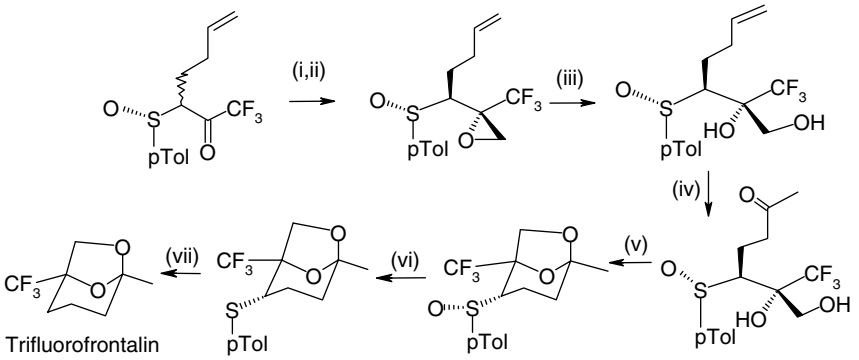
Fluorinated pheromones have been synthesized in order to determine the impact of fluorination on detection by insects. Possible effects on the behavior response would be of interest in order to discover compounds able to lower the reproductive potential of destructive insects.

1. Fluorinated analogues of (*R*)-(−)-sulcatol and of frontalin, which are aggregative pheromones of wood destructive insects have been prepared by means of chiral sulfoxides (Figures 4.40 and 4.41).[104, 105]
2. In studies on the metabolism of disparlure, a pheromone of a forest devastating insect (Gypsy moth), difluoroanalogues have been synthesized (Figure 4.42). They are micromolar inhibitors of an epoxide hydrolase that regulates the metabolic degradation of the pheromone, thus avoiding saturation of sensorial



(i) LDA; (ii) $RfCO_2Et$; (iii) Reduction; (iv) Separation; (v) TFAA, NaI; (vi) Ni Raney

Figure 4.40 Preparation of fluorinated analogues of sulcatol.[104]



(i) CH_2N_2; (ii) separation; (iii) H^+; (iv) $PdCl_2/CuCl_2$; (v) H^+; (vi) TFAA, NaI; (vii) Ni Raney

Figure 4.41 Synthesis of trifluorofrontalin.[105]

hormones.[106] More recently, monofluorinated derivatives have been obtained in a stereoselective manner.[107]

3. Fluorinated analogues of the sexual pheromone of the European corn borer moth (Figure 4.43) have been studied. Effects of the presence of fluorine atoms on the response of male insects to this pheromone have been compared to the effects generated by fluorinated analogues of specific pheromones of related species (close molecular structure). Among all the assessments, only the compound with a terminal CF_3 has appeared to be a good mimic of corn borer moth pheromone, while this compound has a lowered activity for other species. Conversely, the presence of fluorine atoms in the allylic position alters the response of corn borer moth, but not the response of other species.[108] This shows the importance of the repartition of the electron density of the pheromone molecule for binding with the olfactly receptors of the various species of insects. The same molecule may be able to bind with the receptors of several related species, while these receptors are not always the same ones. However, biological responses can be different.
4. The recent synthesis of fluorinated analogues of eldolide, which is a sexual pheromone of a devastating insect of sugar cane has been achieved in studies on electroantennography.[108, 109]

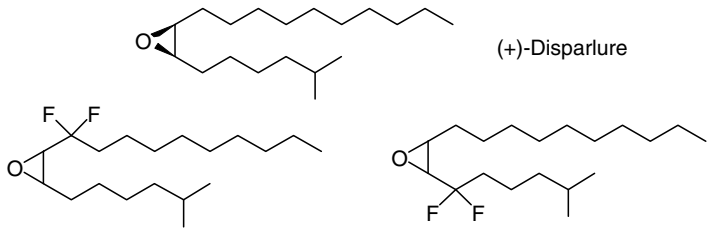


Figure 4.42 Fluorinated analogues of disparlure.

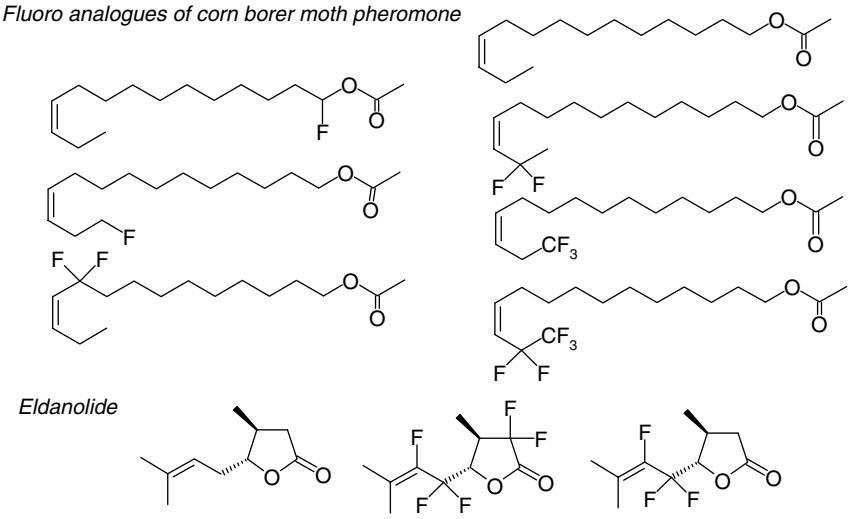
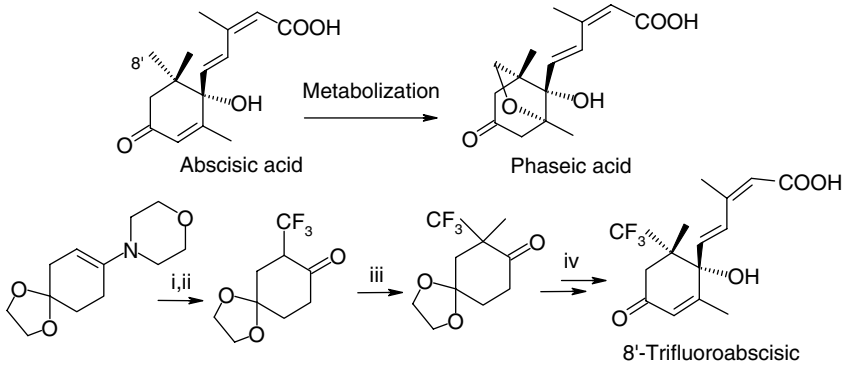


Figure 4.43 Fluorinated analogues of corn borer moth and of eldolide .

Abscisic acid is a vegetal hormone that undergoes fast metabolization through hydroxylation of the methyl 8′. In order to increase its metabolic stability—and so render it usable as a growth factor regulator or herbicide—the 8′-trifluoro analogue has been synthesized from a trifluoromethyl cyclohexandione. This latter is prepared by radical trifluoromethylation of an enamine. The methylation in α of the CF_3 group is a rather difficult step, as basic conditions may lead to the loss of a fluoride ion (Figure 4.44).[110]

Cantharidin is a toxin isolated from fish. Among its numerous biological activities, cantharidin exhibits insecticide and herbicide properties. Cantharidin and norcantharidin are inhibitors of serine and threonine phosphatases, which are important enzymes for the regulation of cell processes and cell proliferation. Mono- and difluoronor-



(i) CF_3I/BEt_3; (ii) HCl; (iii) CH_3I, TBAF (2 equiv.); (iv) 8 steps

Figure 4.44 Synthesis of trifluoroabscisic acid.

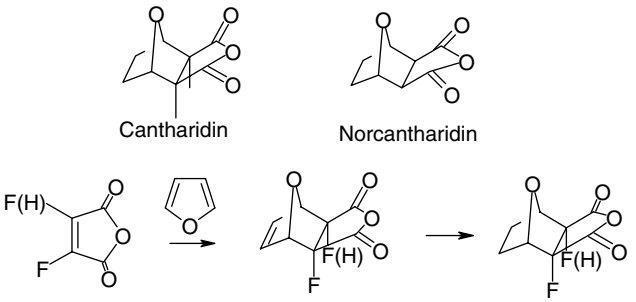


Figure 4.45 Fluorinated cantharidins.

cantharidins have been synthesized by Diels–Alder reactions between mono- and difluoromaleic anhydrides and furan. These reactions selectively afford the adducts with *exo*-fluorines (Figure 4.45).[111]

Pyrethrinoids are powerful natural insecticides that act on the nervous system of insects. They are esters of chrysantemic acid with a substituted cyclopentenol. The replacement of this motif by a more photochemically stable group affords products that are utilizable in agrochemistry. These compounds exhibit a high insecticide activity and are nontoxic for mammals; consequently, they are established in very important markets (e.g., *deltamethrin, permethrin*). Some fluorinated pyrethrinoids have been synthesized and marketed. One goal of these compounds is to enhance the acaricide activity. Some examples are given in Figure 4.46.

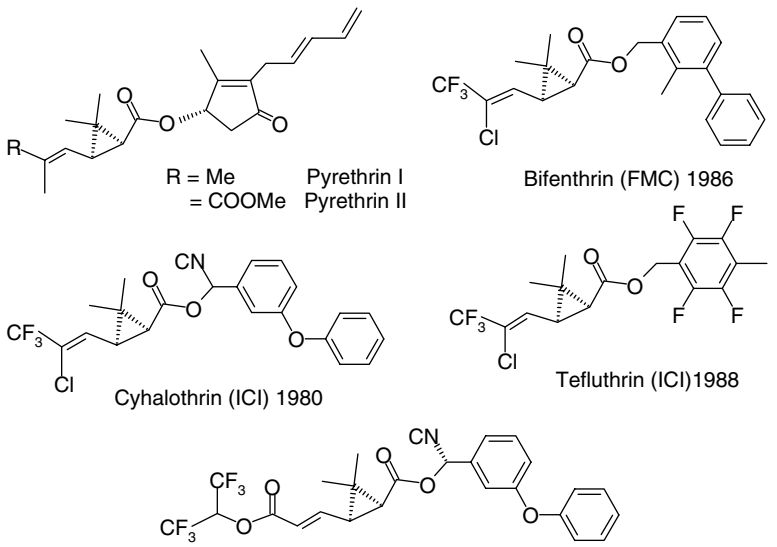


Figure 4.46 Examples of fluorinated pyrethrinoids.

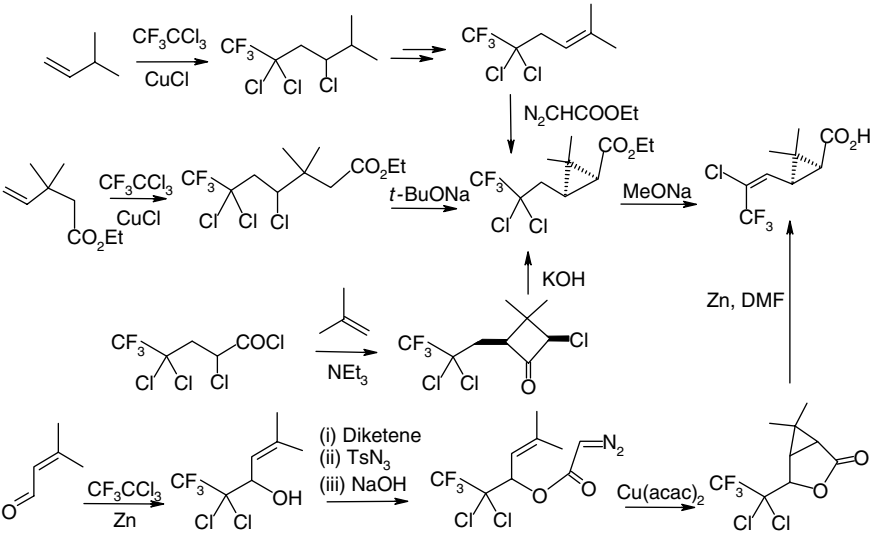


Figure 4.47 Synthesis of precursors of fluorinated pyrethrinoids.[112–114]

The *gem*-chlorotrifluoromethyl ethylene moiety present in many pyrethrinoids can be synthesized through different pathways (Figure 4.47). Trifluorotrichloroethane (CFC-113a) is the most utilized starting material.[112–114]

4.7 ALKALOIDS

Syntheses of only a few fluorinated derivatives of alkaloids have been reported in the literature. This is probably due to the difficulty of synthesizing such structurally complex compounds. Most fluorinated alkaloids have been synthesized within the frame of antitumor drugs research.

4.7.1 *Vinca* Alkaloids

Vinca dimer indole alkaloids (e.g., *vinblastine*) act as spindle poison. They bind tubulin, inhibiting polymerization into microtubules, major elements of the cytoskeleton.[115] *Vinblastine* itself and its analogue *vinorelbine* (Navelbine®)[116] are marketed for cancer therapies (Figure 4.48). Because of the obvious difficulty in synthesizing such highly complex structures, there were no reports on the preparation of fluorinated derivatives until the remarkable work of Jacquesy's group on the synthesis in superacidic media.[115, 117, 118]

When dissolved in superacidic media, complex molecules such as steroids or alkaloids undergo polyprotonation of reasonably distant functions. This prevents the degradation generally observed under usual strong acidic conditions.[117] Moreover, the lack of basic or nucleophilic entities in the medium avoids further processes

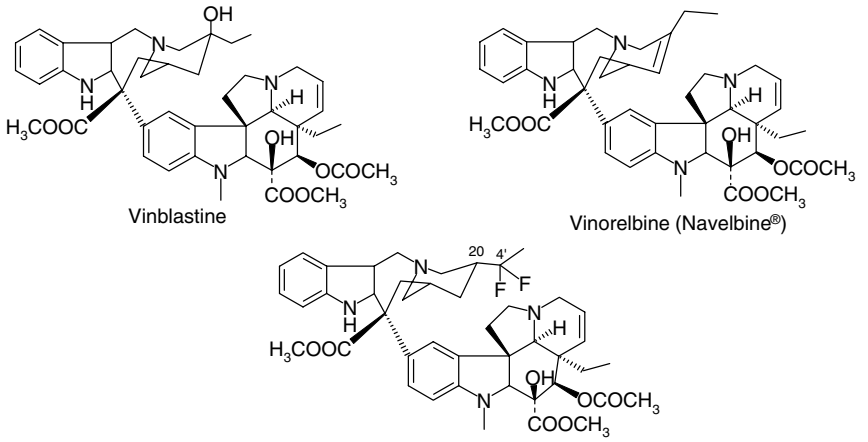


Figure 4.48 Antimitotic drugs derived from *Vinca* dimer alkaloids.

responsible for degradation.[117] This approach allowed the fluorination of *vinorelbine*, providing the highly potent *vinflunine*.

Fluorination of *vinorelbine* was thus performed in superacidic medium ($HF—SbF_5$).[118] A superelectrophilic agent, such as a chloromethyl or a Br^+ cation, is generated *in situ* from a chloromethane ($CHCl_3$, CCl_4) or from NBS. It is able to abstract a hydrogen from the protonated alkaloid, leading to a cation that can be trapped by a halide anion present in the medium.[118, 119] Difluorination remarkably occurs selectively at C-4′ of the clavamine fragment (Figure 4.49).[118, 119]

The first step of the reaction is a polyprotonation that includes protonation of the double bond. The resulting carbocation at C-20 isomerizes into one centered at C-4′ more distant from the protonated nitrogen. This C-4′ cation is then trapped by a chloride anion. The 4′-hydrogen geminal to the chlorine atom is abstracted by an oxidative chloromethyl cation, generated in the medium from the added $CHCl_3$. This provides a new cation at C-4′, which again traps a chloride anion, leading to a 4′,4′-dichloro compound (Figure 4.50).[118, 119] Further halogen exchanges, induced by HF, provide the 4′,4′-difluoro compound. Although the yield is moderate, it is a remarkable reaction with respect to the complexity of both reaction and substrate

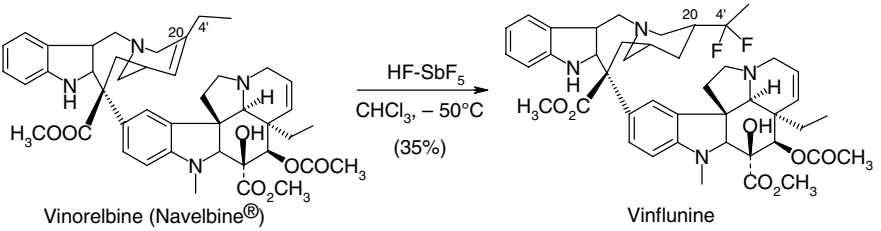


Figure 4.49 Preparation of *vinflunine*.[118, 119]

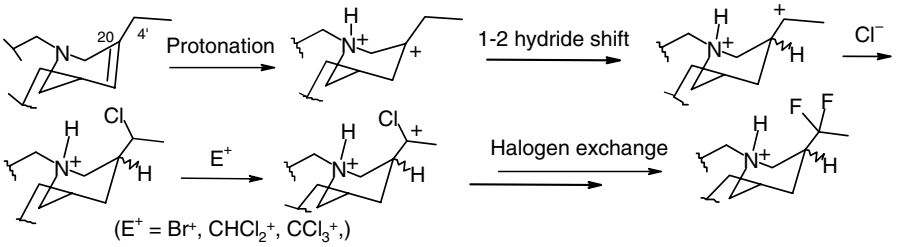


Figure 4.50 Mechanism of the fluorination of the Navelbine.[118, 119]

(Figures 4.49 and 4.50).[105] Despite the use of very corrosive reagents, the reaction is performed on industrial scale.[119]

Vinflunine (Javlor®) is a member of the second-generation *Vinca* dimer alkaloids. This 4′-difluoro analogue is more active than *vinorelbine* in several cancers . It is now in Phase III clinical trials as a chemotherapeutic agent targeted at a variety of cancers (non-small-cell lung and bladder cancers).[120] However, the role of fluorine substitution on activity is still unknown. Neither an effect on affinity for tubulin nor an effect on metabolism is responsible for the increased antitumor efficiency and decreased toxicity.[115, 120]

4.7.2 Cinchona Alkaloids

Fluorination of cinchona alkaloids has also been investigated.[121] For instance, fluorination of quinine acetate under similar superacidic conditions (HF—SbF_5/$CHCl_3$) affords a mixture of difluorocompounds in the 10 position that are epimers in 3 (60% yield, 1 : 1 ratio). This reaction involves a mechanism similar to the one described earlier (protonation, isomerization of carbenium ions, and Cl—F exchange). Curiously, when the reaction is performed on quinine itself, fluorination does not occur and an unprecedented rearrangement takes place (Figure 4.51).[121]

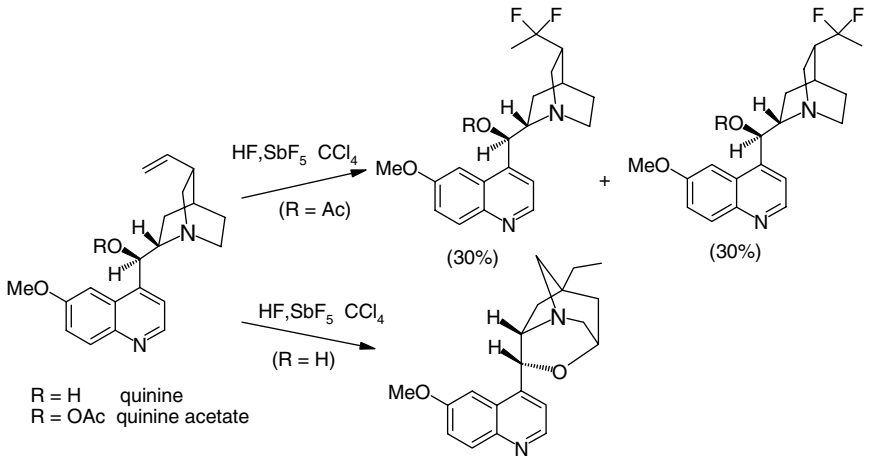
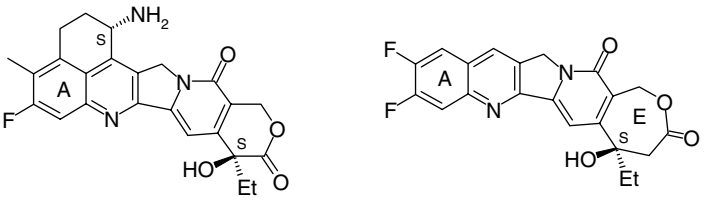


Figure 4.51 Fluorination and rearrangement of quinine in superacidic medium.



Exatecan (Daiichi) Phase III Diflomotecan (Ipsen) Phase II

Figure 4.52 Fluorinated analogues of camptothecin.

4.7.3 Camptothecin

Camptothecin, an alkaloid isolated from a Chinese tree (*Camptotheca acuminate*), is a potent cytotoxic agent acting via inhibition of DNA topoisomerase I.[122] Numerous derivatives of camptothecin have been synthesized in order to improve its pharmacological profile for effective antitumor drugs. Among them, some fluorinated derivatives have been studied and this research has led to two drug candidates. *Exatecan*, fluorinated on the A aromatic ring, is under Phase III development, despite the lack of confirmation of initial hopes during the Phase II trials.[123] *Diflomotecan*, an E-homocamptothecin difluorinated on the A aromatic ring, is currently in Phase II (Figure 4.52) (cf. Chapter 8).[124]

Fluorine has also been introduced onto the E ring. For instance, both epimers of 20-fluorocamptothecin, where the fluorine atom replaces the 20-hydroxyl, have been prepared by total synthesis *via* stereoselective fluorination with DAST of the (*R*) and (*S*) α-hydroxylactone precursors (Figure 4.53).[125a] An asymmetric

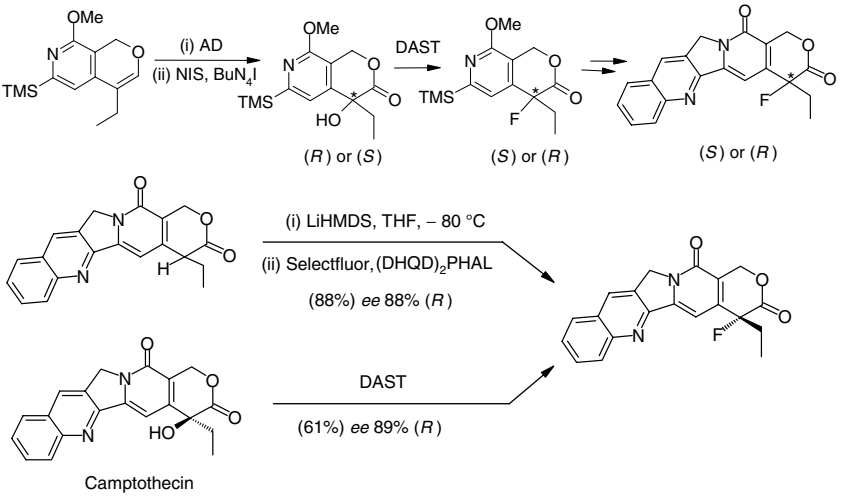


Figure 4.53 Preparation of 20-fluorocamptothecins.[125]

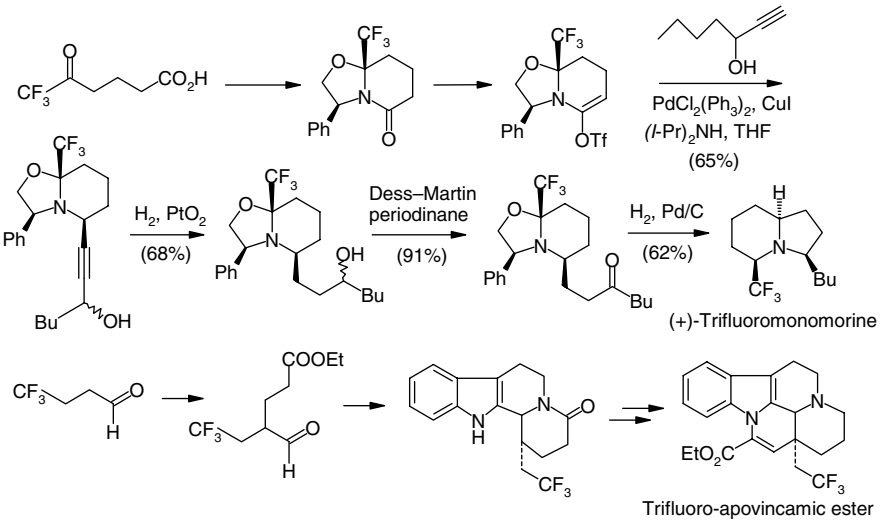


Figure 4.54 Synthesis of fluorinated alkaloids.

fluorination of 20-deoxycamptothecin lithium enolate, using Selectfluor™ in the presence of $(DHQD)_2PHAL$, or alternatively fluorination of camptothecin with DAST, both provide the (*R*)-enantiomer (Figure 4.53).[125b] Unfortunately, these 20-F-camptothecins are less active or inactive in topoisomerase I/DNA assays. They are also less hydrolytically stable.[125]

4.7.4 Other Fluorinated Alkaloids

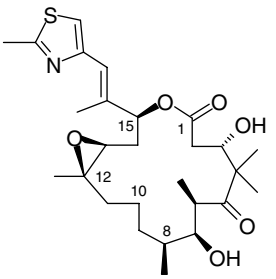
Trifluorinated analogues of monomorin, an indolizidin-type alkaloid that is an ant pheromone,[126] and of vincamine derivatives have been described (Figure 4.54).[127]

4.8 MACROLIDES

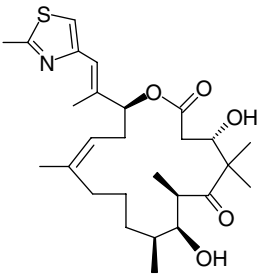
4.8.1 Epothilone

Epothilones are naturally occurring cytotoxic macrolides, which were initially isolated from a mycobacterium. Their antitumor activity is similar to that of the clinically established taxoids (Taxol, Taxotere), by interrupting the dynamic mechanism of microtubule assembly/disassembly via microtubule stabilization. In contrast to taxoids, epothilones are remarkably efficient against multidrug resistant cells.[128]

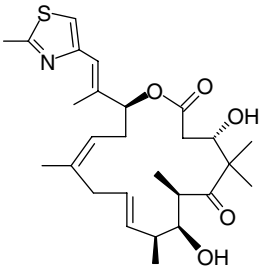
The precursor of EpoB, dEpoB, in which the 12,13-oxido linkage is lacking, also acts on microtubule assembly with a better therapeutic index than EpoB. dEpoB is currently in Phase II clinical trials. Bioassays were performed on (*E*)-9,



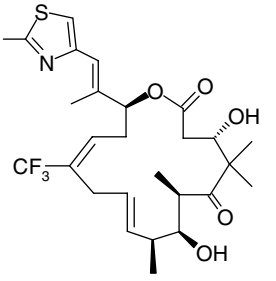
Epothilone B0 (EpoB)



dEpoB



(*E*)-9,10-dehydro-dEpoB



Fludelone

	Fludelone	(*E*)-9,10-dehydro-dEpoB
IC_{50} (nM) (leukemia cells CCRF-CEM)	3.2	0.9
Plasma half life (min) (mice)	212 ± 88	84 ± 6
Half life S9 (h) (human liver)	10.5 ± 2.3	4.9 ± 0.7

Figure 4.55 Fluoroepothilones.[130a]

10-dehydro-dEpoB, the synthetic intermediate resulting from a ring closure metathesis reaction. These assays revealed that the presence of an (*E*)-9,10 unsaturation in the macrolide framework resulted in a marked increasing in potency and in metabolic stability, despite a rapid hydrolysis by esterases *in vivo*.[129] Its trifluoroanalogue (12-CF_3), *fludelone*, exhibited an attenuated cytotoxicity in CCRF-CEM leukemia cells compared with that of (*E*)-9,10-dehydro-dEpoB. Nevertheless, *in vivo* experiments performed on human tumor xenografts in immunodeficient nude mice showed that *fludelone* is much more active and possesses a longer (2×) plasma half-life (Figure 4.55).[130]

Convergent synthesis is based on formation of the macrolide ring through a ring closure metathesis reaction (RCM) and could be performed on the multigram scale (Figure 4.56).[130c] Clinical trials are ongoing.[130d]

4.8.2 Erythromycin

Erythromycins are macrolide antibiotics produced by bacterial fermentation. Fluorination of erythromycin has been studied to ensure a better stability in acidic medium and/or a better bioavailability.

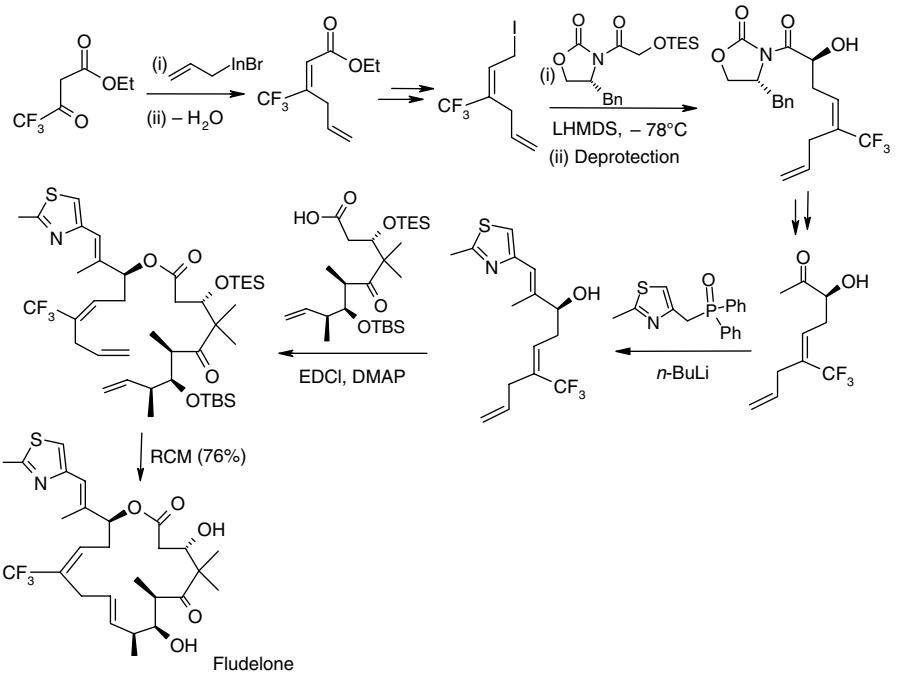


Figure 4.56 Synthesis of the fludelone.[130c]

Flurithromycin is an erythromycin fluorinated at C-8, which was launched several years ago (cf. Chapter 8). Its preparation involves an electrophilic fluorination with CF_3OF[131a] or with an N—F reagent (NFSI)[131b] of 8,9-anhydroerythromycin-6,9-hemiacetal or of erythronolide A. Glycosylations have also been performed by fermentation (Figure 4.57).[131]

Several 2-fluoroerythromycins have been prepared by means of electrophilic fluorination with Selectfluor of the enolate of the β-ketoester fragment.[132] Fluorination is stereoselective and leads to the α-fluoro compound (Figure 4.58). Two derivatives of 2-fluoroerythromycin are in clinical development (*HMR-3562* and *HMR 3787*). These compounds are promising agents to fight respiratory pathogens resistant to erythromycin A (Figure 4.58).[133]

A novel fluorinated erythromycin (16-fluoroerythromycin A) has been produced by *Saccharopolyspora erythraea*, using an ω-fluorobutyrate as precursor of the biosynthesis (Figure 4.59).[134]

4.8.3 Amphotericin B

Amphotericin B (AmB) is a polyenic macrolide used in fungal infections and leishmaniasis, despite severe side effects (Figure 4.60). Fluorination of the macrolide skeleton has been performed using Selectfluor for ^{19}F NMR studies on the mechanism of ion-channel formation in membranes by amphotericin B.[135]

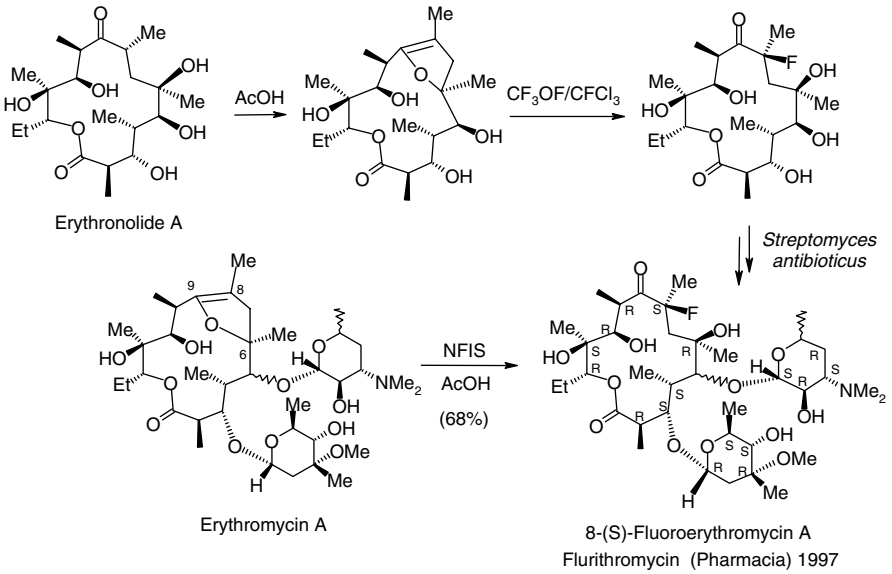


Figure 4.57 Synthesis of flurithromicin (8-fluoroerythromycin).[131]

4.8.4 Avermectin

Avermectin and its derivatives are utilized for their antiparasitic activities in veterinary medicine. They also have anticonvulsant effects. Difluorinated analogues in positions

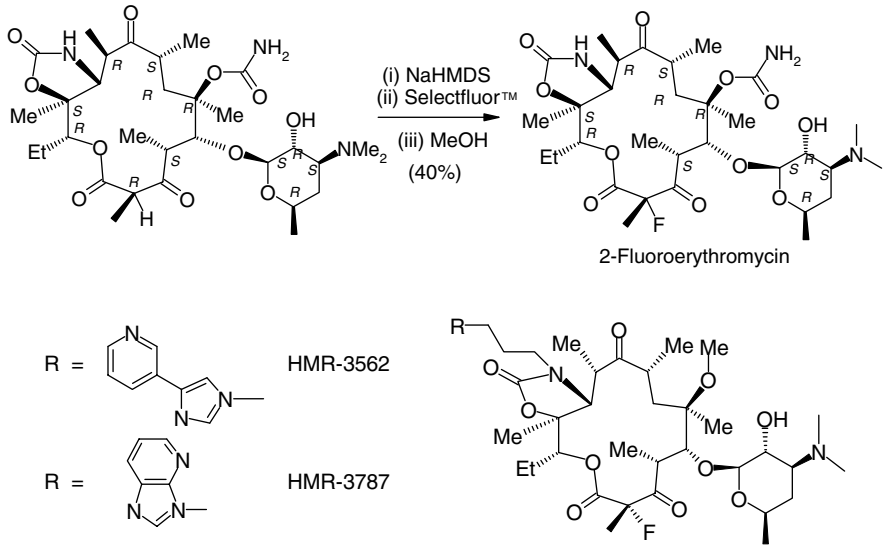


Figure 4.58 Synthesis of 2-fluoroerythromycins.[132, 133]

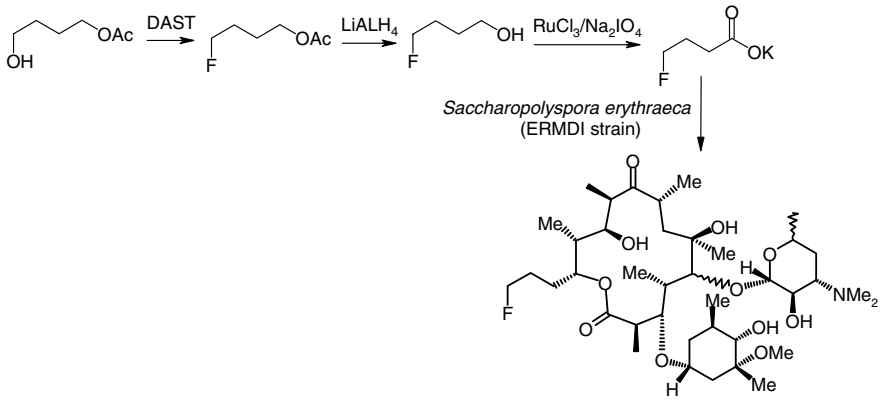


Figure 4.59 Biosynthesis of 16-fluoroerythromycin A by *Saccharopolyspora erythraea* (ERMDI strain).[134]

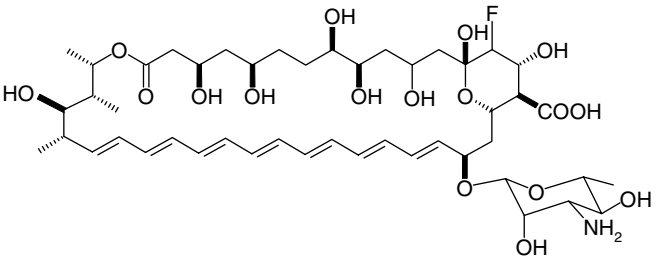


Figure 4.60 Fluorinated derivative of amphotericin B.[135]

4, 4″, 13, and 23 have been synthesized by fluorination of the corresponding ketones with DAST in order to obtain more stable molecules (Figure 4.61). These compounds exhibit *in vivo* activities that are comparable, or even superior, to those of avermectin.[136]

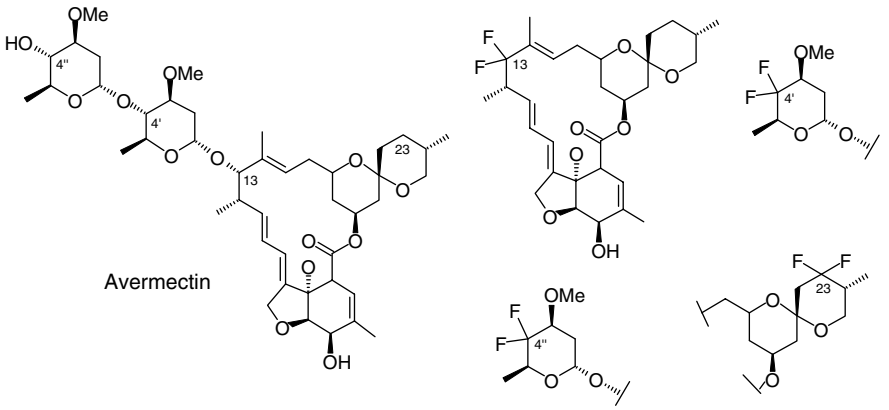


Figure 4.61 Fluorinated derivatives of avermectin.[136]

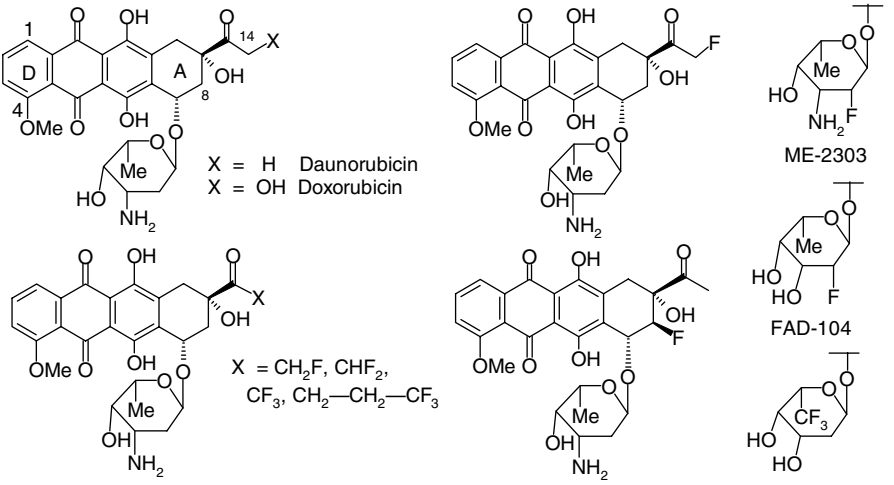


Figure 4.62 Examples of fluorinated anthracyclines.[137–141]

4.9 ANTHRACYCLINES

Anthracyclines are antitumor quinone containing antibiotics produced by different strains of *Streptomyces*. Some of them, such as adriamycin (*doxorubicin*), and *daunorubicin* are broad spectrum antitumor compounds. They act by binding to DNA and interfering with DNA replication and gene transcription. Their limitations for clinical use are cardiac toxicity and drug resistance phenomena.[137, 138] Consequently, intense structure–activity relationship studies have been performed to improve the pharmacological profile as well as to enhance the affinity for DNA. In particular, a number of fluorinated anthracyclines have been prepared with introduction of fluorine atoms into D or A cycles,[139, 140] and into the aglycone side chain linked at C-14.[139]

Fluorination of the aminoglucoside fragment has also been performed to increase its hydrolytic stability (Figure 4.62). Although some compounds reached a preclinical

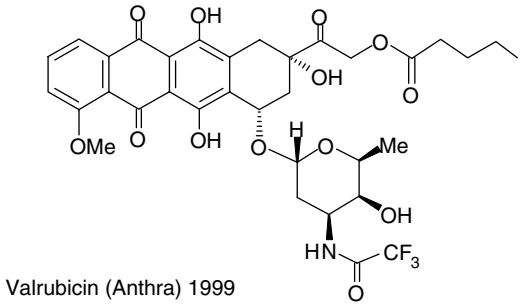


Figure 4.63 Valrubicin.

step of development,[138, 139] only *valrubicine* (trifluoroacetyladriamycin valerate) (Valstar®), which is an ester of adriamycin trifluoroacetylated on the aminoglycosidic fragment, has been fully developed (Figure 4.63) (cf. Chapter 8). It is marketed for the treatment of resistant bladder cancer.

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5

FLUORINATED DERIVATIVES OF α-AMINO ACIDS AND PROTEINS

Fluorination may affect the behavior of α-amino acids toward biological molecules and processes. For instance:

- Interactions with metabolic enzymes: fluorinated amino acids are peptidomimetic units or reactive entities used to design either reversible enzyme inhibitors (analogues of substrates) or irreversible enzyme inhibitors (mechanism-based inhibitors).
- Influence on the conformation, the transport, and the metabolism of peptides and proteins in which they are incorporated.
- Modification of ligand properties (affinity, agonist, or antagonist character) toward amino acid receptors (e.g., excitatory amino acid receptors).
- Effects on the repression of the biosynthesis of endogenic neuroamine when the amino acid is the precursor of this neuroamine.

These effects result from the impact of fluorination on the properties of the peptide at the level of (1) the lipophilicity/hydrophobicity balance and pK_a; (2) the conformation, because of the more demanding volume of the fluorinated moiety; and (3) the hydrolytic and metabolic stability.

Of course, the importance of these different effects depends on the location and nature of the fluorine substitution.

Lastly, when a fluorinated amino acid is incorporated into a peptide or a protein, the fluorine atoms can be used as probes in ^{19}F NMR, and in medical imaging in the case of

Bioorganic and Medicinal Chemistry of Fluorine, by Jean-Pierre Bégué and Danièle Bonnet-Delpon

^{18}F. This provides tools for kinetic and structural studies, as well as for clinical investigations.

The numerous applications of fluorinated amino acids in medicinal chemistry and in enzymology have induced a large number of studies dedicated to their synthesis. Synthetic chemists have provided protein biologists and chemists with an incredible range of fluorinated amino acids. Since this work has been covered in the literature,[1] we only review some representative examples of proteogenic fluorinated amino acid analogues, with special focus on the synthetic aspects proper to fluorine chemistry. The numerous fluorinated peptidomimetic units (e.g., amino alcohols) are not included in this chapter.

First, we consider the fluorinated analogues of natural amino acids, where at least one or several hydrogen atoms have been replaced by fluorine atoms. Then we consider amino acids substituted by a fluoroalkyl group, as the sole structural modification, with special focus on α-fluorinated amino acids. Lastly, we give an outline of polypeptides and proteins in which fluorinated amino acids have been incorporated.

5.1 FLUORINATED ALIPHATIC AMINO ACIDS

5.1.1 Alanines

The antibacterial and antiviral properties of mono-, di-, and trifluoroalanines are connected to their capacity to inhibit, in an irreversible way, many enzymes (cf. Chapter 7).[2] They have been the subject of numerous synthetic studies. We only report on the most recent and significant ones, without detailing the general methods of amino acid chemistry[1a] or the techniques of electrophilic fluorination, which have recently been reviewed.[1b]

Fluoroalanines may be considered α-fluoromethylated glycines. Due to the presence of an acidic hydrogen on the α-carbon, racemization and loss of a fluoride anion are very easy, in contrast to the other α-fluoromethylated amino acids.

Monofluoroalanine is accessible, as a racemate, by means of either classical methods[1a] or fluoromethylation of a masked glycinate anion by a monofluorohalogenomethane (CH_2ClF).[3, 4]

Enantiopure (*S*)-fluoroalanine has been prepared by an enzymatic path starting from 3-fluoropyruvate in the presence of alanine dehydrogenase,[5] and also by chemical synthesis from (*S*)-*p*-tolyl methyl sulfoxide (Figure 5.1)[6] or from the L-serine.[7] The analogue labeled with ^{18}F has been prepared for use in positron emission tomography (PET) used in cancer diagnosis.[8]

Preparations of difluoroalanine have been described. In the first method, the key intermediate is an (*N*,*S*)-acetal, prepared by reaction of ethanthiol with difluoromethyl azalactone (Figure 5.2).[9, 10] A second method involves the alkylation of a glycinate anion by difluorohalogenomethane ($CHClF_2$).[11] This alkylation has also been performed by using CF_2Br_2 as the alkylating agent of the chiral glycinate anion. Further reduction of the bromine with Bu_3SnH affords ethyl (*S*)-difluoroalaninate with an 80% *ee*. Hydrolysis of the ester moiety has not been reported (Figure 5.2).[12]

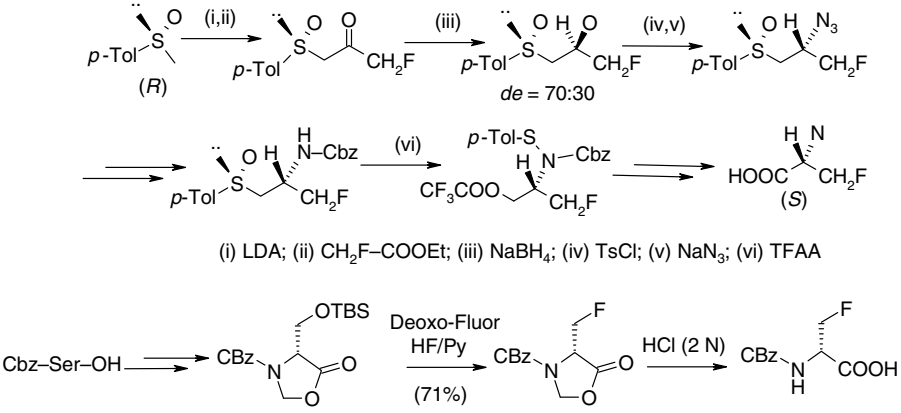


Figure 5.1 Asymmetric synthesis of (*S*)-fluoroalanine.[6, 7]

Trifluoroalanine cannot be prepared by alkylation of a glycine anion with trifluoromethyl halides, since these electrophiles are not able to alkylate enolates. Other approaches have been reported using various substrates, but none is really satisfying. The three main ones are:

1. Introduction of a nucleophilic reagent on a fluorinated substrate, the precursor of the acidic function.[13, 14, 23]
2. Acylation of an *ad hoc* substrate with a fluorinated reagent (e.g., trifluoroacetic anhydride, hexafluoroacetone).[15–17]
3. Reduction of trifluoropyruvate imines.[18–20]

As early as the 1960s, some syntheses based on the addition of nucleophilic reagents (vinyl magnesium bromide, HCN, isonitrile) on *N*-acyl trifluoroacetaldimines (fluoral imine) have appeared. The acidic function is further introduced by an appropriate oxidation or hydrolysis.[13, 14] These approaches have allowed preparation of higher fluoroalkylated homologues of trifluoroalanine and of nonracemic trifluoroalanines (*vide infra*). However, preparation of the acyl imine of fluoral is rather

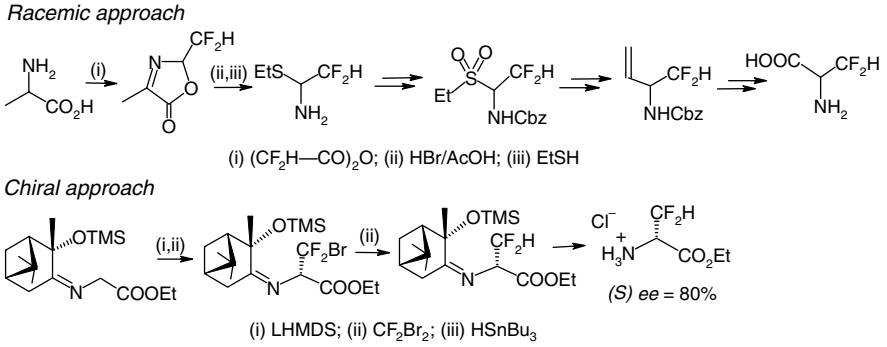


Figure 5.2 Preparation of difluoroalanine.[10, 12]

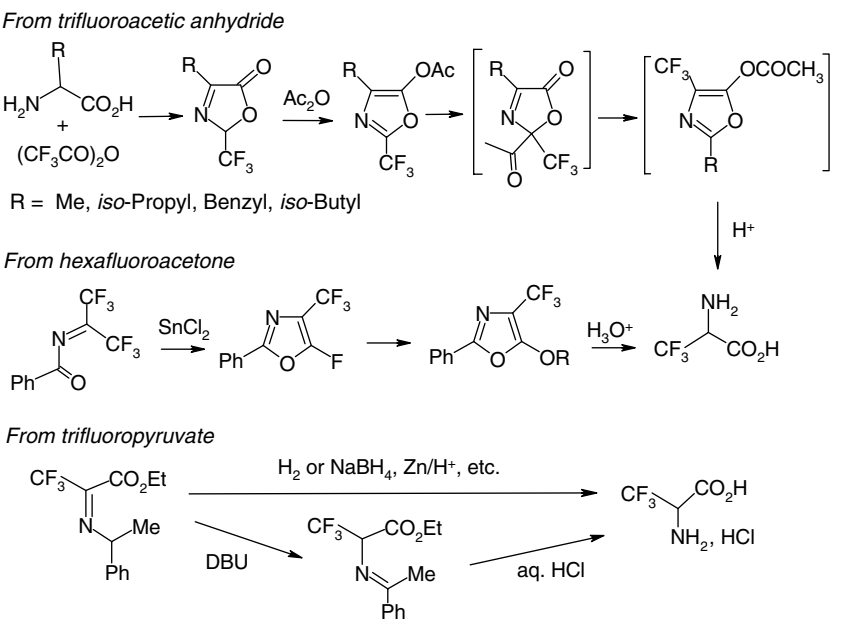


Figure 5.3 Some examples of the synthesis of racemic trifluoroalanine.[15,16,19]

difficult, and some strategies, starting from other precursors, have been refined. For example, trifluoroacetic anhydride reacts with an amino acid to yield trifluoromethyl oxazoline, which leads, after rearrangement, to trifluoroalanine (Figure 5.3).[15] Hexafluoroacetone has also been used: its acylimine is the precursor of trifluoromethyl oxazole, which can be hydrolyzed into trifluoroalanine.[16] Numerous improvements in this procedure have been reported (Figure 5.3).[17]

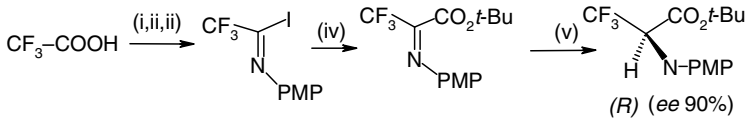
Trifluoroalanine has also been prepared by reducing trifluoropyruvate imines (ethyl trifluoropyruvate is available commercially; it is prepared either from perfluoropropene oxide or by trifluoromethylation of ethyl or *t*-butyl oxalate). These imines are obtained by dehydration of the corresponding aminals or by Staudinger reaction.[1c] They can also be obtained by palladium-catalyzed carbonylation of trifluoroacetamidoyl iodide, an easily accessible compound (cf. Chapter 3) (Figure 5.4).[18] Reduction of the imines affords protected trifluoroalanines. When the imine is derived from α-phenyl ethyl amine, an intramolecular hydride transfer affords the regioisomer imine, which can further be hydrolyzed into trifluoroalanine.[19]

While nonracemic trifluoroalanines can easily undergo racemization or dehydrofluorination, many asymmetric syntheses of trifluoroalanines have been proposed. These syntheses generally involve an asymmetric reduction step of an imine or an enamine. This step can be performed by utilizing either chiral catalysts or chiral auxiliaries.

Asymmetric hydrogenation of imines derived from trifluoropyruvate, in the presence of a chiral complex of palladium (ligand = (*R*)-BINAP), affords ethyl (*R*)-trifluoroalaninate with ca. 90% *ee*.[20] The *ee* values strongly depend on the solvent, and the best results have been obtained with trifluoroethanol. They are far better than those obtained by means of CBS reagent.[18]

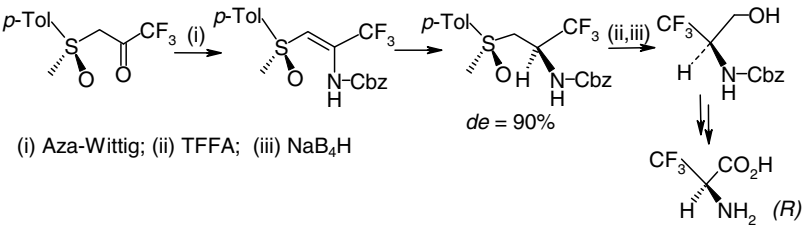
The asymmetric reduction of oximes of 2-trifluoroacetyl furan, by using diborane with a chiral amino alcohol, has also allowed synthesis of both enantiomers of trifluoroalanines in an elegant manner. The key step in this synthesis is the separation of the (*Z*) and (*E*) isomers of the oximes (Figure 5.4).[21]

From trifluoroacetylimidoyl iodide



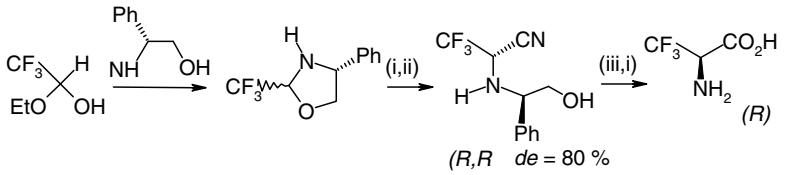
(i) PPh_3, Et_3N; (ii) *p*-anisidine; (iii) NaI/acetone; (iv) $CO,Pd_2(dba)_3$, K_2CO_3; (v) H_2 (100 atm), (*R*)-BINAP, $Pd(OCOCF_3)_2$, TFE, rt, 24 h.

From enantipure p-tolyl methyl sulfoxyde



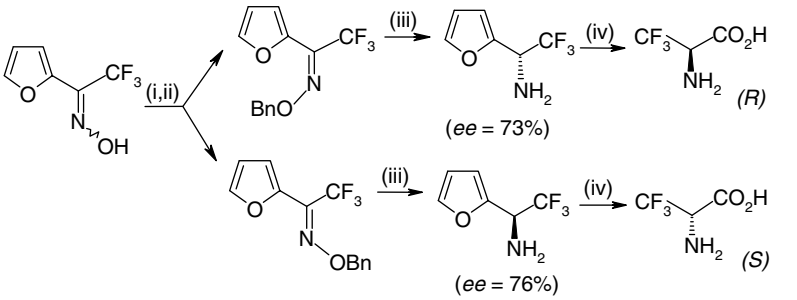
(i) Aza-Wittig; (ii) TFFA; (iii) NaB_4H

From fluoral and phenylglycinol



(i) BF_3,Et_2O; (ii) TMSCN; (iii) $Pb(OAc)_4$; (iv) HCl

From trifluoroacetylfurane



(i) separation; (ii) BnBr; (iii) BH_3/THF, Diphenylprolinol; (iv) O_3/MeOH

Figure 5.4 Asymmetric syntheses of trifluoroalanines.[20–23]

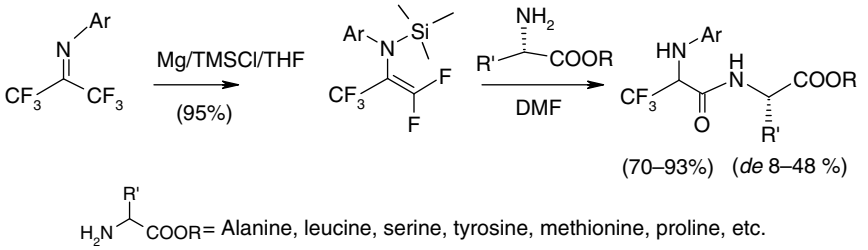


Figure 5.5 Synthesis of trifluoroalanine-containing dipeptides.[27]

Two syntheses of trifluoroalanine involving chiral auxiliaries have also been reported. In the first one, the chiral group is a sulfinyl in the β position of trifluoromethyl enamine. The reduction of the latter occurs with high diastereoselectivity (90% *de*).[22] The second pathway involves a Strecker reaction between TMSCN and the oxazolidine coming from fluoral and phenyl glycinol (80% *de*) (Figure 5.4).[23]

While they are fragile, incorporation of fluorinated alanines into dipeptides has been successfully performed.[24–26] Interestingly, several trifluoroalanine dipeptides have been prepared in an enantiomerically pure form, by addition of amino ester on β,β-difluoroenamines, resulting from the Mg-promoted defluorinative *N*-silylation of *N*-*p*-methoxyphenyl hexafluoroacetone imine (Figure 5.5).[27]

Inhibition of pyridoxal phosphate enzymes by fluoroalanines has been widely studied. Among the numerous examples, alanine racemase,[2, 28, 29] tyrosine phenol lyase,[30] cystathione γ-lyase,[28, 31] and tryptophan indole lyase[31, 32] are particularly relevant (cf. Chapter 7).

Conversely to trifluoroalanine, the homologues (Rf instead of CF_3) can be directly prepared by fluoroalkylation of ethyl glyoxalate imines with perfluoroalkyl lithium (prepared *in situ* by halogen–metal exchange between perfluoroalkyl iodide and methyl lithium) (Figure 5.6).[33] The carbonylation perfluoroalkylimidoyl iodides, previously used for preparation of trifluoroalanine, are also efficient for superior homologues.[18]

5.1.2 Valines, Leucines, and Isoleucines

Amino acids with fluoroalkyl side chains have often been prepared for use in structural studies on the autoassembly of proteins. The presence of a highly hydrophobic substituent on the side chain, such as a fluoroalkyl group, of an amino acid of a polypeptide, may *a priori* deeply influence the interhelical interactions.

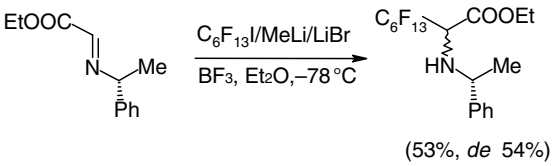


Figure 5.6 Preparation of homologues of trifluoroalanine.[33]

The numerous preparations of mono-, di-, tri-, and hexafluoro derivatives of valine, norvaline, leucine, norleucine, and isoleucine, using classical methods of amino acid chemistry (e.g., amination of an α-bromoacid,[34] azalactone,[35] Strecker reaction,[36, 37] amidocarbonylation of a trifluoromethyl aldehyde,[35] alkylation of a glycinate anion[36] are not considered here. Pure enantiomers are generally obtained by enzymatic resolution of the racemate,[37] chemical resolution,[38] or asymmetric Strecker reaction.[39]

Indium-mediated diastereoselective allylation of L-glyceraldimines with 4-bromo-1,1,1-trifluoro-2-butene provided stereoselectively, after further steps, enantiopure 4,4,4-trifluorovaline or 4,4,4-trifluoroisoleucine.[40] Enantiopure hexafluorovalines have been prepared by separation of the diastereomeric mixture resulting from the Michael addition of a chiral amine onto an ester of bis(trifluoromethyl) acrylic acid. Presence of the two CF_3 groups reverses the orientation of the Michael addition (Figure 5.7).[41, 42]

(*S*)-Hexafluoroleucine has been prepared from hexafluoroacetone by a Wittig–Horner reaction. Reduction of the carbonyl of the α-keto ester with baker's yeast yields the alcohol with *R* configuration. This latter is further transformed into amine. A second approach involves a Wittig reaction between Garner's aldehyde and Middleton's phosphorane. Reduction of the double bond, followed by oxidation of the alcohol function, affords hexafluoroleucine. A third synthesis has been performed starting from L-serine and hexafluoroacetone (Figure 5.8).[43–45] Despite the presence of three carbons between the CF_3 group and the amine function, the pK_a is lowered by two units.[43] The fluorous effect and the helix propensity of hexafluoroleucine incorporated in proteins will be evoked in Section 5.5.2.

(*S*)-γ-Fluoroleucine has been prepared from ethyl glyoxylate, using a Ti/Zn-catalyzed asymmetric glyoxylate-ene reaction (Figure 5.9).[46]

Nonbranched amino acids substituted by a fluoroalkyl chain on a carbon distant at least one methylene from the amino acid function have been prepared as racemates by various methods.[47, 48] Under nonracemic form, ω-perfluoroalkyl norvaline and norleucine ($Rf = C_2F_5$ or more) have been prepared by bromination of an anion of a fluorinated chiral oxazolidinone (derived from $RfCH_2CH_2CO_2H$). Substitution of the bromine atom by an azide and subsequent reduction yield the desired amino acids (Figure 5.10).[49]

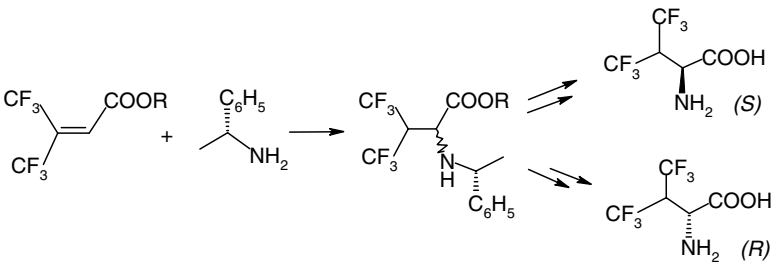
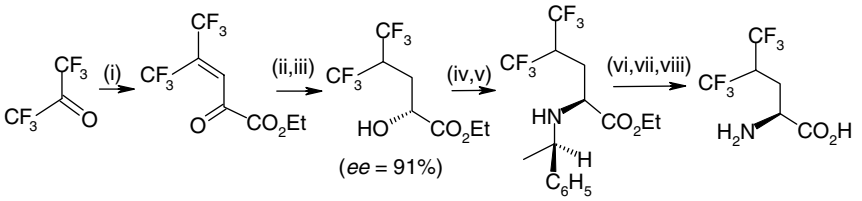
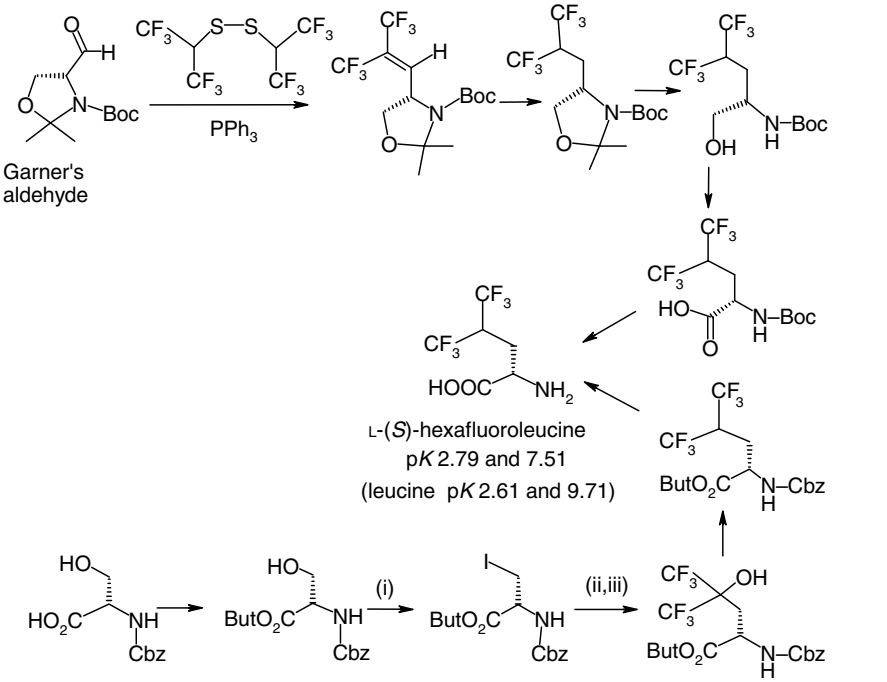


Figure 5.7 Preparation of hexafluorovaline.

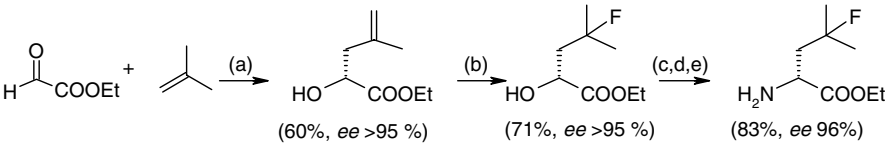


(i) Triphenylphosphoranylidene ethyl pyruvate; (ii) H_2 Pd/C; (iii) Baker's yeast; (iv) Tf_2O; (v) Phenethylamine; (vi) H_2, Pt/C; (vii) HCl 6N; (viii) Propylene oxide



(i) $(PhO)_3PMeI$; (ii) Zn, $CuBr{\cdot}SMe_2$; (iii) CF_3COCF_3

Figure 5.8 Syntheses of (*R*)- and (*S*)-hexafluoroleucines.[44, 45]



(a) $TiCl_2(OiPr)_2$/(*R*)–BINOL/$ZnCl_2$/MS 4A; (b) HF–Py; (c) Tf_2O, Lutidine; (d) $BnNH_2$; (e) $H_2/Pd(OH)_2$

Figure 5.9 Synthesis of (*S*)-γ-fluoroleucine.[46]

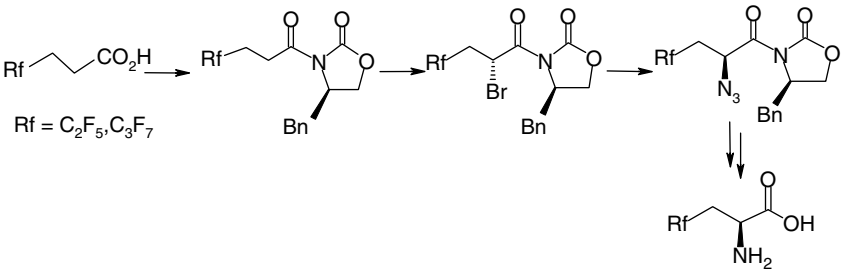


Figure 5.10 Synthesis of perfluoroalkyl nor-(*S*)-valines and nor-(*S*)-leucines.

5.1.3 Prolines

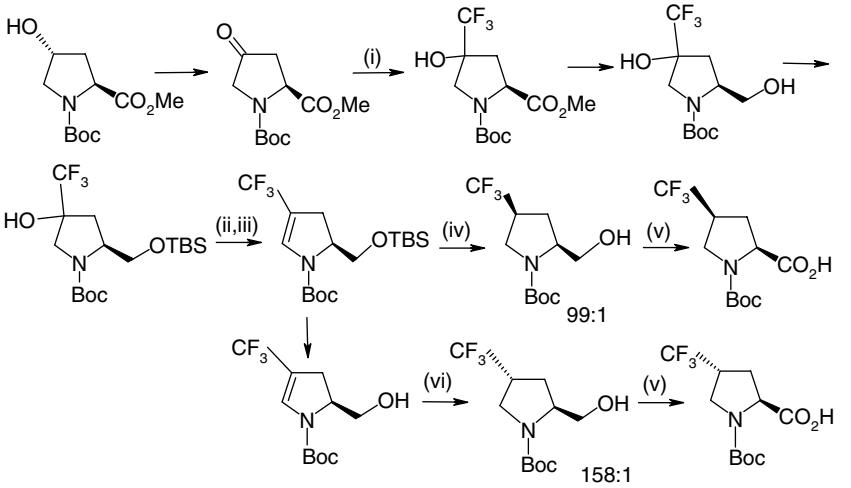
Most of the fluoro derivatives of proline described in the literature are fluorinated in the 4 position. 4-Fluoroprolines are able to mimic 4-hydroxyproline, present in some proteins and polypeptides. On the other hand, 4-fluorination could suppress oxidative metabolism or modified ring conformation of ligands.[50] The ^{18}F labeled analogues may be used as probes in PET (positron emission tomography) for localization of tumors.[51]

4-Monofluoroproline has been prepared by various methods, especially by using DAST on 4-hydroxyproline.[52] 4,4-Difluoroproline is also available by treatment of the corresponding ketone with DAST.[53a] This latter has been prepared with a good *ee* starting from ethyl (*R*)-bromodifluoroalaninate.[53b]

Selective synthesis of the *cis*- and *trans*-4-trifluoromethyl L-prolines is at the center of several synthetic problems. They have been resolved using selective and asymmetric hydrogenations of pyrrolines. A key step is the regioselective dehydration of 4-trifluoromethyl prolinol, which has been selectively oriented toward the Δ-4 position by treating the corresponding tosylate with *t*-BuOK. Reduction of the double bond occurs with good facial diastereoselectivity and leads to *cis*-CF_3-proline. Access to the *trans* compound has been more difficult: it has been solved by performing a hydrogenation oriented by the hydroxyl group. Thus, hydrogenation of the double bond has been performed after the primary hydroxyl is set free. In heterogeneous catalysis, the selectivity is low, while using the Crabtree catalyst (homogeneous catalysis) facial selectivity is excellent (*trans* 99.9%) (Figure 5.11).[54]

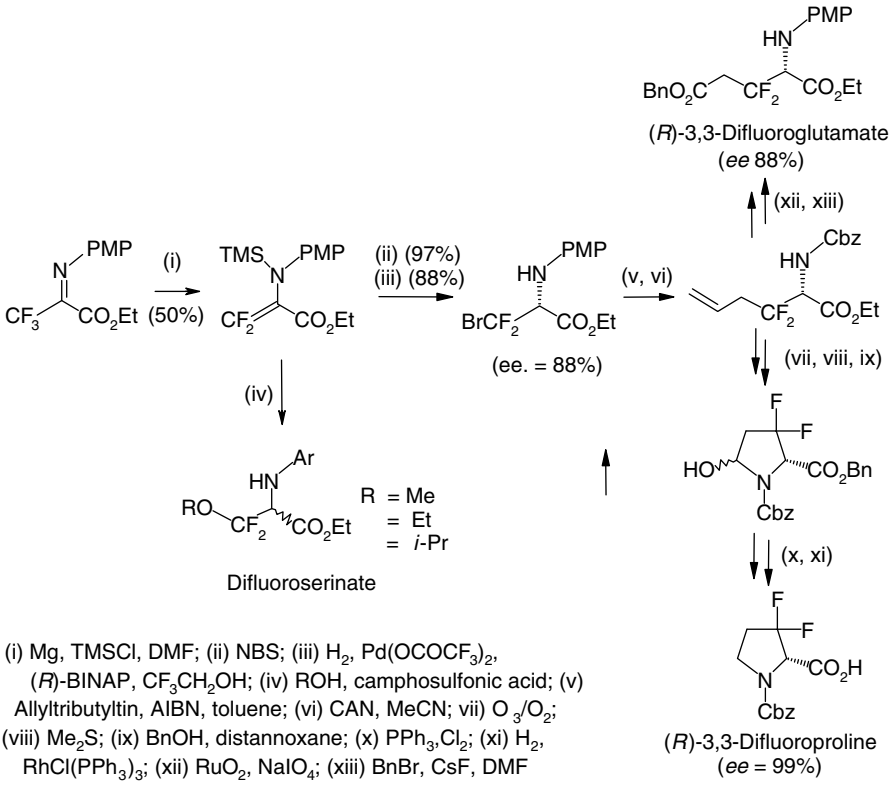
Difluoromethyl proline has been prepared by a related approach.[55] Synthesis of *cis*- and *trans*-4-trifluoromethyl-D-prolines has been performed starting from the Garner aldehyde.[56] 4-Trifluoromethyl, difluoromethylene, or difluoromethyl prolines could also be prepared by 5-*endo-trig* cyclization of *N*-(homoallyl)-sulfonamides.[57]

The chemistry of difluoroenamines allows an elegant asymmetric synthesis of 3, 3-difluoroproline. *gem*-Difluoroenaminoester, resulting from the reductive cleavage of a C—F bond of an imine of ethyl trifluoropyruvate, is selectively reduced, after addition of a bromine, into bromodifluoroalanilate. Radical allylation leads to a difluoroallyl amino acid. This latter is the precursor of both (*R*)-3,3-difluoroproline and (*R*)-3,3-difluoroglutamic acid (Figure 5.12).[58]



(i) $TMSCF_3$; (ii) TsCl, NaH, THF; (iii) *t*-BuOK, THF, –40 °C; iv) H_2 (1 atm), Pd/C, EtOAc; (v) NaClO, $NaClO_2$, TEMPO, CH_3CN, pH 6,7; (vi) H_2 (1 atm), $[Ir(cod)(py)PCy_3]$

Figure 5.11 Synthesis of *cis*- and *trans*-4-trifluoromethyl prolines.[54]



(i) Mg, TMSCl, DMF; (ii) NBS; (iii) H_2, $Pd(OCOCF_3)_2$, (*R*)-BINAP, CF_3CH_2OH; (iv) ROH, camphosulfonic acid; (v) Allyltributyltin, AIBN, toluene; (vi) CAN, MeCN; vii) O_3/O_2; (viii) Me_2S; (ix) BnOH, distannoxane; (x) PPh_3,Cl_2; (xi) H_2, $RhCl(PPh_3)_3$; (xii) RuO_2, $NaIO_4$; (xiii) BnBr, CsF, DMF

Figure 5.12 Synthesis of difluoroproline, difluoroglutamate, and difluoroisoserinate.[58, 69]

5.2 AROMATIC AMINO ACIDS: PHENYLALANINE, TYROSINE, HISTIDINE, AND TRYPTOPHAN

Aromatic amino acids are biogenetic precursors of neuroamines (dopamine, serotonin, histamine, etc.). On the other hand, phenylalanine (Phe) is frequently present in peptide sequences, while tyrosine is an important site of phosphorylation of proteins. Aromatic amino acids and neuroamines fluorinated on the aromatic ring have been the focus of many investigations. Indeed, after incorporation in polypeptides and proteins, they can be used as probes in ^{19}F NMR and in ^{18}F PET.

These compounds can be prepared by using either classical processes for synthesis of amino acids (starting from the *ad hoc* precursor bearing fluorine on the aromatic moiety)[1a] or electrophilic fluorination of the arene moiety (e.g., elemental fluorine, xenon fluoride, acetyl hypofluorite). Although these methods are often poorly regioselective, they are useful for the preparation of ^{18}F labeled molecules used in PET, for example, ^{18}F tyrosine and dihydrophenylalanine (L-Dopa).[1d, 59]

Nonracemic compounds are accessible either by resolution or by enzymatic synthesis with a transaminase, for example, starting from fluorophenylpyruvic acid.[60] They can also be prepared by asymmetric synthesis. The alkylation reaction of equivalents of chiral glycinate anions is very efficient and diastereoselective, due to the presence of the π-system on the aromatic ring (Figure 5.13).[61–63] For example, these methods have allowed preparation of 2-, 5-, 6-, and 2,6-difluoro-L-Dopa, which are useful in studies on the mechanism of decarboxylation of dopa into dopamine.[64]

Compounds substituted on the aromatic ring by a fluoroalkyl group are prepared by classical ways from a fluoroalkyl aromatic precursor or by fluoroalkylation of the aromatic ring. Trifluoromethylation of L-*N*-trifluoroacetyl tyrosine has been performed by irradiation in the presence of trifluoromethyl iodide. The major compound is trifluoromethylated in the 3 position. In the case of histidine, trifluoromethylation is poorly regioselective.[65] Fluoroalkyl ethers of tyrosine have been prepared either starting from *O*-fluoroalkyl benzyl derivatives by using the azalactone method,[66a] or

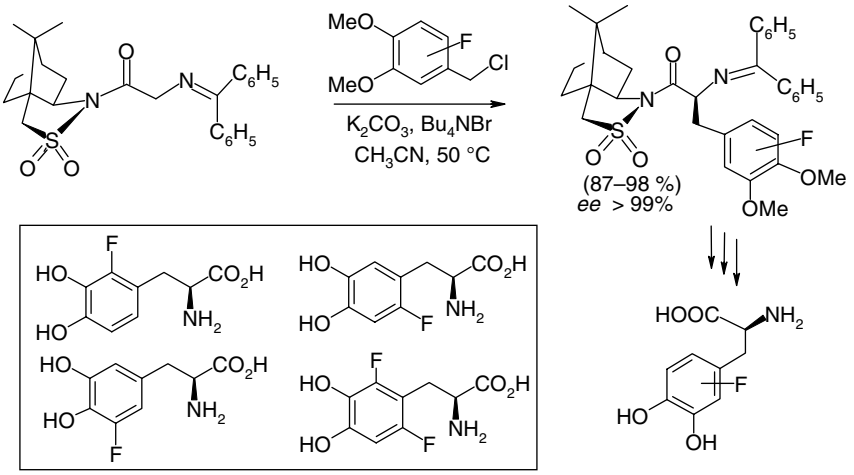


Figure 5.13 Synthesis of nonracemic fluorodopa.[64]

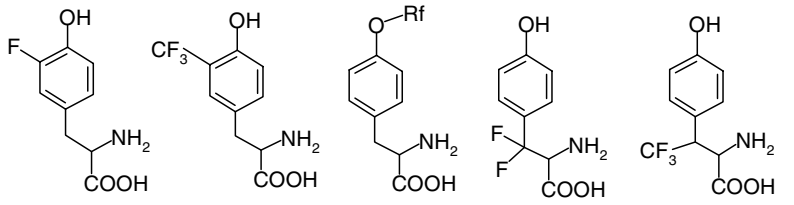


Figure 5.14 Examples of fluorotyrosines.

by *O*-fluoroalkylation of L-tyrosine with a perfluoroalkyl halide. However, partial racemizations have been observed in these reactions.[66a]

Enantiopure β,β-difluorophenylalanine has been prepared from α-phenyl-α, α-difluoroacetaldehyde by a Strecker reaction.[66b]

Racemic β-fluoroalkyl tyrosines and phenylalanines have been prepared by classical methods starting from the corresponding fluoroacetophenones. Synthesis of the nonracemic compounds is much more difficult, as exemplified by the preparation of β-difluoromethyl *meta*-tyrosines (Figure 5.14).[67] β-Trifluoromethyl tryptophan is prepared by alkylation of ethyl acetamido malonate with indolyl-2,2-trifluoroethanol. Surprisingly, the decarboxylation reaction leads stereoselectively to the *syn* isomer (Figure 5.15).[68]

Inhibition of enzymes by fluorinated derivatives of tyrosine have been the focus of many investigations. The inhibition of tyrosine phenol lyase,[21] of

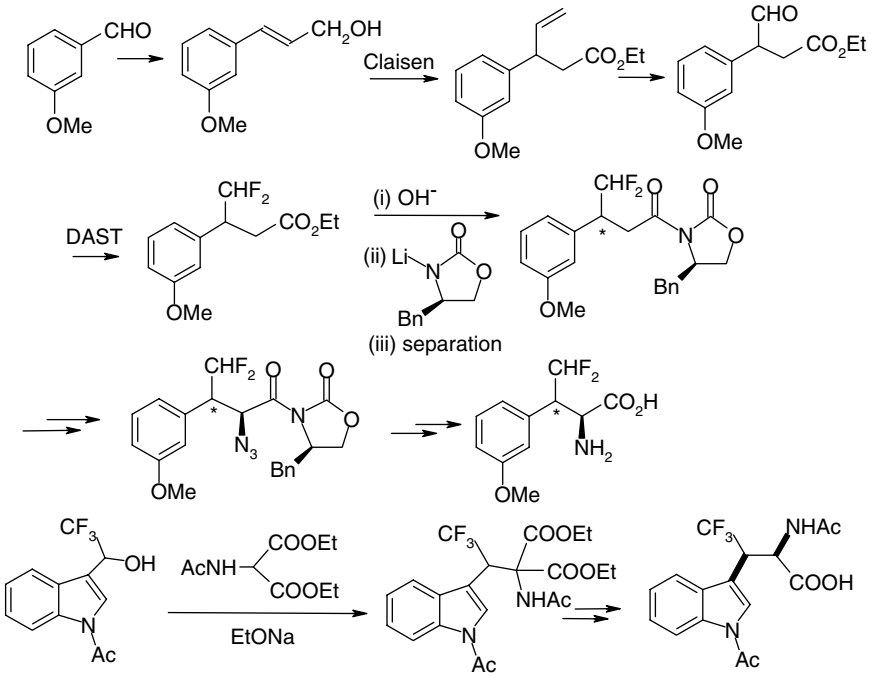


Figure 5.15 Preparation of β-CF_2H-tyrosine and of β-CF_3-*N*-acetyltryptophan.[67, 68]

tyrosine hydroxylase,[69] and of the amino acid decarboxylase can be cited as examples.[70]

5.3 FUNCTIONAL FLUORINATED AMINO ACIDS

5.3.1 Serines and Threonines

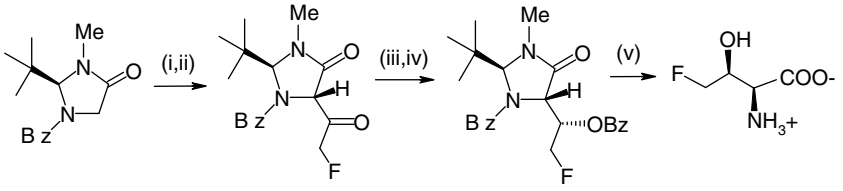
Difluoroserine is unstable, but some *O*- and *N*-protected derivatives of ethyl difluoroserinate have been prepared. As for trifluoroalanine, a good precursor is ethyl trifluoropyruvate. Synthesis is based on the addition of an alcohol on *gem*-difluoroenamine, resulting from the reductive cleavage of a C—F bond of an imine of ethyl trifluoropyruvate (cf. Chapter 2) (Figure 5.10).[71]

(2*S*,3*S*)-4-Trifluorothreonine is one of the rare fluorinated compounds found in nature (cf. Chapter 4).[72] The best method for the synthesis of fluorothreonines is the acylation of an equivalent of glycinate anion by a fluoroacetic derivative. The four stereoisomers of monofluorothreonine have been prepared.[73, 74] A completely stereoselective chiral approach involves the alkylation of the Seebach imidazolidinone by fluoroacetyl chloride (Figure 5.16).[75]

Reduction of a β-aminoketone resulting from the addition of an equivalent of a glycinate anion on ethyl difluoro- or trifluoroacetate is stereoselective and leads to ethyl di- or trifluorothreoninate *threo* (*syn*). Release of the acid, performed by saponification, is accompanied by a partial epimerization into an *allo* compound.[73] However, the amino acids are obtained in enantiopure forms by using a lipase.[76, 77]. It's important to note that (2*S*,3*S*)-difluorothreonine exhibits activity toward the growth of leukemia cell lines comparable to 5-fluorouracil.[77]

Fluoral has been condensed with an equivalent of chiral glycinate anion.[78] The chirality stems from a chiral nickel complex with a chiral Schiff base derived from proline as ligand (Figure 5.17). (2*S*,3*S*)-Difluorothreonine has thus been obtained with an excellent selectivity ($de > 95\%$). This method also allows preparation of numerous fluoroalkyl and fluoroaryl analogues of threonine.[78] Enantiopure difluorothreonine could also be prepared from ascorbic acid.[79]

A straightforward enantioselective synthesis of *allo*-difluorothreonine is based on a three component Petasis reaction (enantiopure difluorolactic aldehyde,



(i) LDA, –100 °C; (ii) FCH_2COCl; (iii) $NaBH_4$; (iv) BzCl; (v) H^+

Figure 5.16 Asymmetric synthesis of (2*S*,3*S*)-4-fluorothreonine.

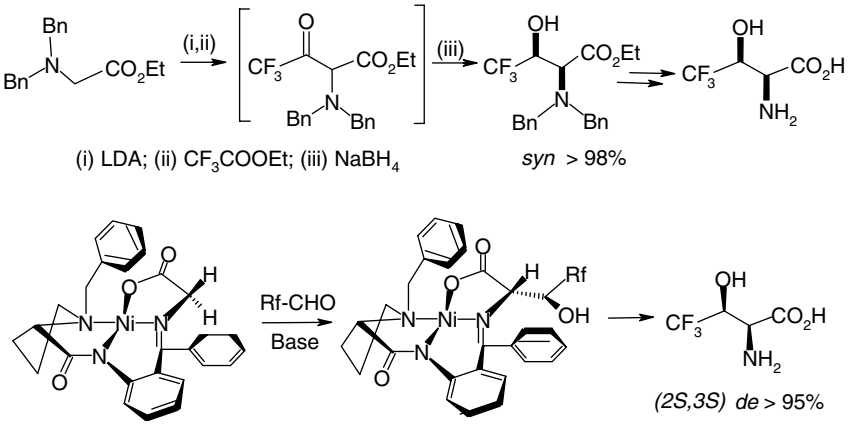


Figure 5.17 Preparations of trifluorothreonine.[73, 78]

2-furylboronic acid, and diallylamine). The obtained amino alcohol affords *allo*-(2*S*,3*R*)-difluorothreonine after oxidation of the furan cycle (Figure 5.18).[80]

5.3.2 Aspartic Acids and Arginines

Aspartic acid and arginines are important substrates for the biosynthesis of purine bases. They are also glycosylation sites in proteins. These reasons have been at the origin of the synthesis of their mono and difluoro analogues.

Difluoroaspartic acid has been prepared by electrophilic fluorination of di-*tert*-butyl 2-ketosuccinate. The amino group is further introduced via an oximation reaction, followed by a reduction.[81] Difluoroaspartic acid may be converted further into difluoroasparagine (Figure 5.19).

Monofluoroaspartic acids and monofluoroasparagines have been prepared as racemates via different pathways.[82, 83] For example, dehydrofluorination of difluor-

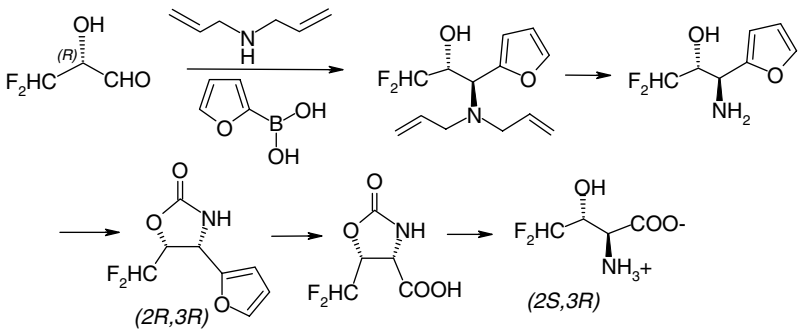


Figure 5.18 Preparation of *allo*-(2*S*,3*R*)-difluorothreonine.[80]

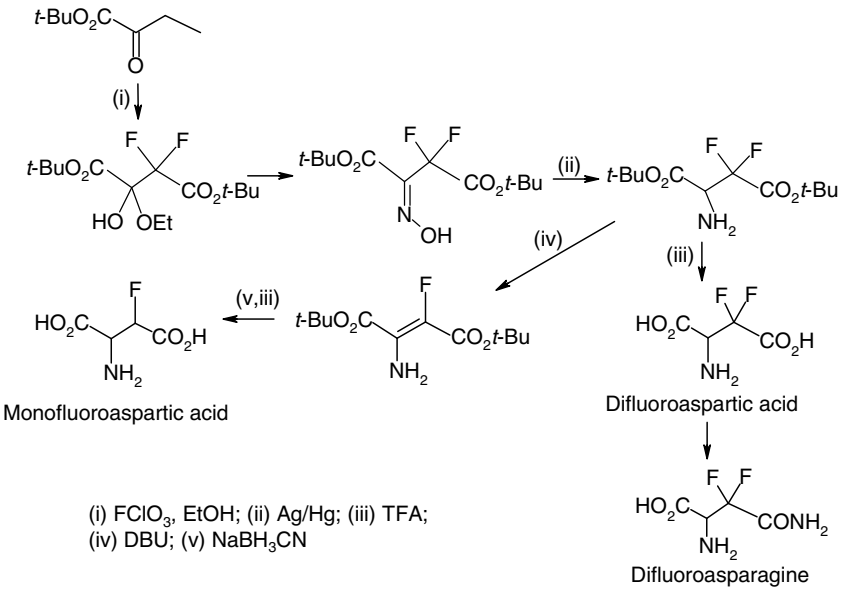


Figure 5.19 Synthesis of 3-mono- and 3,3-difluoroaspartic acids and difluoroasparagine.[81, 82]

oaspartic acid, followed by a reduction, has been described (Figure 5.19).[81] They have been prepared as pure enantiomers starting from tartaric acid derivatives (Figure 5.20).[83]

The cytotoxicity of fluoroaspartic acids and of fluoroasparagines, their inhibition of the biosynthesis of purines and of the glycosylation of proteins, as well as the inhibition

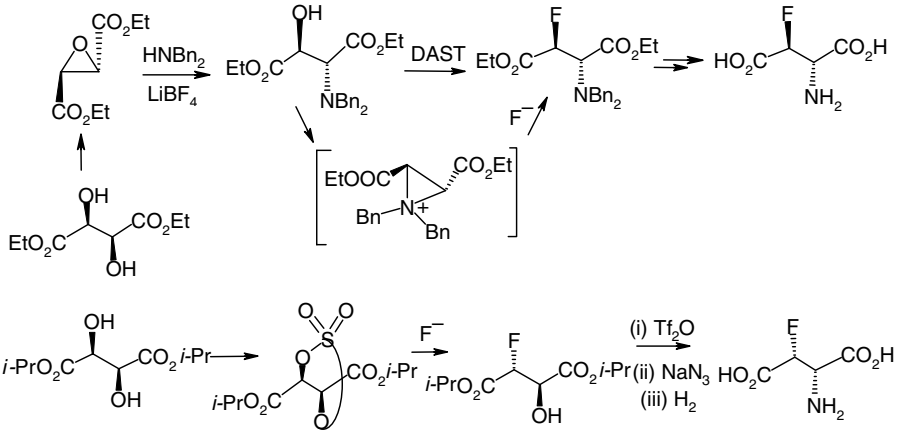


Figure 5.20 Asymmetric synthesis of *syn*-(2*R*,3*S*)- and *anti*-(2*R*,3*R*)-3-fluoroaspartic acids.

of the adenylsuccinate lyase and amino transferases have been the topic of several studies.[82–85]

5.3.3 Glutamic Acids and Glutamines

Glutamic acid and glutamine are the main sources of nitrogen in transamination and amide transfer processes involved in the biosynthesis of biological molecules or macromolecules. Glutamic acid intervenes in the biosynthesis of the conjugated poly-γ-glutamyl of folates and, consequently, in the biosynthesis of DNA. These biological activities have been the reason for numerous syntheses of their fluorinated analogues.

The four stereomers of 4-fluoroglutamic acid have been prepared from 4-hydroxyproline.[86] 4,4-Difluoroglutamic acid and 4,4-difluoroglutamine have been synthesized by an aldol-type condensation between ethyl nitroacetate and the hemiketal of difluoroaldehyde.[87, 88] By analogy with a previous method described for the preparation of 4-difluoro-L-arginine (*vide infra*), the Reformatsky reagent of bromodifluoroacetate has been condensed with the Garner aldehyde. The adduct affords L-4,4-difluoroglutamine after radical deoxygenation of the hydroxyl (Barton–McCombie reaction).[89–91]

The electrophilic fluorination of chiral bicyclic lactams (prepared from the epimers of pyroglutamic acid) by means of *N*-fluoro sulfonimide (NFSI) yields L- and D-4, 4-difluoroglutamic acids and 4,4-difluoroglutamines (Figure 5.21).[92] They have also been prepared with a good *ee* starting from ethyl (*R*)-bromodifluoroalaninate.[53b]

3,3-Difluoroglutamic acid has been prepared by fluorination of the carbonyl of a proline derivative (Figure 5.22).[93] An elegant chiral synthesis involves the alkylation of a chiral glycinate anion by bromodifluoromethane. The radical substitution with allyl tributyltin, followed by oxidation of the double bond, affords (*S*)-3,3-difluoroglutamic acid with a 95% *ee* (Figure 5.22).[12] This latter compound can be prepared from the imine of trifluoropyruvate (98% *ee*, Figure 5.12).

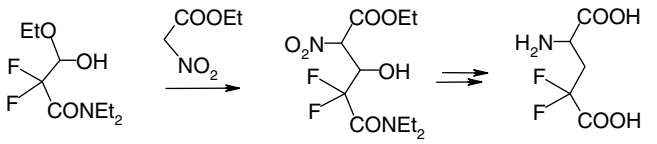
The mono- and difluoro analogues of glutamic acid are interesting probes for studying the biochemistry of folates and the cytotoxicity of antifolates. Thus, fluorinated analogues of tetrahydrofolic acid and of methotrexate have been prepared in order to study inhibition of folylpolyglutamate synthase (FPGS) and of dihydrofolate reductase (DHFR) (Figure 5.22).[31, 87, 93]

5.3.4 Lysine, Ornithine, and Arginine

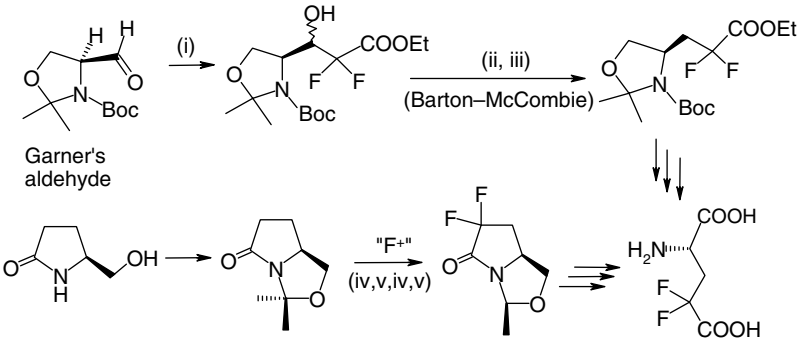
Little work has been done in the field of fluorinated lysines: 5-fluorolysine has been prepared by fluorination of lysine with CF_3OF/HF under UV irradiation,[94] while preparation of 5,5-difluorolysine has been described by treatment of a suitable carbonyl precursor by SF_4.[95]

In contrast, the 4-mono- and 4,4-difluoro analogues of ornithine have been the focus of many investigations. They are accessible starting from the corresponding fluoroglutamic derivatives.[96]

Synthesis of DL-4,4-difluoroglutamic acid



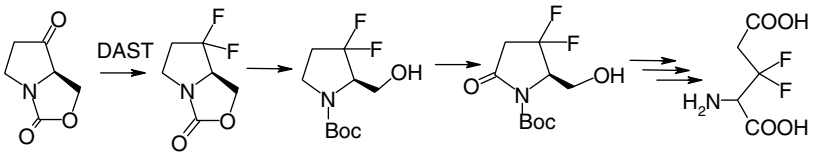
Synthesis of L-4,4-difluoroglutamic acid



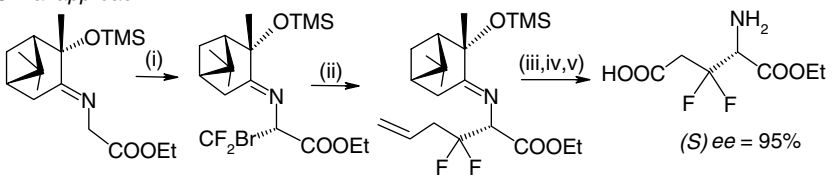
(i) $BrCF_2COOEt$, Zn; (ii) $(Im)_2C{=}S$; (iii) Et_3SiH, Bz_2O_2, $ZnBr_2$; (iv): LDA; (v) NFSI

Figure 5.21 Preparation of 4,4-difluoroglutamic acids.[89–92]

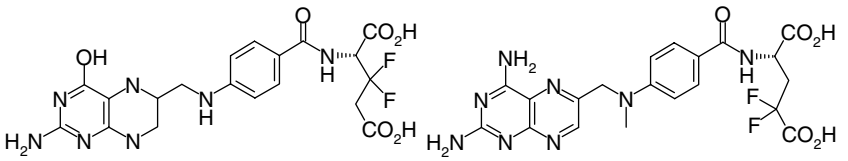
Racemic approach



Chiral approach

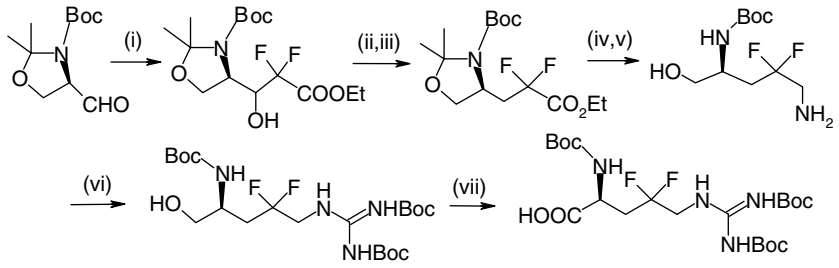


(i) CF_2Br_2, LHMD; (ii) $AllylBu_3Sn$; (iii) H^+; (iv) Boc_2O; (v) RuO_2,$NaIO_4$



3,3-Difluorotetrahydrofolic acid 4,4-Difluoromethotrexate

Figure 5.22 Synthesis of 3,3-difluoroglutamic acid.[12, 93]



(i) Zn, $BrCF_2COOEt$; (ii) $(Im)_2C{=}S$; (iii) Et_3SiH, BzO_2, $ZnBr_2$; (iv) NH_3; (v) RedAl; (vi) N,N'-bis(TBuOOC)thiourea, $HgCl_2$, Et_3N, DMF; (vii) CrO_3—Py/DMF

Figure 5.23 Synthesis of difluoro-L-arginine.[97]

The fluorinated derivatives of arginine can be prepared from fluoroornithines. 4, 4-Difluoro-L-arginine has been synthesized by reacting Garner's aldehyde with the Reformatsky reagent of ethyl bromodifluoroacetate (Figure 5.23).[97] This approach has been applied further to the synthesis of 4,4-difluoroglutamic acid (*vide supra*).[89–91]

5.3.5 Cysteines and Methionines

3,3-Difluorocysteine, like 3,3-difluoroserine, is unstable. However, a protected derivative has been described.[71] Conversely, 3,3-difluoro-L-homocysteine and 3, 3-difluoro-L-methionine are much more stable. They are prepared from difluoro-homoserine. This latter is prepared through a multistep synthesis starting from isoascorbic acid (Figure 5.24).[98]

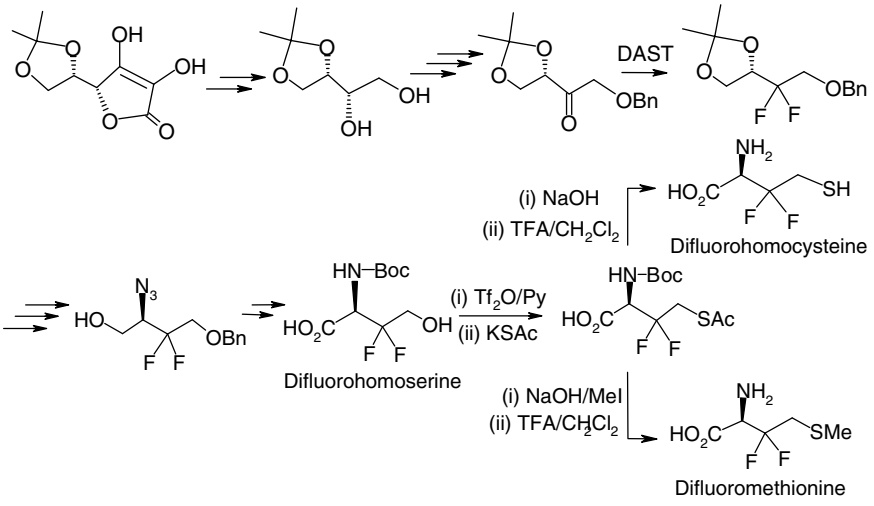


Figure 5.24 Synthesis of difluoro-L-homocysteine and difluoro-L-methionine.[98]

Numerous *S*-fluoroaryl or *S*-fluoroalkyl derivatives of cysteine have been described. Thus, fluorination of *S*-benzyl cysteine has been performed with XeF_2.[98] The photochemical trifluoromethylation of cysteine, or of its disulfide, affords optically pure *S*-trifluoromethyl cysteine.[99] Some electrophilic halogenated compounds (such as trifluorochloroethylene) are able to achieve the *S*-fluoroalkylation of cysteine.[100] As the bioactivation of halons may afford electrophilic compounds that may react with the thiol moiety of cysteines included in proteins, the in vivo toxicity of these adducts has been studied.[101]

S-Mono-, di-, and trifluoro derivatives of methionine and *S*-fluoroalkyl derivatives of cysteine are accessible through fluorination. Thus, fluorination of methionine sulfoxide with xenon fluoride,[99] or more easily using DAST, provided *S*-monofluoromethionine.[102] Photochemical trifluoromethylation of homocysteine leads to *S*-trifluoromethionine.[99] These *S*-fluoroalkyl compounds are also available through fluoroalkylation of homocysteine. Thus, the addition of difluorocarbene (formed from Freon 11 (CHF_2Cl)) affords *S*-difluoromethionine.[103]

Numerous nonproteogenic α- or β-fluorinated amino acids and amino alcohols have been prepared as peptidomimetic units. Unfortunately, due to lack of space, they have not been included in this book. Recent reviews have been dedicated to some of these compounds.[1h, 104]

5.4 α-FLUOROALKYL AMINO ACIDS

α-Fluoromethylated (CH_2F, CHF_2, CF_3) amino acids form an important class of compounds, which is relatively homogeneous on the level of synthesis and biological properties. The presence of a substituent in the α position of an amino acid induces conformational restrictions in the peptides into which it is introduced. Moreover, due to the tetrasubstitution of the carbon, enolization is prevented and the subsequent steric hindrance increases the hydrolytic stability of the peptidic bond. These effects are enhanced if the substituent is hydrophobic and bulky, such as a fluoroalkyl group. Thus, lipophilicity and metabolic stability are enhanced, and secondary structures of the peptides are strongly disturbed.

Due to the absence of a hydrogen atom on the α-carbon, the α-fluoroalkyl amino acids (except, of course, the fluoroalanines, *vide supra*) cannot undergo an elimination of HF. Consequently, they are more stable than fluoroalanines and other β-fluoro amino acids previously described. On the other hand, similar to proteogenic amino acids, β-fluoro amino acids and α-fluoroalkyl amino acids are generally substrates of pyridoxal phosphate depending on enzymes such as racemases and decarboxylases. When an amino acid is a substrate of such enzymes, the enzyme induces the development of a negative charge on the α-carbon, which can initiate a β-elimination process. This reaction affords an electrophilic species (Michael acceptor type), which is able to add a nucleophilic residue of the enzyme. This notion of mechanism-based inhibitor is detailed in Chapter 7.

Generally, the α-fluoroalkyl amino acids cannot be prepared by means of classical methods. Thus, original methods for their synthesis have been required and set up.[1e]

5.4.1 Mono- and Difluoromethyl Amino Acids

Preparation of α-monofluoromethyl amino acids is not easy. Indeed, although the amino acids can easily be hydroxymethylated, substitution of the hydroxyl by a fluorine atom is not always easy (SF_4, DAST). On the other hand, preparation of monofluoroketones (substrates of the Strecker reaction) involves the use of highly toxic fluoroacetonitrile.[105]

As for the mono- and difluoroalanines, fluoroalkylation of the anion of a masked amino acid by a halogenofluoromethane (CH_2ClF, $CHClF_2$, or $CHBrF_2$) is the most general process for the preparation of an α-mono or α-difluoromethyl amino acid. It is worth noting that dichlorofluoromethane ($CHCl_2F$) is often used for the preparation of monofluoro amino acids. This reagent is more reactive than monochlorofluoromethane (CH_2ClF). However, the radical reduction of the chlorine is then a supplementary step (Figure 5.25).[106, 107] As the chirality of the amino acid is lost during formation of the enolate, preparation of nonracemic compounds requires the presence of a chiral auxiliary, such as a Seebach imidazolidinone (Figure 5.25).[108]

α-Fluoromethyl and α-difluoromethyl alanines, tyrosines, phenylalanines, tryptophans, ornithines, and aspartic acids are accessible through this pathway. The derivatives of these amino acids (and of others like the ones of glutamic acid) can also be synthesized by functional modification of a precursor of fluoroalkyl amino acid, as illustrated with the examples in Figure 5.23.[109]

The ban of halogenofluoromethanes (halons) for environmental reasons may reduce the benefit of this straightforward method, at least on the industrial level. Difluoromethyl ornithine (DFMO) was prepared industrially by this path (alkylation with $CHClF_2$). New approaches are currently the focus of research in order to restart its production.

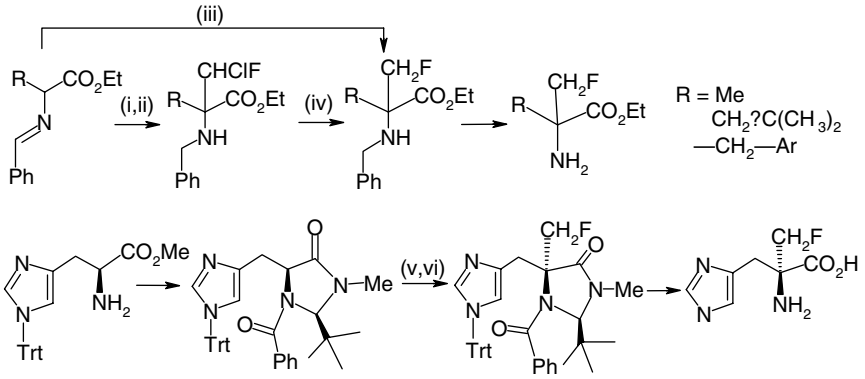
Mono- and difluoromethylation involving the halogenofluoromethanes can be performed on malonic esters. A Curtius reaction, further performed on only one of the ester functions, leads to α-fluoromethyl amino acid (Figure 5.26).[110]

5.4.2 α-Trifluoromethyl Amino Acids

5.4.2.1 Preparation of α-Trifluoromethyl Amino Acids Since trifluoromethylation of an enolate, derived from an amino acid, by a trifluoromethyl halide is impossible (*vide supra*), the inverse process has been used: the alkylation of a fluorinated substrate by a nonfluorinated reagent. Thus, alkylation or arylation by means of organometallic reagents derived from acyl- or sulfinylimines (starting from trifluoromethyl pyruvate) is a general approach to trifluoromethyl amino acids.[111, 112] Many saturated, alkenyl, alkynyl, or even functionalized side chains have been introduced by means of various organometallic derivatives or catalysts (Mg, Li, Zn, Cd, Ti, Pd).[111–113] Releasing the carboxyl moiety of the amino acid is often difficult in acidic medium, and so it is preferentially performed under basic conditions.[111]

Good stereoselectivities have been obtained with the addition of organometallics onto homochiral cyclic acylimines (Figure 5.27),[112] or onto sulfinylimines derived from trifluoropyruvate (Figure 5.28).[114] Asymmetric Strecker reaction of β-sulfinyl

Alkylation with an halogenofluoromethane



(i) NaH; (ii) $CHCl_2F$; (iii) CH_2ClF; (iv) $HSnBu_4$, AIBN; (v) LDA, THF/HMPA; (vi) CH_2ClF, TMEDA

Functional modification

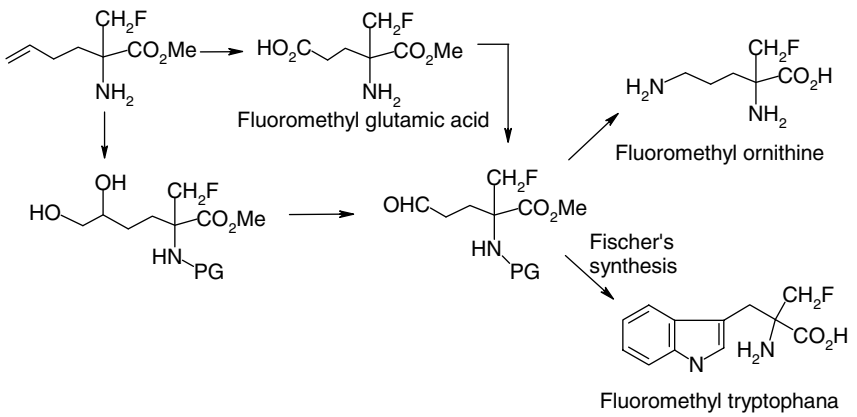


Figure 5.25 Synthesis of α-monofluoromethyl amino acids.[107–109]

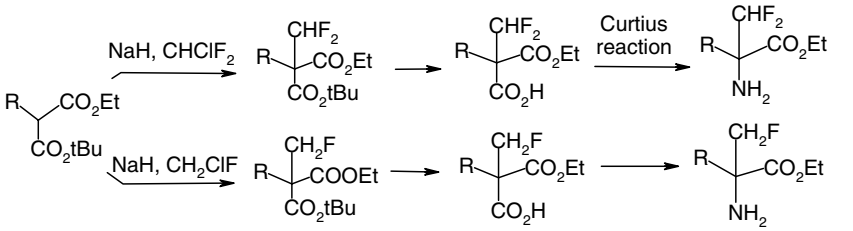


Figure 5.26 Mono- and difluoromethyl amino acids from malonates.

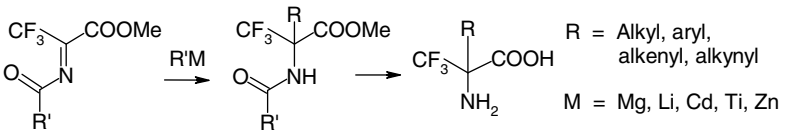


Figure 5.27 Synthesis of α-trifluoromethyl amino acids by addition of organometallics on acyl imines of trifluoropyruvate.[111, 112]

enamines for the formation of stereogenic quaternary centered α-trifluoromethyl amino acids has been reported (cf. Figure 5.4).[115, 116] However, the diastereoselectivities are rather moderate, and chemical or enzymatic separation using esterase, acylase, or amidase activities of the two diastereomers is required to obtain enantiopure amino acids.[1g, 112–115]

The acyl imines of methyl trifluoropyruvate react as heterodienes with electron-rich olefins in [4 + 2] cycloadditions, as exemplified by the synthesis of trifluoromethyl aspartic acid (Figure 5.29).[117]

Some functional modifications allow access to numerous analogues of amino acids, natural or not, starting from synthons prepared by the previous methods. This is illustrated by the preparation of α-trifluoromethyl arginine (Figure 5.30).[118]

Another powerful approach to prepare α-amino acids bearing an aromatic or unsaturated side chain in β (but also many other compounds) is based on the reactivity of 5-fluoro-4-trifluoromethyloxazole, a starting material easily accessible from hexafluoroacetone.[119] The fluorine atom in the 5 position is easily displaced by an allylic or benzylic alcohol. Then, the obtained ethers spontaneously undergo a Claisen rearrangement to afford, after acidic hydrolysis, an α-trifluoromethyl amino acid

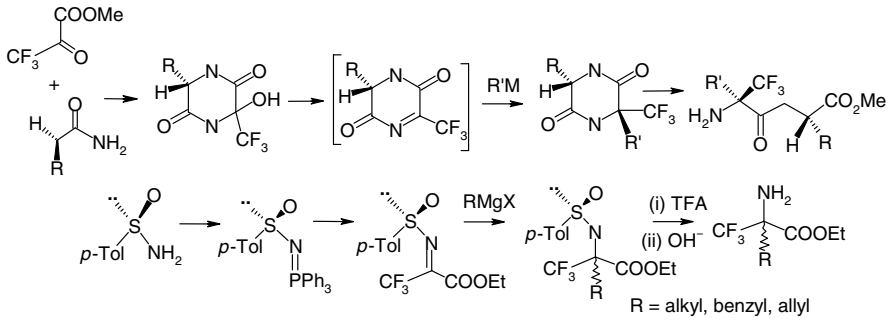


Figure 5.28 Addition of organometallics on chiral acyl- and sulfinylimines of ethyl trifluoropyruvate.[112, 114]

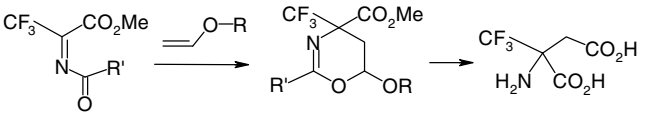


Figure 5.29 Synthesis of the trifluoromethyl aspartic acid through a [4 + 2] cycloaddition.[117]

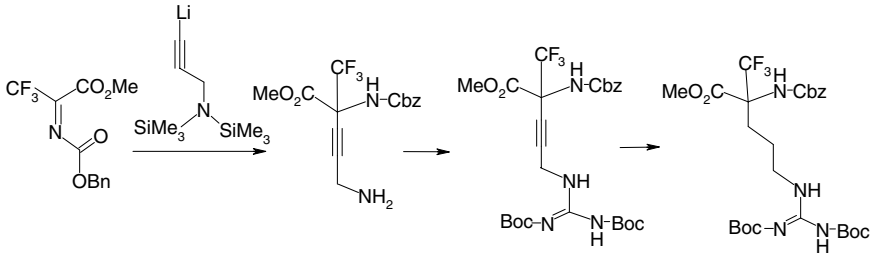


Figure 5.30 Preparation of orthogonally protected α-trifluoromethyl arginine.[118]

(Figure 5.31). Functional modification of the double bond leads to numerous analogues of proteogenic or nonproteogenic α-trifluoromethyl amino acids.[119]

We now take account of the specific character of the incorporation of these α-substituted amino acids into polypeptides. Enzyme inhibition by α-fluoromethyl amino acids is detailed in Chapter 7.

5.4.2.2 Incorporation of α-Trifluoromethyl Amino Acids into Peptides

While the trifluoromethyl group does not have an important influence on the peptidic coupling on the C-terminal side, it is completely different for the coupling on the N-terminal side. Due to the low nucleophilicity of the amine and the steric hindrance induced by the trifluoromethyl group, this peptidic coupling (except for the derivatives of glycine and alanine) requires specific methods. In return, some couplings can be performed selectively with other amino groups of the molecule, without the need to protect the α-CF_3 amine. The formation of diketopiperazines is generally avoided.

Numerous peptides have been prepared starting from trifluoromethylalanine.[5, 31, 120] Cyclopeptides containing α-trifluoromethyl amino acids have also be prepared.[121] Some peptidic coupling performed with other α-trifluoromethyl amino acids involve protease catalysis (subtilisin, α-chymotrypsin, carboxypeptidase Y, trypsin, etc.).[5, 120c–e, 122, 123]

Replacement of some amino acids in a peptide by an α-trifluoromethyl amino acid influences the stability of the peptide toward different proteases (e.g., α-chymotripsins). Thus, for steric reasons, introducing a trifluoromethyl group in the P_1 position

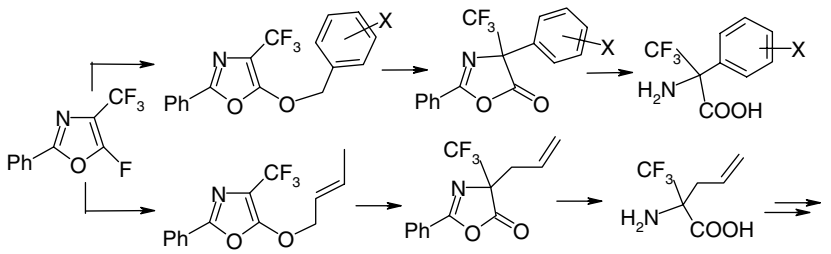


Figure 5.31 Synthesis of α-trifluoromethyl amino acids starting from trifluoromethyl fluorooxazole by Claisen rearrangement.[119]

increases the hydrolytic stability. This protection is also observed for peptides that are substituted in the P_3 position by the fluorinated amino acid. Their degradation rates are slower than the ones of their methyl analogues.[31c]

The influence of the trifluoromethyl group on the conformation and the charge distribution of the peptide may affect, in a negative manner, interaction with the macromolecule target. This phenomenon has been observed with peptidic hormones containing α-trifluoromethyl amino acids. The P substance (PS), which is an undecapeptidic neurotransmittor especially involved in the transmission of the pain message, is cut *in vivo* by an endopeptidase. This occurs mainly at the level of Phe-7 and Phe-8. The pentapeptide that corresponds to the N-terminal part, in which Phe-7 has been replaced by α-TFM phenyl alanine, has been synthesized. The activity on the contraction of the illeon of guinea pigs is also observed, but at much higher concentrations than the ones of PS.[31c]

In the same way, studies have been performed on the replacement of glutamic acid by α-trifluoromethyl glutamic acid in a peptidic hormone: TRH (thyrotropin-releasing hormone: pGlu-His-Pro-NH_2). In this case, a decrease in the affinity (two to three orders of magnitude) with regard to the TRH has been observed, despite the fact that F-TRH is perfectly well protected against proteolysis.[31c] Comparable results have been obtained for GnRH (gonadotropin-releasing hormone).[31c]

5.5 INCORPORATION OF FLUORINATED AMINO ACIDS INTO PEPTIDES AND PROTEINS

In spite of the difficulty, various reasons have incited chemists and biologists to incorporate fluorinated amino acids into polypeptides and proteins. The first reason is the possibility of studying the tridimensional structure and molecular dynamics of biologically active peptides and proteins by using fluorine atoms as probes in ^{19}F NMR.[124] The second reason is connected to medicinal chemistry; that is, taking advantage of the replacement of an amino acid by its fluorinated analogue on a biological and pharmaceutical level—for example, better transport properties of amino acids with potential therapeutic interest. The third reason is the study of the effects of the incorporation of fluorinated amino acids on the structural and physicochemical properties of proteins (conformation, folding, coil, and autoassociation), with consequences on thermal and chemical stability of the protein.[123,125,126]

These aspects are illustrated with some examples concerning polypeptides and proteins.

5.5.1 Polypeptides

The methods of peptidic synthesis, in the liquid phase as well as in the solid phase, have led to the preparation of numerous polypeptides that contain a fluorinated amino acid. Most of the examples concern peptidic hormones and neuropeptides, with replacement of either (1) a phenylalanine (or of a tyrosine) by an analogue containing a

fluorine atom on the aromatic ring, (2) a leucine (or of a valine) by an ω-tri- or hexafluorinated analogue, or (3) a methionine by *S*-F_3-methionine.

The effects of the presence of a fluorinated amino acid on the activity of these peptides are changeable: the activity can be maintained, enhanced, or lowered; the effect can be that of an agonist or antagonist. However, often the biological effect is enhanced, while the affinity is lowered. The loss of affinity is compensated by an increased biodisponibility due to the better hydrolytic and metabolic stability of the polypeptide that contains the fluorinated amino acid.

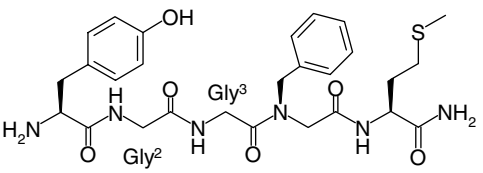
Various amino acids have been replaced by 4-F-Phe or hexafluorovaline in peptidic hormones: oxytocin (4-F-Phe → Tyr),[127] bradykinin (4-F-Phe → Phe),[128] and angiotensin II. The consequences are diverse, but the stability toward hydrolytic enzymes is generally enhanced. Thus, incorporation of F_6-valine in an octapeptide antagonist of angiotensin II (Sar-AII) notably enhances its *in vivo* antagonist activity.[129] Analogues of TRH (thyrotropin-releasing hormone), in which histidine is replaced by a fluorohistidine (4-F-His and 2-F-His → His), have better *in vivo* activities, while the affinities are lower.[130]

Fluorinated analogues of neuropeptides—dynorphin A,[131] dermorphin,[131a] P substance,[132] and enkephalins (2,3,4-F-Phe and 2,3,4-F-Tyr → Tyr)[133–135]—have been studied in order to find analgesics without the drawbacks of morphine. The natural opioid neuropeptides undergo fast degradation by aminopeptidases, which renders them useless as drugs. The presence of hydrophobic fluoro amino acids could *a priori* increase stability toward peptidases, facilitate transport, and enhance affinity with the receptor through stronger hydrophobic interactions.

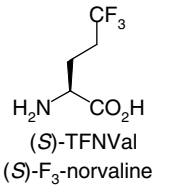
Trifluoroleucine has been introduced in leu-enkephalin instead of Leu-5. The μ activity is diminished *in vivo*, but the δ activity is enhanced.[136] Replacement of Gly-2 by (*R*)-trifluoronorvaline enhances the *in vivo* analgesic activity in the mouse by a factor of 10 (Figure 5.32). In contrast, replacement of Gly-3 has no effect. Considering that the affinities toward the μ, δ, and κ receptors between fluorinated and nonfluorinated amino peptides are comparable, these data seem to show that protection of the degradation by enkephalinase (cut Tyr-Gly) is probably responsible for the increase of *in vivo* analgesic activity with respect to met-enkephalin.[136]

The S-ribonuclease is the complex formed between an eicosapeptide and the S-RNAse. While replacement of various amino acids by fluorinated analogues does not modify the activity of the native complex, replacement of His-12 by 4-F-His has a strong influence. Indeed, the S-ribonuclease, formed between the bovine pancreatic S-RNAse and the fluoro peptide that contains 4-F-His, has no more catalytic activity, but it is stable. This loss of enzymatic activity is probably due to the significant lowering of the pK_a of the catalytic His (−2.5 units), which results from the presence of the fluorine atom.[137] It is known that histidine plays an important role in nucleophilic and acid–base processes, which are connected to the catalytic activity of numerous enzymes.

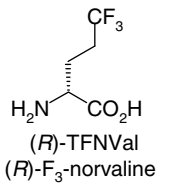
The di- and (especially) trifluoromethionines have been incorporated in polypeptides instead of methionine. In these cases, biological effects have been observed: the chemotactic response of human neutrophiles toward *N*-formyl-*S*-F_3-Met-Leu-Phe is enhanced by a factor of 10.[138]



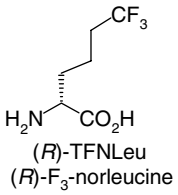
	Analgesic activity ED_{50} (10^{-9} M)
Morphine	0.07
Tyr-(*R*)-NVal-Gly-Phe-Met-NH_2	0.04
Tyr-(*S*)-TFNVal-Gly-Phe-Met-NH_2	25
Tyr-(*R*)-TFNVal-Gly-Phe-Met-NH_2	0.007
Tyr-(*R*)-TFLeu-Gly-Phe-Met-NH_2	0.07
Tyr-Gly-(*R*)-TFVal-Phe-Met-NH_2	12



(*S*)-TFNVal
(*S*)-F_3-norvaline



(*R*)-TFNVal
(*R*)-F_3-norvaline



(*R*)-TFNLeu
(*R*)-F_3-norleucine

Figure 5.32 Analgesic activity of the fluoro-enkephalins on the mouse.[136]

Fluoro amino acids have been incorporated into peptides, in order to ease the transport or reduce the systemic toxicity. Thus, trifluoroalanine, a powerful inhibitor of alanine racemase, is an essential enzyme for the biosynthesis of the cell wall of bacteria. It has a low antibiotic activity because of its very poor transport. In order to facilitate this transport, the amino acid has been incorporated into a peptide. This delivery allows a reduction of the doses, and thus the toxicity of the treatment is lowered.[137] 3-Fluorophenylalanine (3-F-Phe) is a substrate of phenylalanine hydroxylase, which transforms it into 3-F-Tyr. 3-F-Tyr has a high toxicity for animals, due to its ultimate metabolization into fluorocitrate, a powerful inhibitor of the Krebs cycle (cf. Chapter 7). 3-F-Phe has a low toxicicity toward fungus cells, but when delivered as a tripeptide 3-F-Phe becomes an efficient inhibitor of the growth of *Candida albicans*. This tripeptide goes into the cell by means of the active transport system of peptides, where the peptidases set free the 3-F-Phe.[139]

5.5.2 Proteins

The possibility of studying the structure and dynamic properties of proteins by ^{19}F NMR requires the use of labeled proteins with fluorine. Various approaches can be envisioned: trifluoroacetylation or derivatization of side chains by direct fluorination or trifluoromethylation or with small fluorinated molecules.[140, 141] It is also possible to incorporate a fluorinated amino acid into a protein, by using either a classical chemical synthesis or a biosynthetic approach. It is obvious that the chemical synthetic

approach, which is efficient for peptides, is useless in this case due to the great number of coupling steps and the low yield of the synthesis. Thus, the biosynthetic approach has been shown to be the most efficient method of incorporating fluoro amino acids into proteins.

The most common strategy involves an auxotrophic bacteria, that is, a microorganism that is unable to biosynthesize one of the amino acids required for its growth. In our case, the culture has to be performed in a medium that contains the fluoro analogue of this amino acid, instead of the normally required amino acid. While the rates of incorporation can be high, the protein yields are often low, due to the diminution in cellular viability. The protein yield can be increased if it is possible to induce the expression of the desired protein.[142] However, the inhibition effect of most of the fluorinated amino acids on the growth of bacterial cells is a hindrance for good incorporation of the fluorinated analogue into the bacterial protein.[140, 144]

In parallel to the preparative purpose, this research has led to studies of the biosynthetic mechanisms or the cell functions of some amino acids.[1f, 143]

Taking into account the modifications of steric hindrance—of pK_a, of pK_b, and so on—introduced by the presence of fluorine atoms, it is obvious that only a fluorinated amino acid with few modifications, or with modifications that are far from the amino and acidic functions, has some chance to be incorporated by a microorganism. This explains why the only known examples are F-Phe, 3-F-Tyr, 5-F-Tryp, (*S*)-trifluoromethionine, and 4-F-Pro; however, trifluorovaline, trifluoroleucine, and 2-F-histidine have also been incorporated into bacterial proteins.[143, 144] Despite the numerous difficulties, a lot of "fluorinated" proteins and enzymes have thus been biosynthesized with various microorganisms (e.g., *E. coli, S. cerevisae*).[1f]

According to the nature of the amino acid, to the positions of the incorporated molecules, and finally to the nature of the protein itself, the functionality of the enzyme is retained, modified, or even eliminated.

An important domain of research is the dynamic and structural studies by ^{19}F NMR, where the fluorine atoms serve as probes. However, in some cases, they can also induce proper interactions. There have been studies on the globular states of proteins (molten globular state),[144a] and also studies on the auto-organization of polypeptides and proteins as, for example, the formation of superhelixes between chains of α-helixes resulting from hydrophobic interactions (coiled-oil),[145] or the folding of chaperone PapD.[146] The influence of the CF_3 groups of trifluoro- and hexafluorovalines and leucines on the autoassembly and on the stability has been studied on the peptidic fragments of about thirty amino acids.[145, 147]

Highly fluorinated amino acids, such as hexafluoroleucine and hexafluorovaline, enhance the stability of several helical proteins. This enhancement has been attributed to the higher hydrophobicity of the fluorocarbon side chain compared to that of the natural hydrocarbon side chain.[148]

The stability of collagen is due to the formation of triple helixes, which is due to the presence of a Gly-Pro-4(OH)-Pro triplet. The influence of the replacement of 4-(*R*)-OH-Pro by 4-F-Pro on the stability of collagen has been the focus of studies on polypeptide models.[149] These studies highlight the importance of stereoelectronic

and conformational effects connected to replacement of the hydroxyl group by fluorine, with consequences on the stability and on the physical properties of the protein.[144a,145,150]

4-F-Pro has incorporated into the collagen itself.[147] The presence of F-Pro avoids the formation of triple helixes, which provokes a faster degradation of this collagen.[147] It has been observed that the (*R*) or (*S*) configuration of the fluorine atom of F-Pro, which replaces Pro-48, has the opposite effects on the stability of collagen.[151] It is assumed that this phenomenon is due to conformation effects. Indeed, the presence of the fluorine atom and the (*R*) or (*S*) configuration of the fluorine atom at C-4 influences the relative stability of the *cis* and *trans* conformations of the polyamide bond, which is a major element for the stabilization of collagen helixes.[140]

Many bacterial enzymes and proteins, which are modified by the introduction of F-Phe or F-Tryp, have been obtained.[1f] Mammalian proteins containing F-Pro or other fluorinated amino acids have also been obtained, either in a direct manner (*in vivo*) or, more efficiently, by the expression of the gene in a bacteria. Thus, trifluoromethionine has been incorporated by *E. coli* in the lysozyme of a bacteriophage. Because this enzyme contains three methionines, it has been used to study the interactions of this protein with its ligands by ^{19}F NMR.[152]

While the amino acid, which has been replaced by its fluorinated analogue, is essential for the functionality of the protein, some biological consequences can occur. Thus, incorporation of 2-F-His into mammalian proteins (4-F-His cannot be incorporated), in cell culture or *in vivo*, is accompanied by inhibition of the induction of several enzymes (e.g., inhibition of acetyltransferase activity of the pineal gland). This probably stems from the formation of defective or inactive enzymes. Indeed, histidine plays an important role in the nucleophilic and acid–base processes connected to the catalytic activity of numerous enzymes.[153]

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6

SACCHARIDIC FLUORINATED DERIVATIVES

Fluorinated sugars, nucleosides, and parent compounds have received significant attention, due to their numerous potential applications. Some representative issues of fluorinated sugars are (1) enzyme inhibitors (e.g., glycosidases, glycosyltransferases), (2) nucleosides with antiviral and antitumor properties, (3) radio labeled sugars used as probe sensors in medical imaging, and (4) amphiphilic sugars with applications as biocompatible surfactants and liquid crystals.

In this chapter, fluorinated saccharidic compounds are considered in the following order: fluorinated analogues of furanoses and nucleosides, followed by pyranoses and then fluoromethylated sugars. Finally, a brief summary of perfluoroalkylated sugars and of their amphiphilic properties is given.

On the nomenclature level, replacing one of the hydroxyls by a fluorine atom in a sugar affords a deoxyfluorosugar. When this hydroxyl is the anomeric one, the resulting compound is then a glycosyl fluoride. The word *fluorosugar* indicates a sugar in which a fluorine atom replaces a hydrogen. Fluoroalkyl sugars have one or several supplementary carbons that bear fluorine atom(s). Fluoro-*C*-glycosides and fluoro-*C*-disaccharides are compounds in which the anomeric hydroxyl or oxygen is replaced by a CHF or CF_2. In nucleosides, the numbering begins with that of the base, while the numbering of the furanose moiety is assigned with a prime suffix ($'$): as a nucleoside, a 2-fluoro-2-deoxyfuranose becomes a 2′-fluoro-2′-nucleoside. Some examples of fluorinated sugars are reported in Figure 6.1.

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6.1 GLYCOSYL FLUORIDES

This book does not deal with glycosyl fluorides. Indeed, they are mostly synthesis reagents that are used as glycosyl donors in both chemical and enzymatic syntheses of polysaccharides.[1–5] Another application of glycosyl fluorides is as mechanistic probes in studies of glycosidase and glycosyltransferases. This aspect is approached in Chapter 7.[2, 5, 5]

Numerous methods to prepare glycosyl fluorides can involve nucleophilic fluorination reagents (e.g., HF, DAST) or electrophilic reagents (e.g., Selectfluor™) (cf. Chapter 2).[1, 2, 5] The synthesis and reactivity of glycosyl fluorides have been summarized in some reviews.[1–4,7]

6.2 MONO- AND DIFLUORINATED ANALOGUES OF SUGARS

6.2.1 Fluorinated Furanoses and Nucleosides

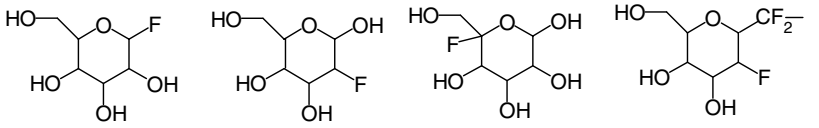
Antiviral and antitumor properties of nucleoside analogues have given rise to a considerable number of studies. These compounds are often inhibitors of the enzymes that are involved in the biosynthesis of nucleosides, in DNA replication and transcription phenomena, and in metabolic transformation (e.g., phosphorylation of a nucleoside). For these reasons, fluorinated analogues of nucleosides have been especially studied, and this phenomenon has increased due to the search for anti-HIV drugs.

Fluorination of a nucleoside concerns either the base or the furanose moiety. This chapter mostly focuses on nucleosides that are fluorinated on the furanose osidic moiety. A short summary of nucleosides that are fluorinated on the base moiety is given at the end of this section, and a more extensive overview is given in Chapter 7 (enzyme inhibitors).

One of the rare fluorinated products found in nature is a fluorinated nucleoside called nucleocidine (4′-fluoro-5-*O*-sulfamoyladenosine). This compound has been isolated from microbial cultures (cf. Chapter 4).[8]

The complete fluorination of a furanose has been achieved (Figure 6.2). It seems to be the only example of the synthesis of a perfluorinated analogue of a relatively complex natural product.[9]

2-, 3-,or 5-Fluorodeoxyfuranoses, 2- or 3-fluoro 2,3-dideoxyfuranoses, unsaturated 2- and 3-fluoro-, and corresponding difluorofuranoses have all been widely studied. In this section, we consider the entire fluorinated furanose family, since introduction of fluorine is often done on any other of the cited substrates.



Glycosyl fluoride | Fluoro-deoxysugar | Fluorosugar | Fluoro-*C*-glycoside

Figure 6.1 Nomenclature of fluorinated sugars.

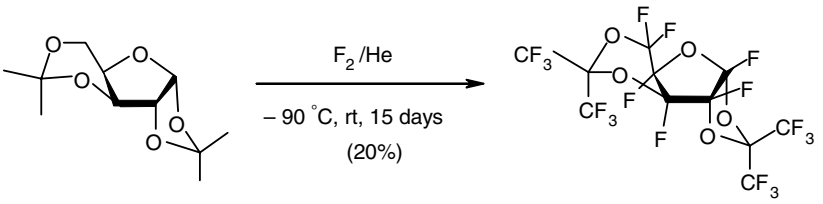


Figure 6.2 Fluorination of diisopropylidene-D-xylofuranose.[9]

6.2.1.1 2-Fluoro-2-deoxyfuranoses and 3-Fluoro-3-deoxyfuranoses

The pandemic of HIV and the discovery of inhibitors of viral and retroviral enzymes (e.g., AZT, which is an inhibitor of the reverse transcriptase of HIV: RT-HIV) have given rise to considerable research. In this connection, deoxynucleosides, which were previously studied as potential antitumor drugs, are receiving renewed attention by researchers. Among these latter compounds, fluorodeoxynucleosides have been the focus of many investigations.[10]

By far, 2-fluoro-2-deoxyfuranoses have been the most studied compounds. Indeed, at a structural level they are the closest analogues of 2-deoxynucleosides. Due to its electronic effect, the fluorine atom in the 2′ position inhibits development of a positive charge on the anomeric carbon (which is responsible for the hydrolytic cleavage of nucleosides). In order to enhance the stability of 2-deoxynucleosides in acidic medium, and thus make oral administration of an antiviral compound easier, introduction of a fluorine atom in the 2 position is a commonly used strategy. The resulting protective effect toward proteolysis has been well demonstrated, as exemplified by the fluorinated analogues of ddI and ddA (cf. Chapter 3, Figure 3.13). However, the presence of this fluorine atoms often induces modifications in the antiviral properties of the molecule.[10, 11]

After phosphorylation, the nucleosides that are derived from 2-fluoro-2-deoxy-D-arabinofuranoses exhibit antiviral and antitumor properties via activity on DNA polymerases. Some of these compounds have been, or are, undergoing clinical trials (Figure 6.3).[10]

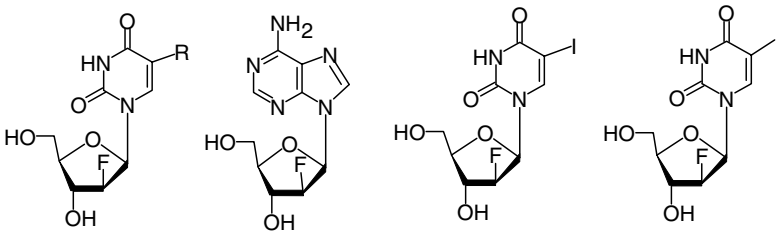


Figure 6.3 Nucleosides derived from 2-fluoro-2-deoxy-D-arabinofuranose.

2-Fluoro-2-deoxynucleosides and 3-fluoro-3-deoxynucleosides are generally prepared either by coupling between the fluorodeoxyfuranose and the base, or by fluorinating the nucleoside (the nucleophilic fluorination reactions are sometimes compatible with the presence of the base).[2, 7]

The precursors of fluorodeoxyfuranoses are accessible through fluorination of the furanose by several methods (Figure 6.4):

- By reaction of the DAST reagent with the free hydroxyl of the furanose (with protecting groups on the other hydroxyls). This reaction generally proceeds with inversion of the configuration.[12–15]

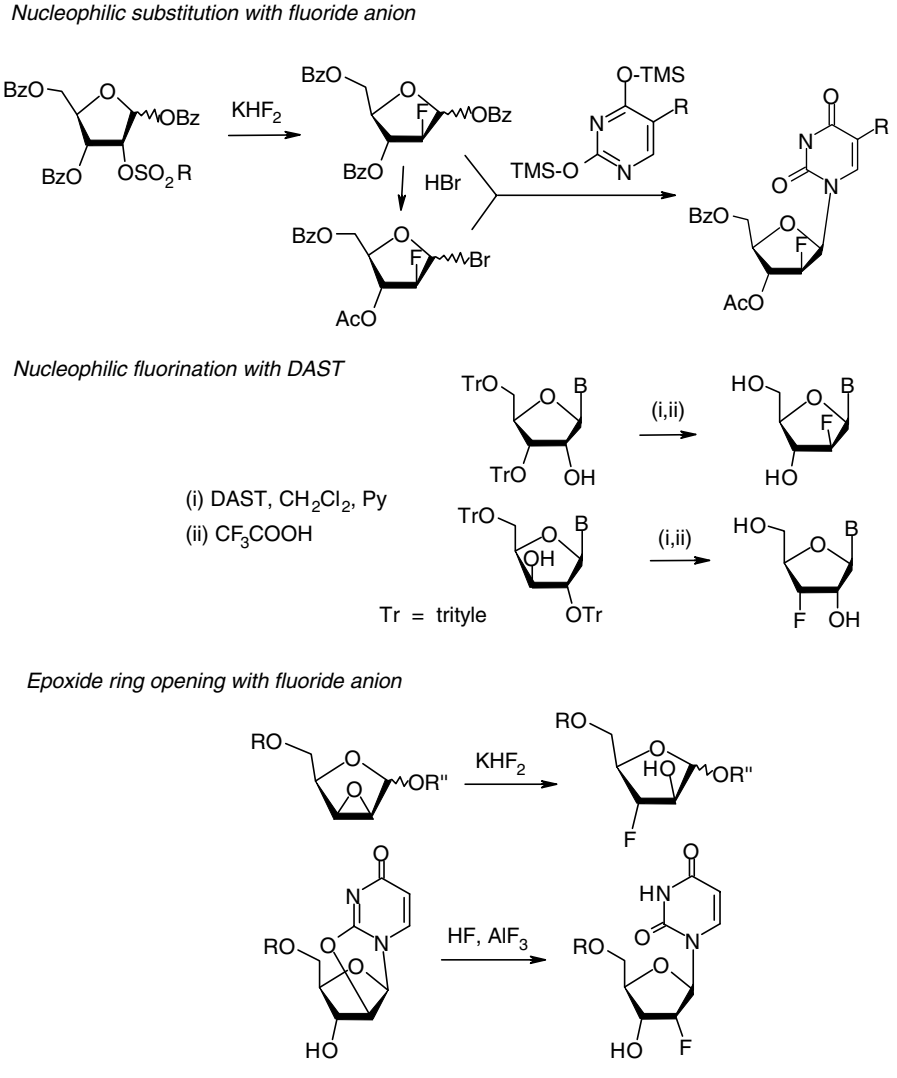


Figure 6.4 Preparation of 2′-fluoro-2′-deoxy- and 3′-fluoro-3′-deoxynucleosides.

- By nucleophilic substitution of a sulfonate by fluoride ions. This reaction also proceeds with inversion of the configuration.[13]
- By opening an oxirane or by displacement of cyclic sulfate or of an anhydronucleoside by fluoride ions (KHF_2).[13, 16–18]

Glycosylation of a base with a protected fluorodeoxyfuranose affords the fluorinated nucleoside. Thus, the protected 2-fluoro-2-deoxyarabinofuranose (commercially available)[19] or the corresponding bromide can be condensed with a protected base.[20] However, glycosylation by 2-fluoro-2-deoxyarabinose is sometimes difficult, particularly in the case of purines. For this reason, introduction of the fluorine atom on the protected nucleoside by means of DAST is sometimes preferred.[13, 15] These various approaches are also used to prepare 2′-fluoro-3′-deoxynucleosides.[13, 14]

5-Deoxy-5-fluoro compounds are generally obtained through displacement of the primary sulfonate with TBAF.[5, 7]

6.2.1.2 Difluoro-2,3-dideoxy-2,3-furanoses 2′,3′-Dideoxynucleosides, such as ddC (*Zalcitabine*) and ddI (*Didanosine*), are highly efficient antiviral compounds, especially toward HIV. Their fluorinated analogues in position 2′ or 3′ have thus been studied.[21] The precursor fluorodideoxyfuranose is prepared through nucleophilic fluorination of monodeoxyfuranose. This latter compound is obtained either through hemisynthesis from a natural product or by total synthesis from a chiral acyclic molecule. γ-Ribonolactone is the precursor used in the two examples of the first approach. For preparing 2-fluoro-2,3-dideoxyfuranose, this lactone is transformed into DPA-lactone, followed by DAST fluorination.[22] To access 3-fluoro-2,3-dideoxyfuranose, the 2- and 5-hydroxyls are protected, and then the remaining free hydroxyl is fluorinated with DAST, or transformed into triflate, which is then displaced with TBAF. A preliminary inversion of the configuration of the hydroxyl group in position 3 can be required, according to the desired configuration of the fluorine atom (Figure 6.5).[23]

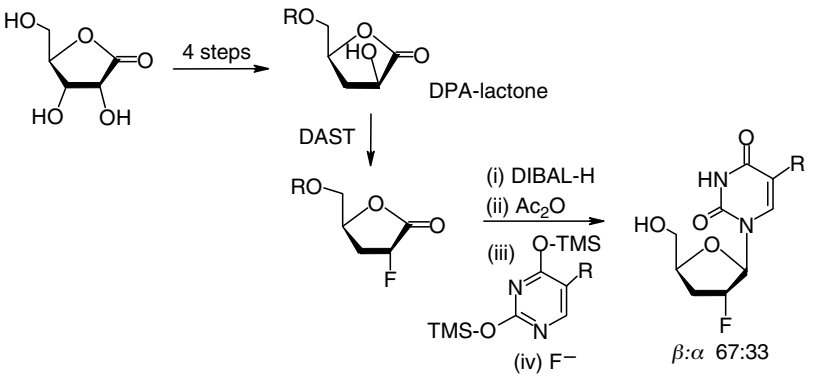
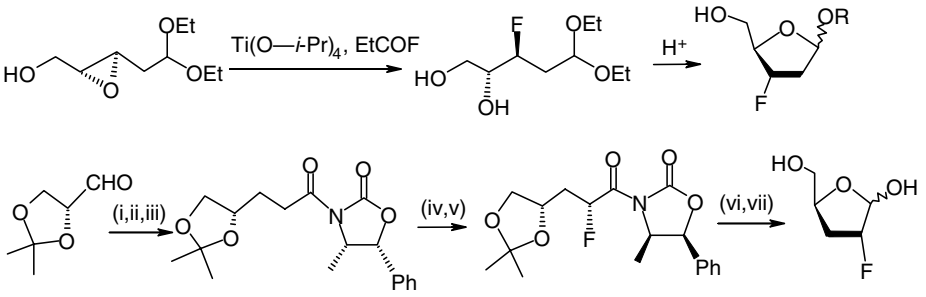
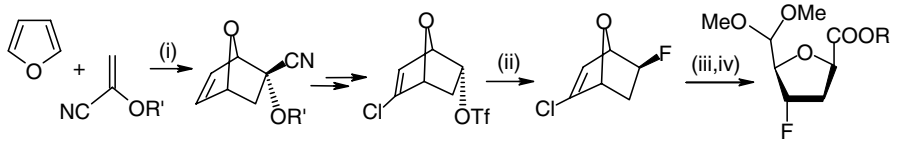


Figure 6.5 Preparation of 2-fluoro-2,3-dideoxyfuranose through fluorination.



(i) Horner–Emmons; (ii) Reduction; (iii) Amidation;
(iv) LHMDS; (v) NFSI; (vi) MgOMe; (vii) DIBAL-H



(i) ZnI_2; (ii) TBAF; (iii) O_3; (iv) Me_2S, $HC(OMe)_3$

Figure 6.6 Synthesis of fluoro-2,3-dideoxyfuranoses starting from acyclic precursors.

Some syntheses of 2- or 3-fluoro-2,3-dideoxyfuranoses have been described starting from L- or D-glyceraldehyde or from other acyclic precursors. They involve a Wittig–Horner reaction, followed by a Sharpless epoxidation (Figure 6.6).[24–26]

Various isomers of 2,3-difluoro-2,3-dideoxynucleosides have been synthesized (Figure 6.7). The configuration of the fluorine atoms plays an essential role in the antiviral activity.[10,27,28] In the case of the D-lyxo compound, coupling with thymine has failed, due to the participation of the protecting group.[29]

6.2.1.3 gem -Difluorodeoxyfuranose Compounds from the 2,2-difluoro-2-deoxyribo series and the corresponding nucleosides have been the focus of many investigations, due to their antiviral and antitumor properties. Thus, 2′,2′-difluorodeoxycytidine (*gemcitabine* or Gemzar®) is prescribed for various cancers (lung—NSCLC, pancreas). After considering the metabolic phophorylation of *gemcitabine*, the main mechanism of action of this drug is through inhibition of ribonucleotide diphosphate reductase (cf. Chapter 7 and 8). 2,2-Difluoro-2-deoxyribose is prepared by adding the Reformatsky reagent prepared from ethyl bromodifluoroacetate onto (*R*)-2,3-*O*-isopropylidene glyceraldehyde. The resulting product is further coupled with silylated pyrimidine. Control of the stereoselectivity of the addition of the Reformatsky reagent is difficult, and it has been widely studied (Figure 6.8).[30, 31] In order to circumvent this problem, different approaches involving D-pyranose derivatives have been assessed (Figure 6.9).[32]

DAST fluorination of 3-ketofuranose does not allow preparation of 3,3-difluorodeoxyfuranose, because of the steric hindrance of the protected 2-hydroxyl.[33]

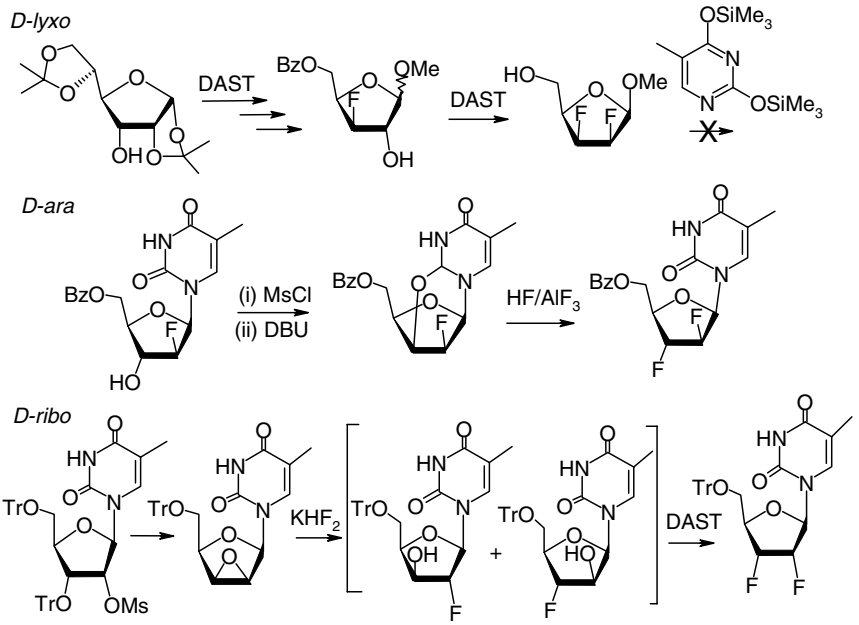
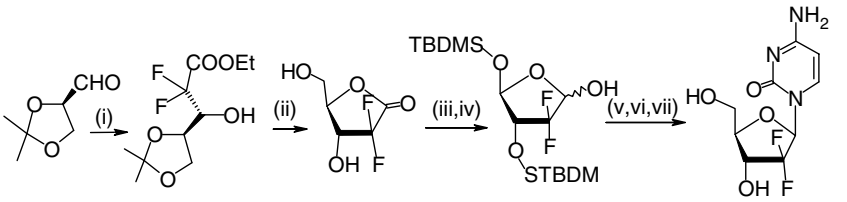


Figure 6.7 Preparation of the four isomers of 2,3-difluoro-2,3-dideoxyfuranose.

Fluorination of the nucleoside has also failed, providing very low yields.[34] In consequence, 3,3-difluoro-2,3-dideoxyfuranoses and the related nucleosides are generally prepared by fluorination of 2,3-dideoxyfuranoses. However, the latter has to be prepared with a large number of steps from a natural precursor, such as L-xylose (Figure 6.10).[34] Some total syntheses of 3,3-difluoro-2,3-dideoxyfuranoses have been performed from glyceraldehyde (Figure 6.10).[35]

2′,3′-Unsaturated nucleosides with fluorine atoms on the 2′ or 3′ position have also been investigated for their potential antiviral properties (HIV and HBV).



(i) Zn, $BrCF_2COOEt$; (ii) H^+; (iii) $tBu(Me)_2$ SiOTf; (iv) DIBAL-H;
(v) $MeSO_2Cl$; (vi) ditrimethylsilyloxypyrimidine

Figure 6.8 Preparation of gemcitabine (2′-deoxy-2′,2′-difluorocytidine).

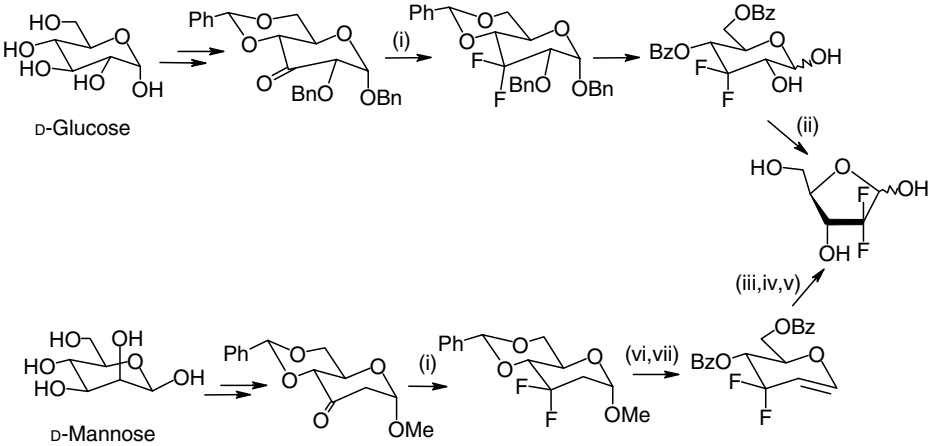


Figure 6.9 Synthesis of 2-deoxy-2,2-difluoro-D-ribose from D-pyranoses.

2-Fluorofuranose precursors are prepared via Horner–Emmons reaction on L-glyceraldehyde acetonide (Figure 6.11). Due to the allylic position of the base, these compounds are much more unstable than the related saturated molecules (cf. Figure 3.17, Chapter 3). The presence of the fluorine atom enhances the hydrolytic stability of these compounds. Some of these molecules have good antiviral activities on infected cells.[36, 37]

The nucleosides that are fluorinated on position 3′ are prepared through dehydrofluorination of *gem*-3′,3′-difluorinated compounds (*vide supra*).[34]

5-Fluoronucleosides that have an exocyclic double bond can be prepared from a fluorosulfoxide. This latter compound is obtained by electrophilic fluorination of the corresponding sulfide with Selectfluor™ (F-TEDA-BF_4) (Figure 6.12).[38]

6.2.1.4 Carbacyclic and Fluorinated Sulfur-Containing Analogues

Numerous carbacyclic, or sulfur-containing, analogues of mono- and difluoronucleosides have been synthesized as potential antivirals.[39–41] In the carbacyclic series, the starting compound is hydroxymethylcyclopentene oxide. Rearrangement of this oxirane creates a new unsaturation that can be oxidized further into another epoxide. An amino function can then be introduced on the 4 position and can be used "to build" the base (Figure 6.13). [42, 43]

Thiofuranose precursors are prepared from suitably protected furanose. The fluorination step involves classical methods. It is necessary to further introduce anomeric functionalization (Figure 6.13).[44]

6.2.1.5 Nucleosides Derived from Fluorinated Bases

Many nucleosides have been synthesized from different fluoropyrimidines (uracil, thymidine, cytosine) or fluoropurine (adenine, guanine) bases, which are generally prepared by electro-

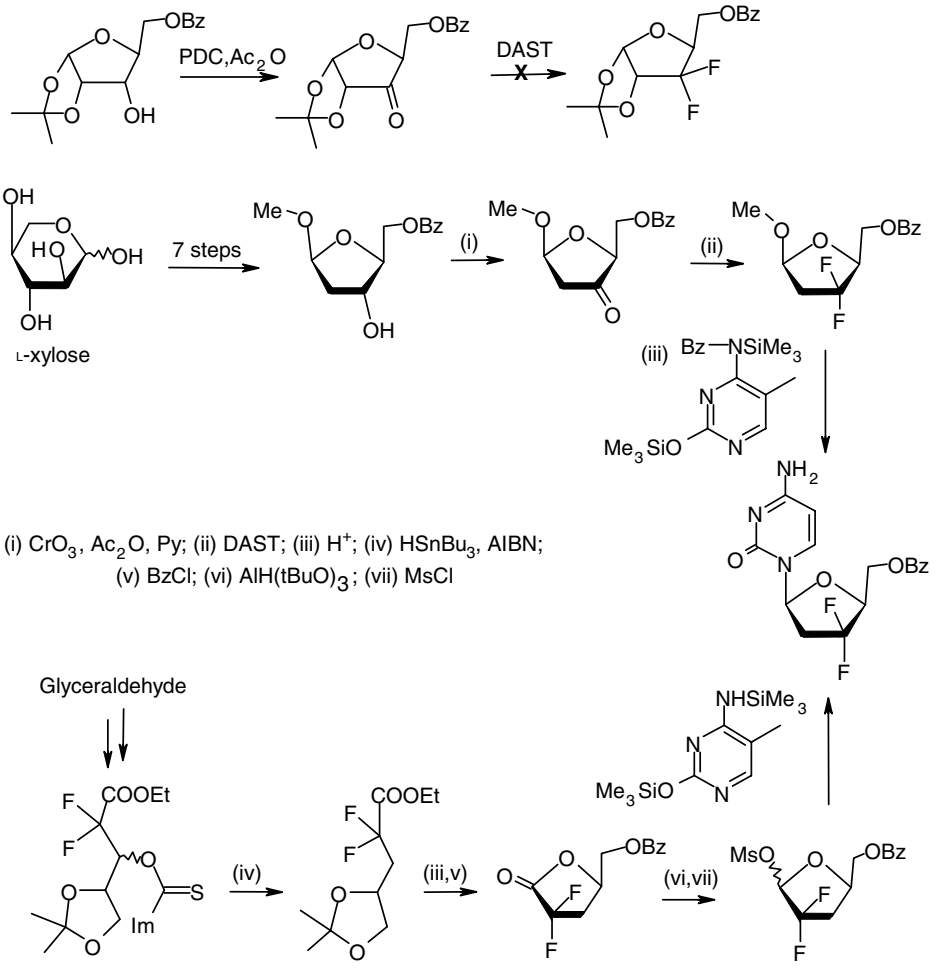


Figure 6.10 Preparation of 3,3-difluoro-2′,3′-dideoxynucleotides.

philic fluorination of the base (cf. Chapter 2). Potentially, they are inhibitors of the enzymes of DNA and RNA biosynthesis and have great importance for antitumor and antiviral applications. Indeed, these fluoronucleosidic compounds are often used as prodrugs in order to facilitate oral administration of the fluorobase.

The fluorine atom can be present in position 5 in uracil derivatives, or in position 1 in that of purine, as in *fludarabine*, which is used in the treatment of some leukemias (Figure 6.14; cf. Chapter 8). Nucleoside derivatives of fluorouracil (e.g., *capecitabine*) are prodrugs that allow the oral administration of 5-FU in cancer chemotherapy. The mechanism of action of these nucleosides is detailed in Chapters 7 and 8. Nucleosides having a trifluoromethylated base have been described: for example, *trifluridine* is active on herpesvirus (Figure 6.14).

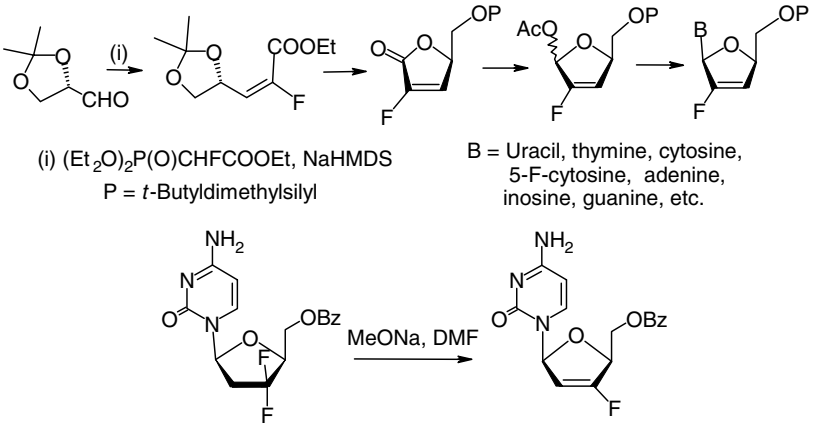


Figure 6.11 Preparation of 2′- and 3′-fluoro-2′,3′-unsaturated nucleosides.

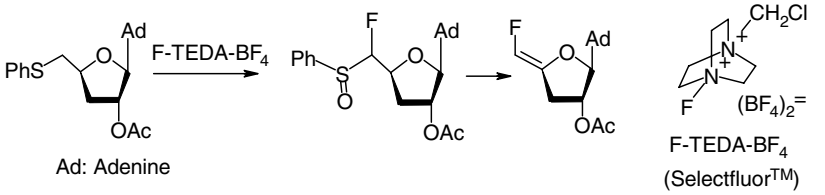


Figure 6.12 Preparation of the 5′-(fluoro)vinyl-deoxyfuranoadenosine.[38]

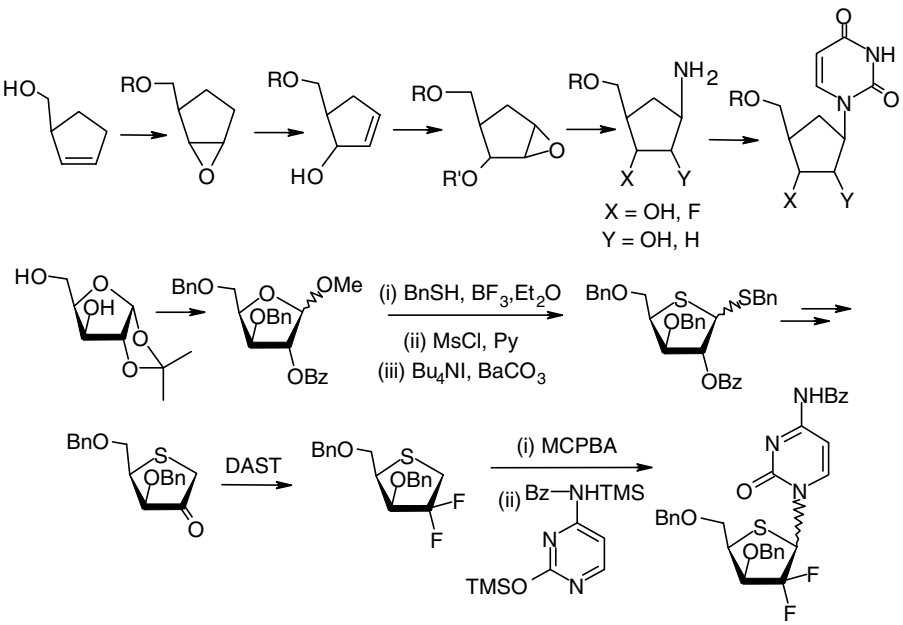


Figure 6.13 Carbocyclic and thioarabino analogues of fluorodeoxynucleosides.

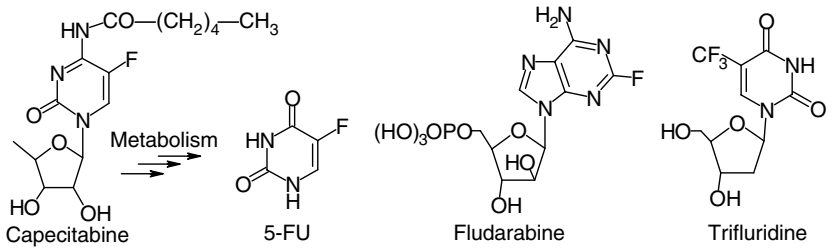


Figure 6.14 Examples of nucleosides with fluorine atoms on the base.

These molecules are prepared through radical trifluoromethylation of the base (cf. Chapters 2 and 8).

The presence of fluorine atoms on the heterocyclic base of a nucleoside can play a decisive conformational role in the matching and stacking of bases.[45]

6.2.2 Fluorinated Pyranoses

6.2.2.1 Monofluorodeoxypyranoses Due to their role in ^{18}F medical imaging, 2-fluoro-2-deoxypyranoses are the most important compounds of the fluoropyranoses.[46] They are also used as probes to study enzymatic mechanisms of reaction catalyzed by glycosidases and glycosyltransferases.[47] Fluorodeoxypyranoses can also be inhibitors of these enzymes (cf. Chapter 7).

Nucleophilic fluorination is particularly useful in the synthesis of 2-fluoro-2-deoxypyranoses (e.g., DAST fluorination, displacement of a leaving group by a fluoride ion, oxirane ring opening with HF–amine complexes). Electrophilic fluorination also allows the synthesis of 2-fluoro-2-deoxypyranoses.

(a) Electrophilic Fluorination Electrophilic fluorination of glycals (elemental fluorine, O—F reagents, xenon fluoride) has also been widely studied. However, due to the availability of safe and easy-to-handle N—F reagents (cf. Chapter 2), earlier reagents are now only used for ^{18}F labeling (*vide infra*). The reaction of D-galactal with Selectfluor (F-TEDA-BF_4) has been studied under various conditions. The primary product of the reaction comes from the *syn* addition of Selectfluor onto the double bond. This adduct can further react with a nucleophile to afford a compound substituted on the anomeric carbon with a fluorine atom at position 2 (Figure 6.15). When the reaction is performed in the presence of water, 2-fluoro-2-deoxysugar is obtained in good yield. These reactions have been extended to glycals that are derived from other pyranoses and from disaccharides.[46] The stereochemistry of the reaction is controlled by the relative steric hindrance of the two sides of the cycle. For this reason, it is dependent on the choice of the protecting groups.[46]

The activated 2-fluoro-2-deoxypyranoses obtained through this method are useful precursors of glycopeptides (Figure 6.15)[2] and of 2-deoxy-2-fluorodisaccharides.[48]

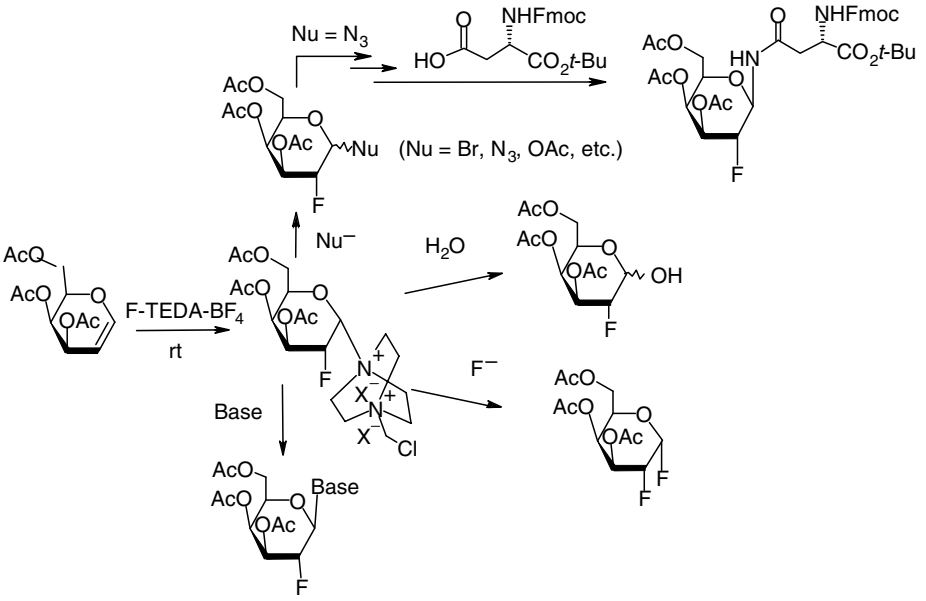


Figure 6.15 Electrophilic fluorination with Selectfluor.

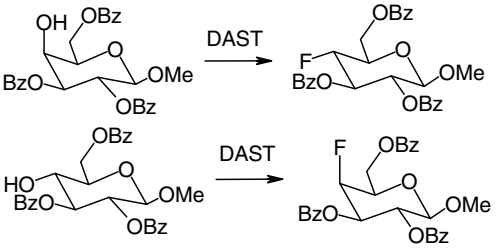
(b) Nucleophilic Fluorination Substitution of a hydroxyl by a fluorine atom by means of DAST or TASF (tris(dimethylamino)sulfonium difluoromethylsilicate) or of a sulfonate group with a fluoride anion is the most common way to access fluorodeoxypyranoses. These reactions occur with inversion of configuration.

Thus, 2-fluoro-2-deoxy-, 3-fluoro-3-deoxy-, 4-fluoro-4-deoxy-, and 5-fluoro-5-deoxy pyranoses can be prepared by treating the corresponding triflate with TASF.[49] 4-Fluoro-4-deoxy-D-galactoses have also been prepared by reacting the free hydroxyl with DAST.[50] Fructose derivatives offer access to 2-fluoro-2,6-deoxytalopyranoses.[51] These various fluorodeoxygalactoses and fluorodeoxyglucoses have been used in studies on interactions between the corresponding nucleotides and the metabolism enzymes (UDP-galactopyranose epimerase, UDP-glucose dehydrogenase).[50] The opening of epoxides or of cyclic sulfate also allows preparation of fluorodeoxypyranoses (Figure 6.16). However, in all these substitution reactions, participation of the neighboring groups can occur and can disturb the reaction. 4-Fluoro-4-deoxy-D-sorbose has been prepared by opening of an oxirane precursor in the presence of KHF_2. However, reaction with the oxirane with opposed configuration affords a complex mixture, due to its rearrangement.[52]

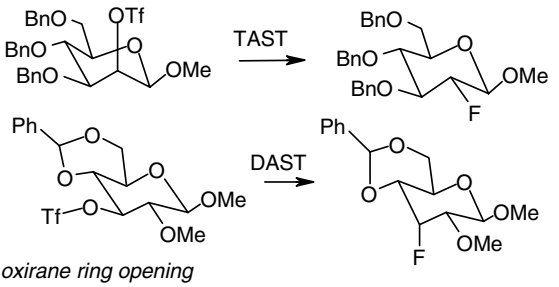
Generally all these approaches have strong limitations due to secondary reactions or possible rearrangements. The outcome of these reactions depends on the relative configurations of the substituents of the molecule (Figures 6.16 and 6.17).

(c) Hexoses Labeled with ^{18}F Sugars labeled with ^{18}F are used in medical imaging: they are useful for diagnosis in cancer, cardiology, and neurology through

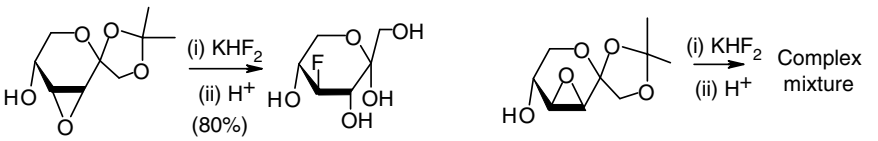
Fluorination of hydroxyl with DAST



Fluorination by nucleophilic displacement of triflate



Fluorination by oxirane ring opening



Fluorination by cyclic sulfate ring opening

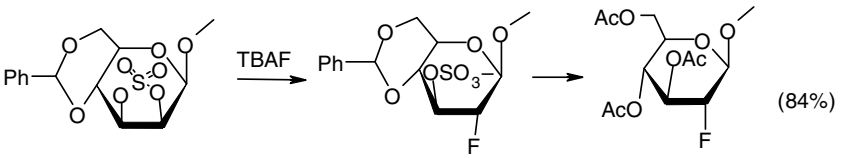


Figure 6.16 Preparation of deoxyfluoropyranoses by nucleophilic fluorination.

positron emission tomography (PET). [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) is routinely used in the clinical setting. The use of [^{18}F] FDG permits one to monitor the metabolism of glucose, which is the main energy source of the human body. After injection, distribution of [^{18}F] FDG in the body is fast: just like for glucose, its extraction by cells is efficient. [^{18}F] FDG is phosphorylated by hexokinase into [^{18}F] FDG-6-phosphate. This latter compound does not undergo further metabolism, due to the presence of the fluorine atom in position 2.

The detection of tumors with [^{18}F] FDG is based on the increase of glucose metabolism in tumor cells: the transport of [^{18}F] FDG in tumor cells is enhanced compared to healthy tissue. Accumulation of [^{18}F] FDG is measured and visualized by

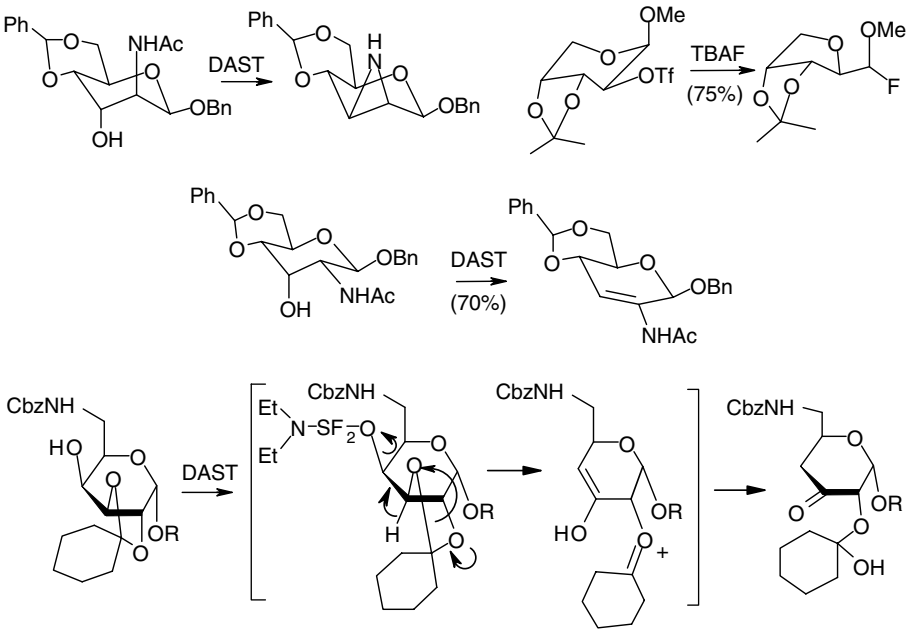


Figure 6.17 Examples of rearrangements during nucleophilic fluorination.

a PET video. In cardiology, the goal is to identify viable myocardial tissues that can undergo revascularization. Indeed, the energy of healthy myocytes mostly comes from the metabolism of fatty acids when glycolysis provides energy for damaged cells. In neurology, PET imaging with [^{18}F] FDG is used to identify the epileptic source before surgical intervention. During an epileptic crisis, the source exhibits a very high activity of glucose metabolism. Visualization of glucose metabolism in the brain is also a useful tool for the early diagnosis of various dementias (e.g., Alzheimer disease). Glucose is the only energy source of the brain. Its consummation is thus strongly connected to neuronal activity.[46]

Considering the short half-life of ^{18}F (110 min), synthesis of a labeled compound must be fast. The other important constraint is the very small number of available fluorination reagents. The first syntheses of [^{18}F] FDG were performed using electrophilic fluorination with $^{18}F_2$. $^{18}F_2$ is produced by bombardment of ^{20}Ne atoms through cyclotron radiation. In spite of improvements in the electrophilic method (use of acetyl hypofluorite), the use of K^{18}F as the nucleophilic fluorinating agent is prominent. This compound is produced by bombardment of ^{18}O-enriched water with high energy protons. Currently, [^{18}F] FDG is prepared by reacting the triflate of D-mannopyranose with labeled fluoride ions (K^{18}F) that are activated with [2.2.2]-Kryptofix™ (Figure 6.18).[53]

Other sugars labeled with ^{18}F that are used in PET imaging ([^{18}F] FDGal, 2-[^{18}F]-2-deoxytalose, 1-[^{18}F]-1-deoxy-D-fructose) are also prepared by means of nucleophilic fluorination (Figure 6.19). 1-[^{18}F]-1-Deoxy-D-fructose cannot be used as a probe since it

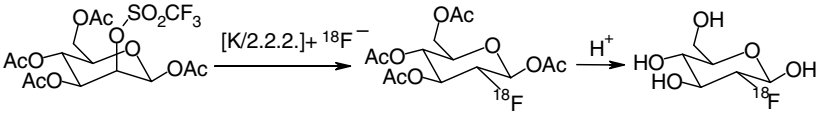


Figure 6.18 Preparation of [^{18}F] FDG.[53]

does not accumulate in organs or tumors. In contrast, [^{18}F] FDGal can accumulate inside tumors. Although it is not a physiological substrate for mammals, it can be accepted by galactokinase, and then metabolized by the metabolic pathway of galactose.

2-Acetamido-2-deoxy-D-glucose is a component of a mucopolysaccharide: hyaluronic acid. It has been demonstrated, by PET imaging with the corresponding ^{18}F labeled compound, that this glucose derivative is incorporated into the connective tissue at the interface of a tumor and healthy tissue. Thus, it can be used as a tumor label. 6-[^{18}F]-6-Deoxy-L-ascorbic acid also deserves attention, as it maintains the antioxidant properties of ascorbic acid. Thus, it can be useful to study the biochemical

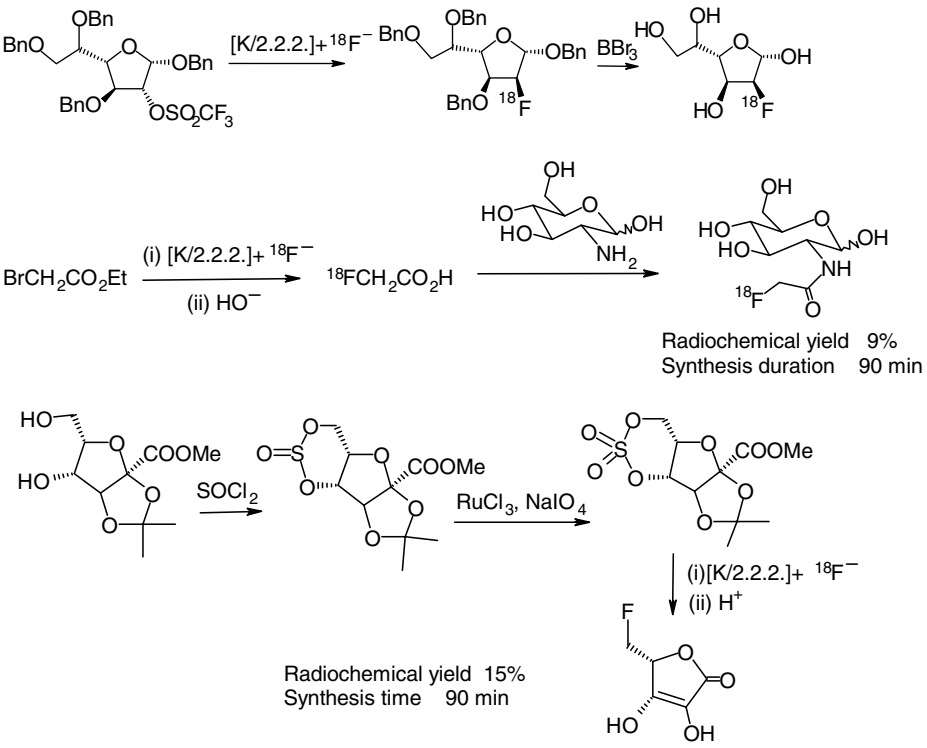


Figure 6.19 Preparation of sugars labeled with ^{18}F: 2-[^{18}F]-2-deoxytalose, N-[^{18}F]-fluoroacetyl-D-glucosamine, and 6-fluoro-6-deoxy-L-ascorbic acid.

functions of antioxidants, and also to get information on the physiopathological states resulting from oxidative damage.[46]

6.2.2.2 gem-Difluorodeoxypyranoses Conversely to the corresponding furanoses, *gem*-difluorodeoxypyranoses have not been studied very much. These compounds can be prepared by fluorination of the corresponding ketones with DAST.[54, 55] The further glycosylation of a nucleobase (e.g., cytosine) leads to pyranose analogues of 2′,2- and 3′,3-difluoro-2′,3-deoxynucleosides.[56]

Condensation of the Reformatsky reagent of ethyl bromodifluoroacetate with an imine affords difluoroazetidinone. This latter compound is a precursor of 2,2-difluoro-2-deoxyaminopyranoses.[57a]

Some 4,4-difluoroglycosides have been prepared recently by ring closing metathesis (RCM) (Figure 6.20).[57b]

6.2.2.3 Fluorinated Cyclitols and Aminocarbasugars Fluorocyclitols are inhibitors of phosphatidylinositol-3-kinase.[58b] Some monofluorocyclitols

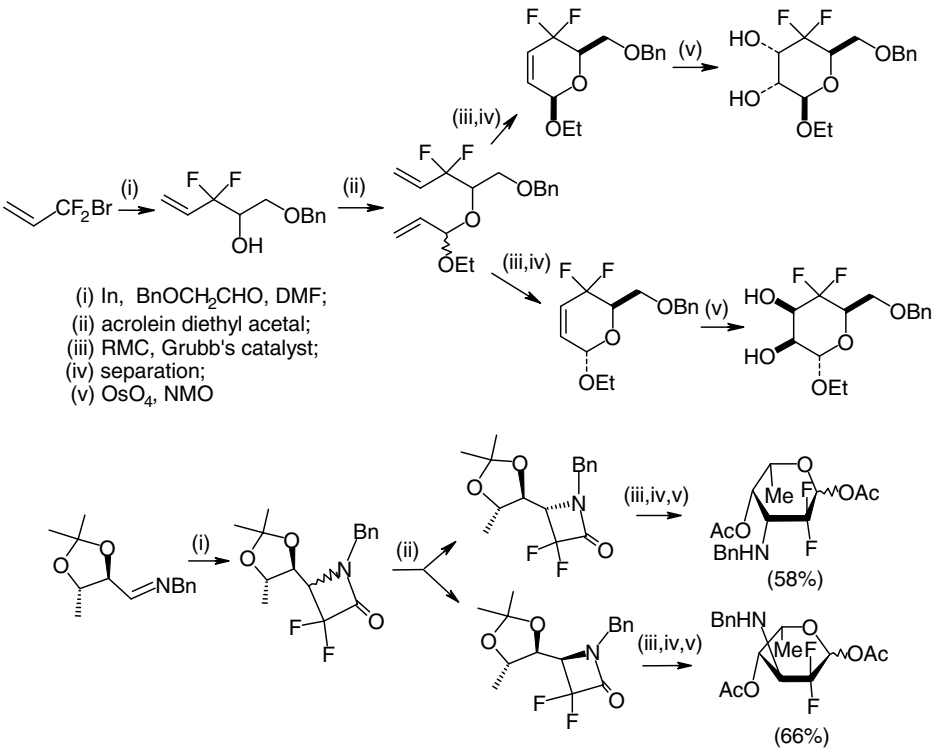
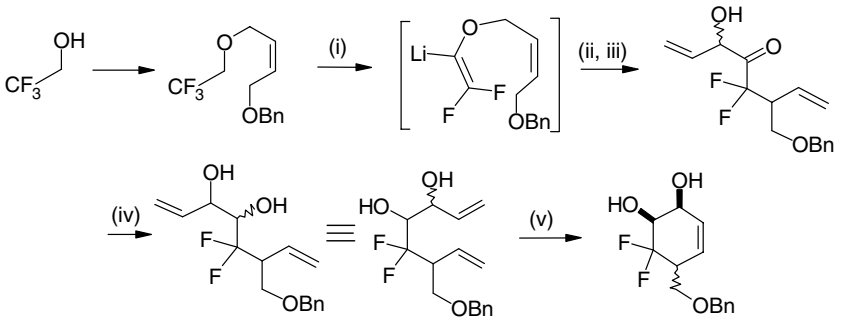


Figure 6.20 Preparation of 2,2-difluoro-2-deoxyaminopyranoses.[57]



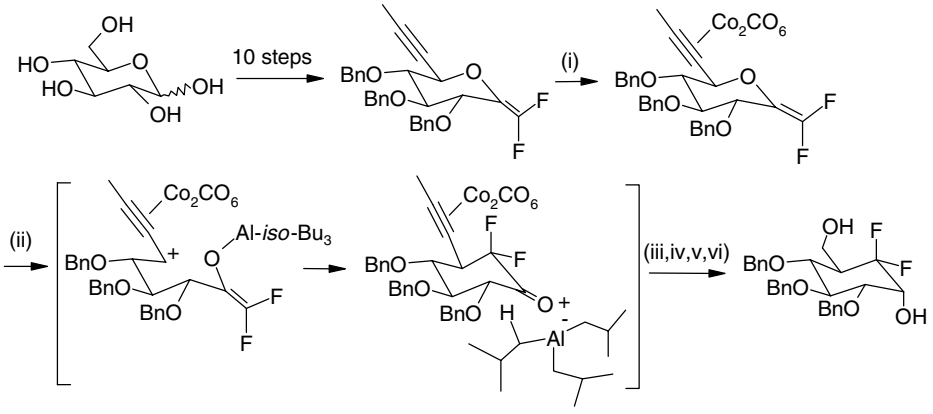
(i) *n*-BuLi; (ii) acrolein; (iii) reflux ($CHCl_3$): (iv) $NaBH_4$; (v) RCM

Figure 6.21 Synthesis of difluorocyclitols from trifluoroethanol.

have been prepared through nucleophilic fluorination with DAST: 5-fluoro-5-deoxy-*myo*-inositol[58a] and some monofluorodeoxyiminopyranoses that are fluorinated analogues of deoxynojirimycine (an inhibitor of glycosidases).[59]

A short route to difluorocyclitols involves trifluoroethanol as starting material. In the presence of *n*-BuLi, the allylic ether of CF_3CH_2OH undergoes a dehydrofluorination-metallation, followed by a [3,3]-Claisen rearrangement. The diene adduct is then cyclized via RCM reaction, affording precursors of various deoxydifluorocyclitols (Figure 6.21).[60]

Another original synthesis of 5-difluorocarba analogues of α- and β-D-glycopyranose has recently been reported.[61] It employs a rearrangement of an *exo*-difluoromethylene precursor. The proposed mechanism for the rearrangement involves ring opening by the Lewis acid $(i\text{-Bu})_3Al$ and stabilization of the cationic intermediate by dicobalt hexacarbonyl. $(i\text{-Bu})_3Al$ then acts as a hydride donor and reduces the difluoroketone on the α side in a diastereoselective manner (Figure 6.22).[61]



(i) $[Co_2(CO)_8]$; (ii) Al-*iso*-Bu_3; (iii) CAN, NEt_3; (iv) $Pd(CO_3)$, H_2 MeOH; O_3; (v) $NaBH_4$

Figure 6.22 Synthesis of 5-difluorocarbaglucopyranoses.[61]

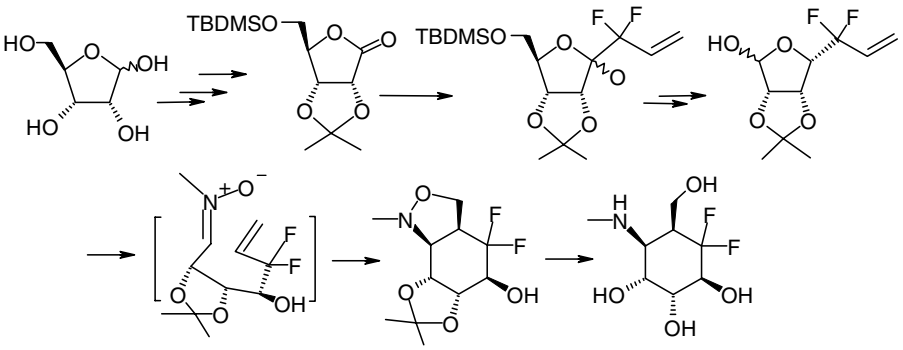


Figure 6.23 Synthesis of a difluoroaminocarbasugar by dipolar cycloaddition.[62]

Synthesis of an aminodifluorocarbasugar has also been described starting from D-ribose via intramolecular [1,3]-dipolar cycloaddition (Figure 6.23).[62]

6.3 FLUOROMETHYL DERIVATIVES OF SUGARS

Difluoromethyl and trifluoromethyl groups can replace a hydrogen or a hydroxyl in a sugar. When the replaced hydroxyl is the anomeric one, the resulting compounds are fluoromethyl-*C*-glycosides. First, we deal with difluorovinyl compounds, which are common intermediates in the synthesis of difluoromethyl, trifluoromethyl, and *C*-glycoside compounds. We then focus on difluoro- and trifluoromethyl sugars. The perfluoroalkyl homologues are considered in another section.

6.3.1 Difluorovinyl Compounds

These compounds come from methylenation reactions of the corresponding carbonyl derivative by means of an ylide. Several experimental conditions have been described. In most cases, CF_2Br_2 and HMPT (hexamethyl phosphorotriamide) are employed.[63] The reaction occurs with aldehydes[64] as well as with ketones[64–66] in the furanose and pyranose series. The reaction can also be performed with lactones: the fluoromethyl group is then introduced in the anomeric position.[67] With these substrates, the Julia olefination, which uses difluoromethyl sulfone, has also been reported to be an efficient method.[68] Some examples of these reactions are shown in Figure 6.24.

3′-Fluoro and 3′,3-difluoromethylene nucleosides have been prepared as inhibitors of ribonucleotide diphosphate reductase (cf. Chapter 7).[69]

6.3.2 Difluoromethylene-*C*-Glycosides

6.3.2.1 Starting from Difluorovinyl Glycosides Saccharidic derivatives that have a difluoromethylene group in the pseudo-anomeric position are important synthetic intermediates for preparation of difluoro-*C*-glycosides, difluoro-*C*-phosphonates, and difluoro-*C*-disaccharides.[70c]

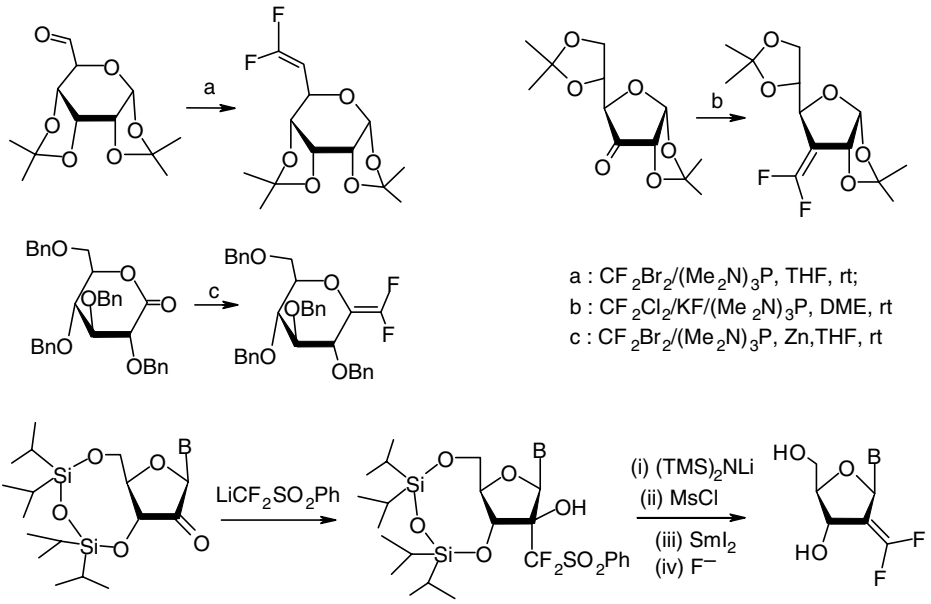


Figure 6.24 Synthesis of saccharidic 1-, 2-, 3-, and 5- difluorovinyl compounds.

The enolic double bond of a difluorovinyl group in the anomeric position is able to add a radical. It can thus afford a difluoro-*C*-glycoside, either directly or indirectly. When the alkylating radical is generated from a 6-halogenopyranoside, the reaction can lead to difluoro-*C*-disaccharide.[71a] These reactions are even more efficient if the radical has an electrophilic character (e.g., with an α-halogenoester instead of an alkyl radical).

However, better results have been reported when the polarity of the reaction is reversed. In this indirect path, an initial radical addition of a thio- or selenophenyl group affords a compound that can be the precursor of a difluoromethyl radical. This latter species can further add onto an activated double bond. These radical approaches have also allowed the synthesis of glycopeptides[71b] and difluorophosphonates (Figure 6.25).[71c,d]

6.3.2.2 Starting from Difluorinated Nucleophilic Reagents Difluorinated nucleophilic reagents are generally reactive toward the oxonium ion, which is generated in the anomeric position of a sugar, or of the aldehyde function of a linear aldose. Difluoroenoxysilanes have been used to synthesize difluoro-*C*-glycosides (cf. Chapter 2). Reactions of difluoroenoxysilanes have been extended to the synthesis of difluoro-*C*-disaccharides (Figure 6.26).[70]

The Reformatsky reagent of ethyl bromodifluoroacetate has been condensed on aldehydes that are derived from D-glucose and from D-galactose. After separation, each diastereomer is transformed, through hydroxymercuration and reduction, to selectively afford a difluoro-*C*-glycoside having a carboxylic function. This function allows access to glycopeptides (Figure 6.27).[72]

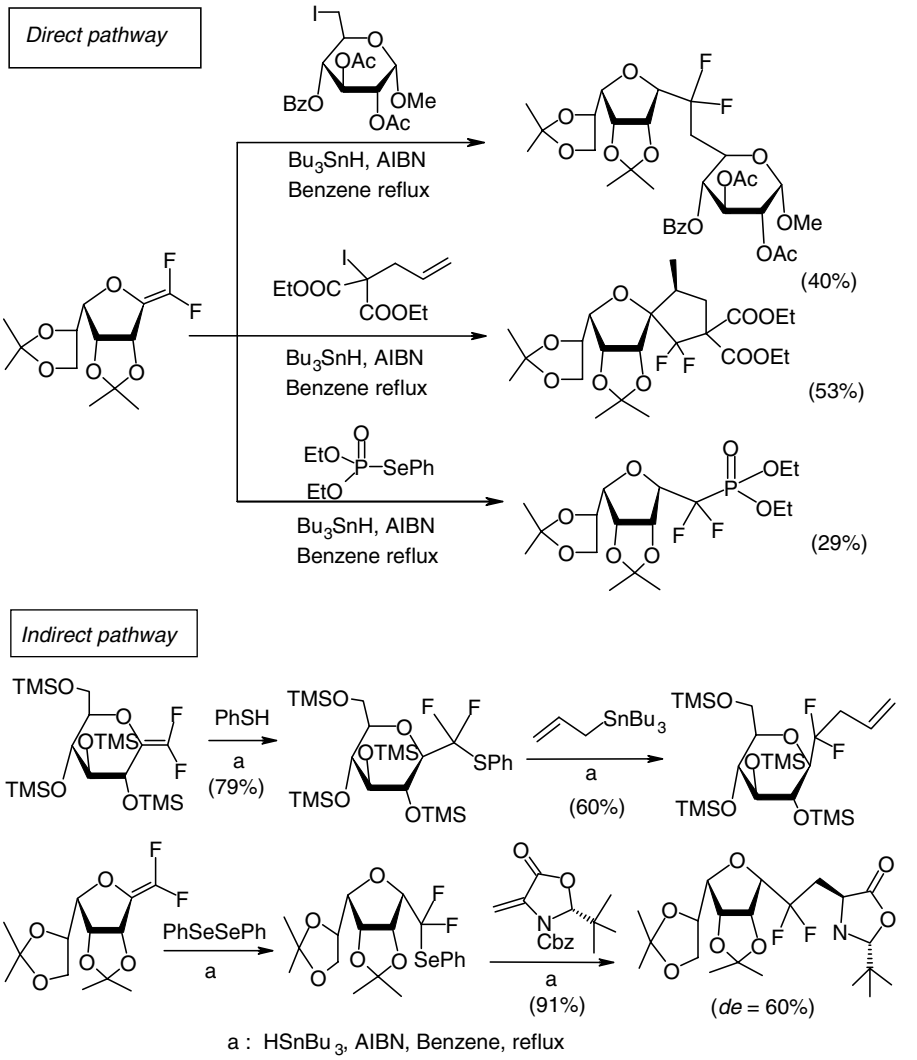


Figure 6.25 Synthetic applications of pseudo-anomeric difluoromethylene furanosides.[71]

6.3.2.3 Saccharidic Difluorophosphonates Difluoromethylene phosphonates have been the focus of numerous works. Indeed, these compounds are able to mimic the phosphate bond in the synthesis of enzyme inhibitors. This interest is obvious for the furanose series: in this case, they are non scissible analogues of 5-phosphate nucleosides (cf. Chapter 7). Difluoromethylene phosphonates can be prepared via a radical path starting from compounds that have the difluoromethylene moiety in the pseudo-anomeric position. Nevertheless, methods based on metal derivatives of difluorophosphonates are generally easier and broadly applicable.

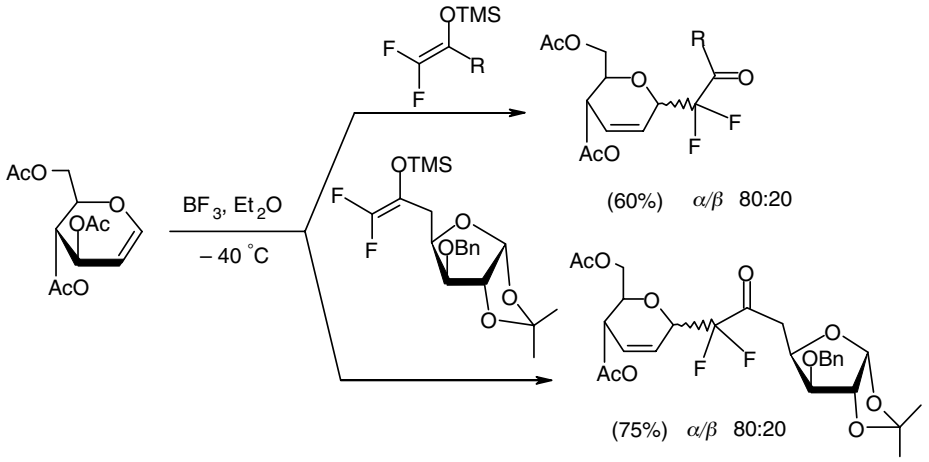


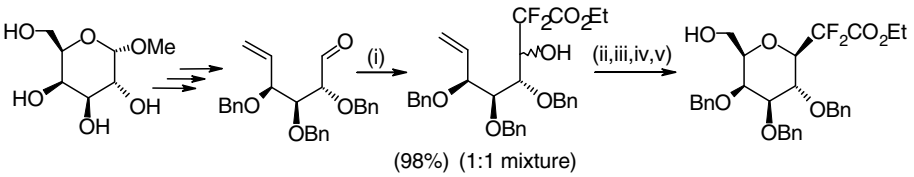
Figure 6.26 Synthesis of difluoro-*C*-glycosides and difluoro-*C*-disaccharides starting from difluoroenoxysilanes.[71]

Indeed, metallation of diethyl difluoromethyl phosphonate affords an anion. This species can displace a primary triflate in position 5[73–75] or add onto an aldehyde (in position 5). In this last case, deoxygenation of the resulting alcohol is required to obtain difluoromethylene phosphonate (Figure 6.28).[74, 76] The anion of diethyl difluoromethyl phosphonate can also displace the anomeric C—O bond of 2-aminofuranoside. It can then allow further access to difluoro-*C*-phosphonates that are derived from iminosugars (cf. Chapters 2 and 7).[76b]

6.3.3 *C*-Difluoromethyl Glycosides

Three approaches can be used to prepare *C*-difluoromethyl glycosides: hydrogenation of difluorovinylic precursors, difluoromethylation reactions, and synthesis from difluoromethyl synthons.

The catalytic hydrogenation of difluorovinylic compounds affords *C*-difluoromethyl glycosides and 2-, 3-, or 5-*C*-difluoromethyl sugars (*vide supra*) (Figure 6.29). In the α-pyranose series, hydrogenation of the exocyclic double bond occurs on the β



(i) Zn, $BrCF_2COOEt$; (ii) separation; (iii) $Hg(OCOCF_3)_3$; (iv) $NaHCO_3$; (v) $NaBH_4$, DMF

Figure 6.27 Synthesis of difluoro-*C*-glycosides through organometallic path.[72]

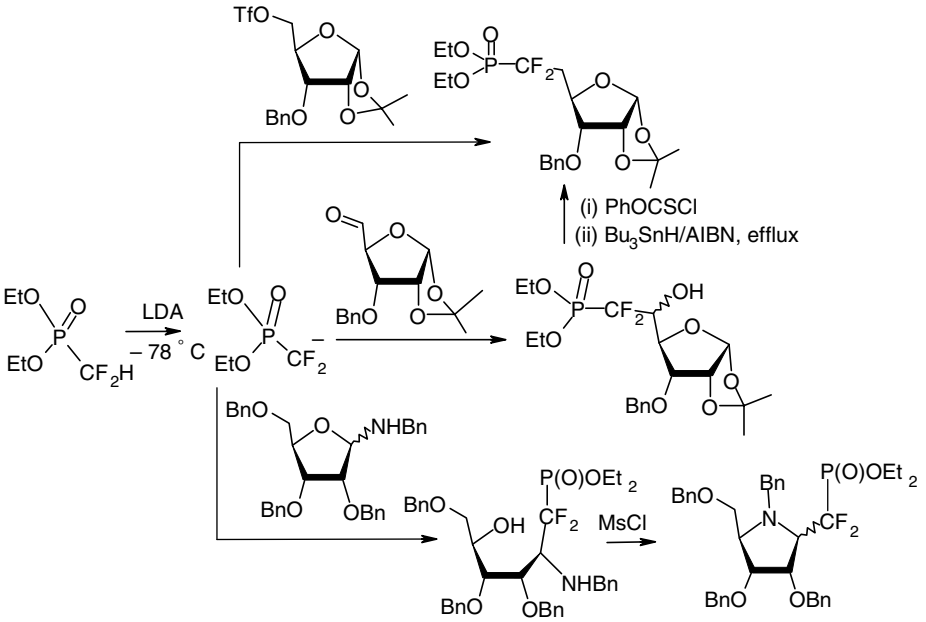


Figure 6.28 Preparation of saccharidic difluorophosphonates.

face.[77] In the furanose series, reduction is controlled by the steric hindrance of the 3,4-substitution (configuration and protecting groups). When performed on the pseudo-anomeric position, hydrogenation is often stereoselective.[78]

The radical difluoromethylation of glycal with freon (CF_2Br_2, CF_2ClBr) has been described.[79–81] It must then be followed by the radical reduction of bromine or chloride. This reaction is generally stereoselective and affords 2-difluoromethyl-*C*-glycosides (Figure 6.30).[80, 81]

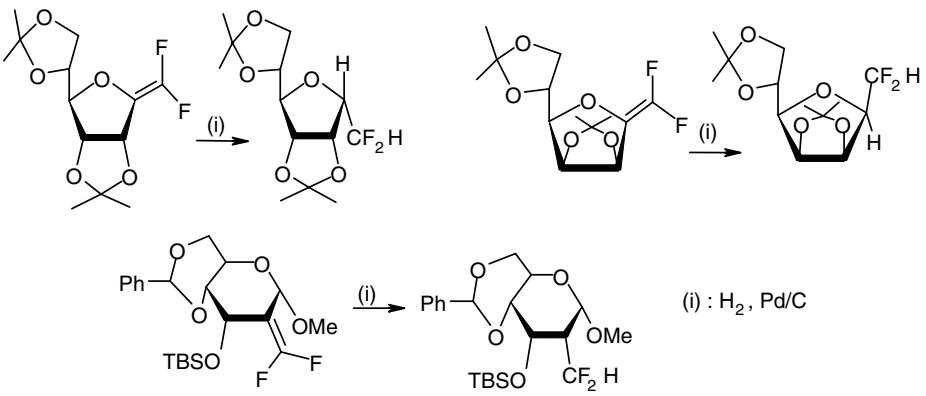
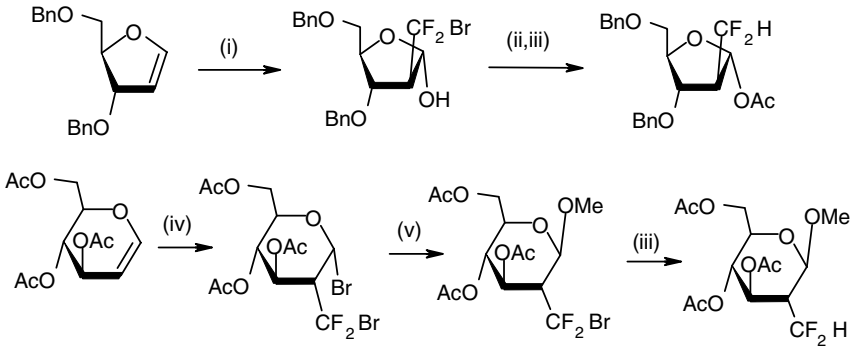


Figure 6.29 Preparation of difluoromethyl saccharides through reduction.



(i) CF_2Br_2, Na dithionite; (ii) Ac_2O, NEt_3; (iii) $HSnBu_3$ AIBN

(iv) CF_2Br_2, $NaHCO_3$, MeCN/H_2O; (v) $AgCO_3$/MeOH

Figure 6.30 Preparation of *C*-difluoromethyl sugars by radical addition of CF_2Br_2.

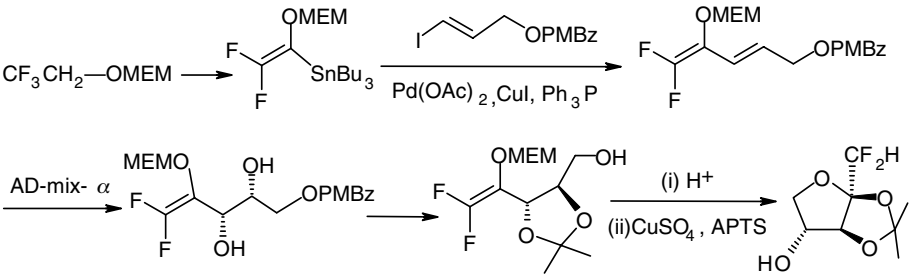


Figure 6.31 Synthesis of *C*-difluoromethyl xylulose from trifluoroethanol.[82]

Two asymmetric syntheses of *C*-difluoromethyl sugars from fluorinated building blocks have been reported. The first one describes the preparation of a derivative of 4-difluoromethyl-1-deoxy-D-xylulose. This synthesis is based on an original cross-coupling between a vinyl halide and a difluorovinyltin compound (prepared from trifluoroethanol). This step is then followed by an asymmetric Sharpless dihydroxylation (AD-mix-α) (Figure 6.31).[82]

The second asymmetric synthesis deals with the preparation of a *C*-difluoromethyl iminosugar. The key step of this synthesis is a hetero–Diels–Alder reaction with a chiral imine of difluoroacetaldehyde (Figure 6.32).[83]

6.3.4 Trifluoromethylated Sugars

The trifluoromethyl group has been introduced on every position, except position 5 in the furanose series and position 6 in the pyranose series. These reactions can be performed through several pathways: by nucleophilic trifluoromethylation with the

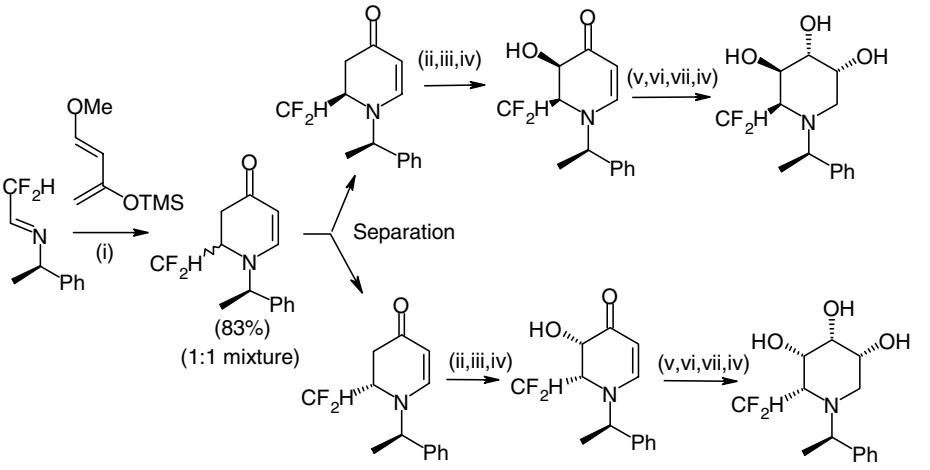


Figure 6.32 Preparation of 1,6-dideoxy-6,6-difluoro iminosugar via cycloaddition.[83]

Ruppert reagent (CF_3TMS), by radical trifluoromethylation, and finally by total synthesis starting from alicyclic precursors.[70c]

6.3.4.1 Nucleophilic Trifluoromethylation The Ruppert reagent adds onto the carbonyl group (ketone, aledhyde) of sugars (Figures 6.33 and 6.34). This reaction is generally not stereoselective and affords a mixture of diastereomer. Thus, starting from D-xylose, a mixture of L-fucose and 6-deoxy-D-altrose derivatives is obtained.[84] Starting from threitol, the stereoselectivity problem has been solved via an oxidation into trifluoromethyl ketone followed by its stereoselective reduction (Figure 6.33).[85]

When the trifluoromethylation occurs on a ketonic carbonyl (such as position 2 or 3 in furanose series), it must be followed by a Barton–McCombie deoxygenation of the hydroxyl. It thus leads to the 2- or 3-*C*-trifluoromethyl deoxyfuranoses. The transformation of these latter compounds into deoxynucleosides has been reported. Trifluoromethyl 2′,3′-dideoxynucleosides and Δ-2′3′-vinylic nucleosides have also been prepared according to this approach (Figure 6.34).[86–90] The CF_3 group protects the glycosyl base bound from proteolysis in acidic medium, especially in the case of Δ-2′3′ compounds.[91]

Barton–McCombie deoxygenation is not always stereoselective: the diastereomeric ratios strongly depends on the nature of the protecting groups and of the ester moiety.[86, 88] However, in 2-*C*-trifluoromethyl-2-deoxyfuranose, the α compound is the major product of the reaction, due to steric hindrance of this α side. In 3-*C*-trifluoromethyl-3-deoxyfuranose, deoxygenation by tributyltin hydride yields only the α product, if it is performed with oxalate instead of thiocarbonate.[87] Another possibility to obtain this selectivity is to perform the reaction with 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose (Figure 6.34).[89b]

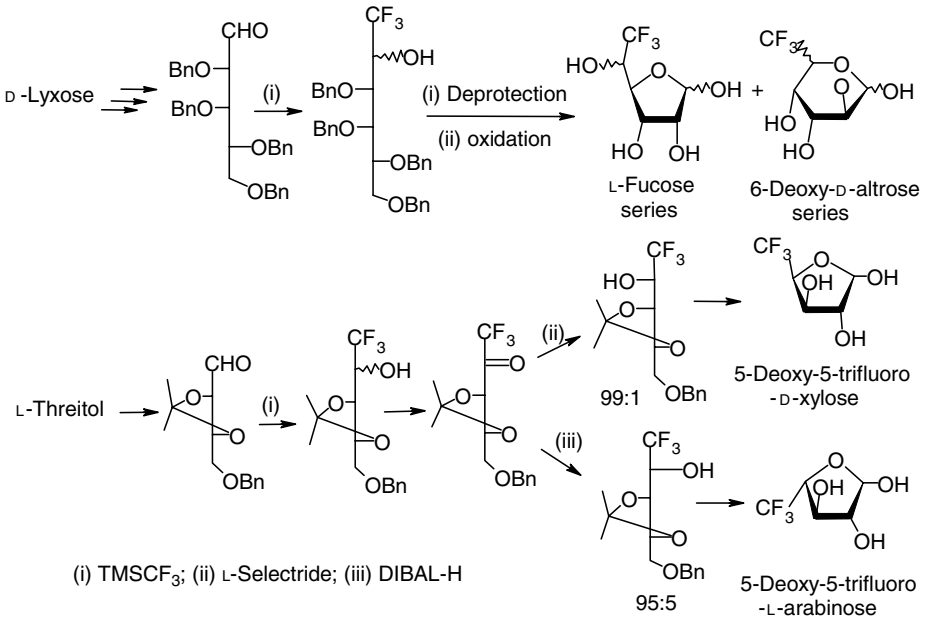


Figure 6.33 Synthesis of trifluoromethyl sugars starting from aldehydes with the Ruppert reagent.

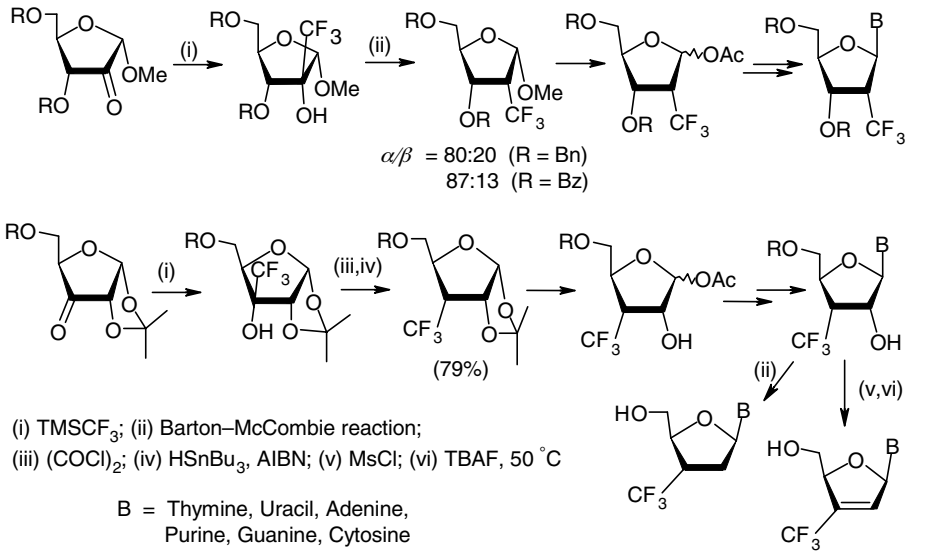


Figure 6.34 Preparation of 2- and 3-*C*-trifluoromethyl deoxyriboses.

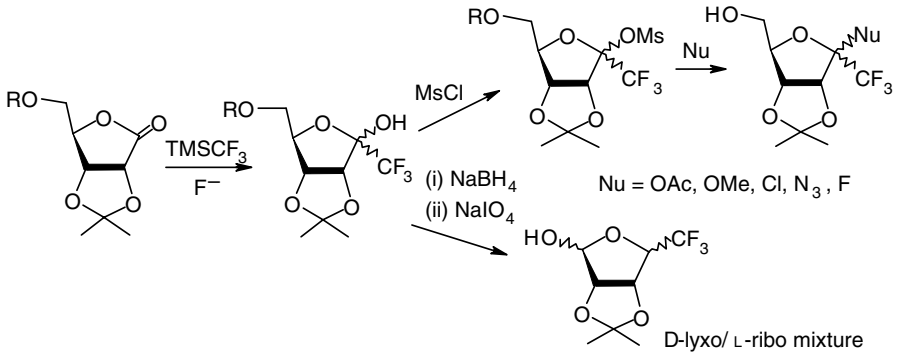
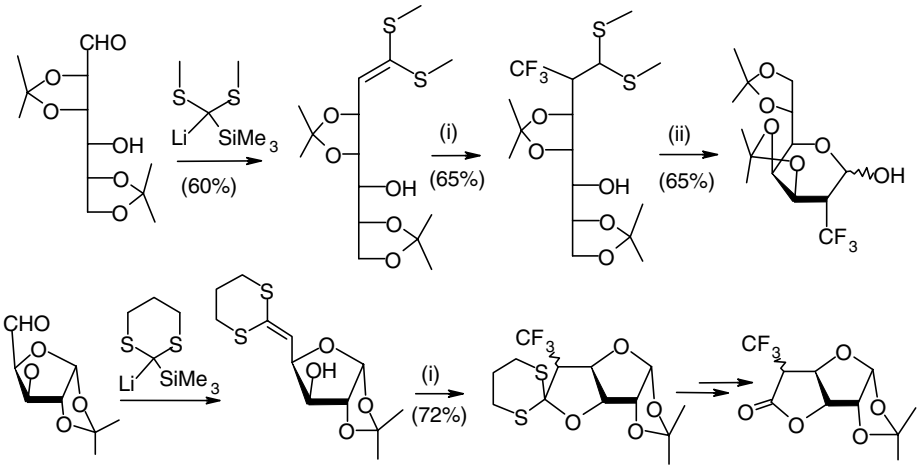


Figure 6.35 Trifluoromethyl *C*-furanosides.

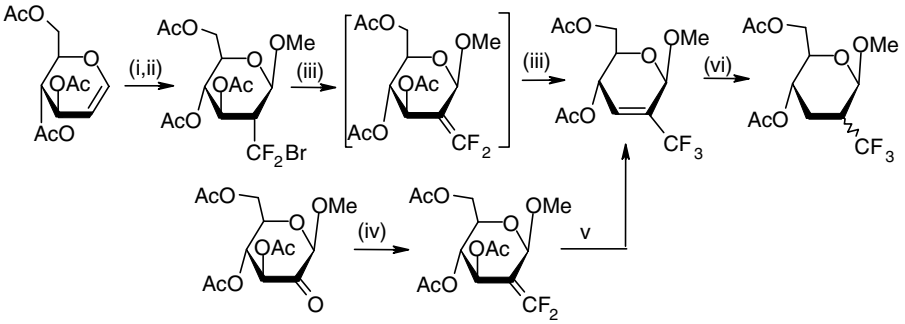
The addition of CF_3TMS on a lactone group in position 1 allows introduction of CF_3 on the anomeric position. Due to its electron-withdrawing effect, the CF_3 group inhibits the possible formation of the oxocarbenium ion intermediate of the anomeric substitution. Consequently, the substituent introduced on the anomeric position (OAc, Cl, F, OMs, etc.) is much less labile (Figure 6.35).[92]

6.3.4.2 Radical Trifluoromethylation The radical trifluoromethylation has been successfully applied to ketene dithioacetals that are derived from sugars.[93, 94] The reaction is performed with bromotrifluoromethane and initiated with sodium dithionite. Ketene dithioacetals are prepared via Peterson olefination of protected aldehyde sugars. This method allows one to introduce a trifluoromethyl group in position 2 (Figure 6.36).[93, 94]



(i) CF_3Br, HCO_2Na,SO_2, $NaHCO_3$, Py, DMF; (ii) DBH—$CaCO_3$

Figure 6.36 Radical trifluoromethylation of ketene dithioacetals.[93, 94]



(i) CF_2Br_2, Na dithionite; (ii) $AgCO_3$ /MeOH; (iii) TBAF, MeCN/H_2O; (iv) CF_2Br_2, HMPT; (v) DAST; (vi) H_2, Pd/C

Figure 6.37 Reduction of *C*-difluorovinyl pyranose.[95]

As previously reported, the radical addition of CF_2Br_2 on glycals (initiated by sodium dithionite) affords difluorobromomethylated compounds. These latter molecules are easily dehydrohalogenated in the presence of TBAF. Under such conditions, these difluorovinyl compounds can add a fluoride ion (from TBAF). The subsequent elimination of the acetate moiety yields trifluoromethyl unsaturated compounds. The double bond can then be reduced (Figure 6.37).[77, 95] The same kind of reaction occurs in the presence of DAST with *gem*-difluoromethylene compounds, which are obtained by addition of an ylide onto an ulose (Figure 6.37).

6.3.4.3 Synthesis from Non-Osidic Precursors Some total syntheses of trifluoromethylated sugars have been described, starting from non-acidic precursors, fluorinated or not.

(a) Starting from Glyceraldehyde Trifluoromethylation of *O*-cyclohexylidene glyceraldehyde under Barbier conditions (CF_3I, Zn/DMF) is not stereoselective. However, after separation of the two diastereomers of the obtained alcohols, 6,6,6-trifluoro-L-daunosamine is obtained with a rather good stereomeric excess (Figure 6.38).[96]

Synthesis of 2-trifluoromethyl-2′,3′-dideoxynucleosides has been realized by the radical trifluoromethylation reaction. The reaction is performed by reacting FSO_2CF_2-CO_2CH_3/CuI and an unsaturated bromoester, resulting from a Wittig reaction between glyceraldehyde and ethyl α-bromophosphonoacetate (*Z*/*E*, 90 : 10). Catalytic hydrogenation of the double bond is poorly stereoselective. The two obtained lactones (ratio 1.67:1) are then separated, before being converted into nucleosides (Figure 6.38).[97]

(b) Starting from Methyl Trifluoropyruvate 2-*C*-Trifluoromethyl-D-ribose and 2-*C*-trifluoromethyl–D-arabinose have been prepared from methyl trifluoropyruvate according to two pathways. The first one is based on a McMurry cross-coupling

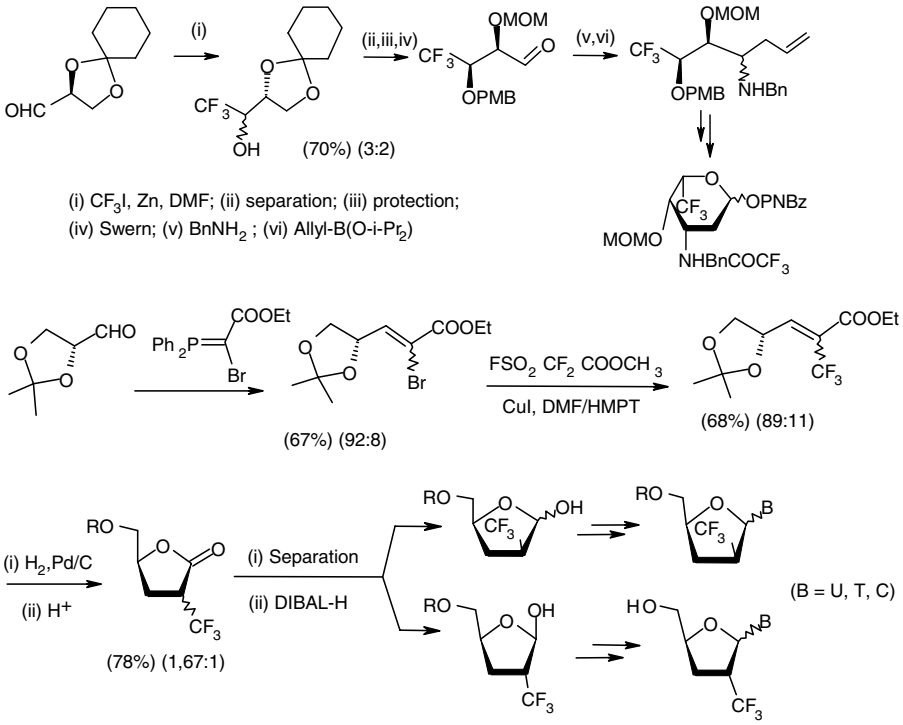


Figure 6.38 Synthesis of trifluoromethyl sugars through trifluoromethylation of non-osidic precursors.

between *O*-isopropylidene glyceraldehyde and methyl trifluoropyruvate. The separation of the two obtained stereomers (ratio 5 : 2) allows one to further obtain 2-*C*-trifluoromethyl-D-ribose and 2-*C*-trifluoromethyl-D-arabinose.[98] The second route involves the addition of an organoaluminum reagent (obtained from Me_3Al and an allyl alcohol ether) onto trifluoropyruvate (Figure 6.39).[99] For ribose, the pyranose form is more stable (79 : 21), but the presence of the CF_3 group highly favors the furanose form in solution (92 : 8). This inversion of stability is also observed for the anomeric hydroxyl: the α form is the major one in the case of the trifluoromethyl compound.

(c) Starting from an α,β-Unsaturated-β-Alcoxy Trifluoromethyl Ketone A [4 + 2] cycloaddition between an α,β-unsaturated-β-alcoxy trifluoromethyl ketone and an enol ether leads stereoselectively to an *endo* adduct (95% excess). The presence of a chiral auxiliary on the ketone yields the corresponding product with a 60% *de*. Diborane reduction, followed by deprotection, affords 2,6-dideoxy-6,6,6-trifluoro-D-arabinopyranose (Figure 6.40).[100]

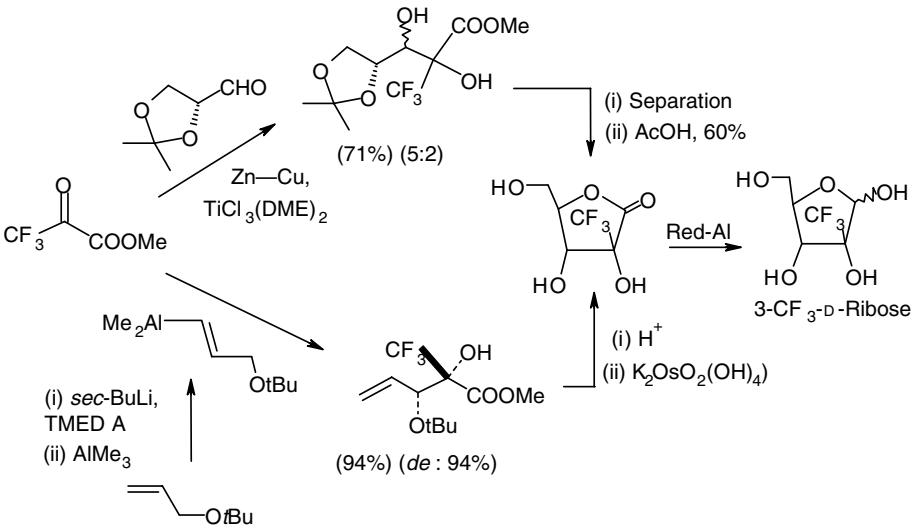
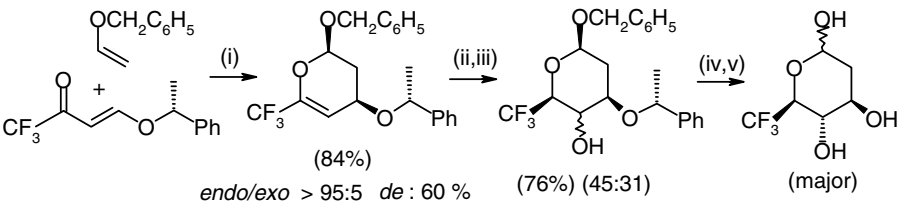


Figure 6.39 Preparation of 2-*C*-trifluoromethyl-D-ribose.[99, 100]

(d) Starting from Bromotrifluoropropene The most efficient way to generate the anion of trifluoropropyne is the treatment of 2-bromotrifluoropropene with 2 equivalents of LDA. The condensation of this anion with aldehydes affords propargylic alcohols as a racemic mixture. The enantiopure compounds are further obtained by lipase resolution. The partial reduction of the triple bond, followed by an asymmetric dihydroxylation, allows one to obtain the various stereomers of 2,6-dideoxy-6,6,6-trifluoropyranose. Synthesis of the L-oliose corresponding compound is described in Figure 6.41.[102].

(e) Starting from Furane Preparation of non racemic trifluoromethylated butenolide has been described by trifluoroacetylation of 2-TMS-furane (Figure 6.42). Further mono- or dihydroxylation, or even reduction of the double bond, offers access to various derivatives of 6,6,6-trifluoro derivatives of 3- or 2,3-deoxypyranoses (Figure 6.42).[101] It should be noted that adding small quantities (2 mol%) of a



(i) $TiCl_4$, – 78 °C;(ii) BH_3,Me_2S;(iii) H_2O_2, NaOH;(iv) separation;(v) H_2, Pd/C

Figure 6.40 Preparation of trifluoromethyl deoxypyranose via hetero-Diels–Alder reaction.[101]

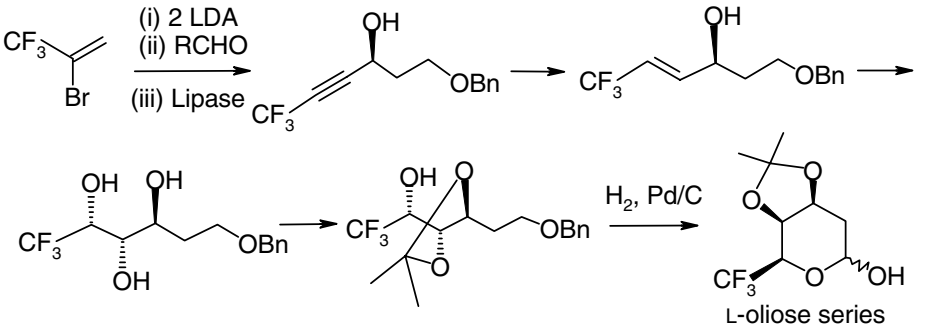
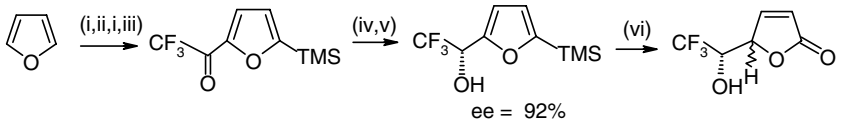


Figure 6.41 Synthesis of 6,6,6-trifluoro-6-deoxypyranoses from furane.[102]



(i) BuLi; (ii) TMSCl; (iii) CF_3CO_2Et; (iv) $NaBH_4$; (v) Lipase; (vi) MMPP/AcOH

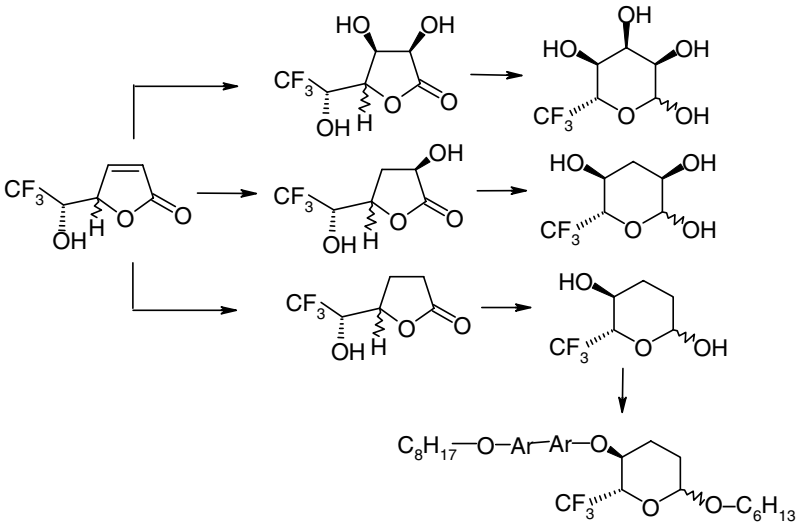


Figure 6.42 Synthesis of 6,6,6-trifluoro-6-deoxypyranose from furane.[101, 103]

long-chain ether of 6,6,6-trifluoro-2,3,6-trideoxypyranose to these compounds induces spontaneous polarization of a ferroelectric achiral smectic mesophase.[103]

6.4 PERFLUOROALKYLATED SUGARS

The presence of long perfluoroalkyl chains gives sugars surfactant and emulsifier properties, with interesting applications in the biomedical field. These applications

have stimulated synthesis of perfluoroalkyl sugars. Like for trifluoromethylation, nucleophilic and radical perfluoroalkylations are the most utilized methods. However, preparation of perfluoroalkyl compounds have some specific requirements.[70c]

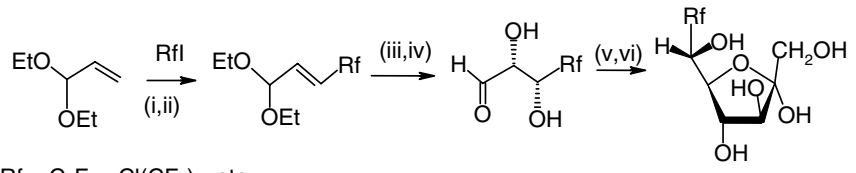
6.4.1 Preparation of *C*-Perfluoroalkyl Sugars

6.4.1.1 Nucleophilic Perfluoroalkylation Perfluoroalkylation with organozinc is relatively difficult (ultrasonic activation is required), and the products are generally obtained in poor yields.[104] However, the reaction proceeds very well with Grignard reagents: conversely to the trifluoromethyl Grignard reagent, superior homologues (i.e., perfluoroalkyl magnesium halides) are very stable and are excellent perfluoroalkylating agents.[105, 106] Perfluoroalkylsilanes also add easily onto osidic carbonyl functions. However, these reagents are much less reactive than CF_3TMS, and the product yields are generally lower.

The stereoselectivity of all these nucleophilic perfluoroalkylations are generally better than those observed with non fluorinated organometallic species, especially for Grignard reagents.[105]

6.4.1.2 Radical Perfluoroalkylation Radical perfluoroalkylations are efficient with halogenofluoromethanes (e.g., CF_2Br_2, CF_2BrCl),[107] as well as with their superior homologues.[108] Perfluoroalkyl iodides add onto glycals, and the corresponding products are obtained in excellent yields.[109] However, the yields are poor with exocyclic double bonds. Radical perfluoroalkylation of ketene dithioacetals is more efficient than radical perfluoroalkylations of glycals.[110]

The original preparation of 6-*C*-perfluoroalkyl-D-fructose has been reported. The first step of this synthesis is the perfluoroalkylation of acrolein acetal. The key step of the synthesis is an aldol condensation between D-3-fluoroalkylglyceraldehyde and dihydroxyacetone phosphate, with RAMA as biocatalyst (RAMA is an aldolase found in rabbit muscles) (Figure 6.43).[111]



Rf = C_8F_{17}, $Cl(CF_2)_6$, etc..

(i) $Na_2S_2O_4/NaHCO_3$, MeCN/H_2O; (ii) KOH/MeOH; (iii) AD-mix-α; (iv) HBF_4, MeCN; (v) DHAP/RAMA; (vi) phosphatase.

Figure 6.43 Enzymatic synthesis of 6-*C*-perfluoroalkyl-D-fructose.[111]

6.4.2 *O*- and *S*-Fluoroalkyl Glycosides

Synthesis and application of these compounds depend a lot on the position of the Rf chain. Three cases can be considered:

1. Compounds having O—CF_3 (or O—Rf) and S—CF_3 (or S—Rf). They are relatively stable derivatives with interesting amphiphilic properties. Moreover, in some cases they are glycosidase inhibitors.
2. Fluoroalcohol ethers, such as —O—CH_2—Rf, or ketals of fluoroalkyl ketones. Their synthesis has been described only recently.
3. Ethers and ketals in which the Rf chain is separated from the oxygen atom by two or three carbons. In spite of the screen effect due to the di- or trimethylene spacer, fluorine atoms still exert a notable effect. As in the previous case, their synthesis generally requires non conventional methods.

6.4.2.1 O—CF3 and S—CF3 Compounds and Superior Homologues

Tris(dimethylamino)sulfonium trifluoromethanolate ($(Me_2N)_3S^+CF_3O^-$) is a reagent that is able to displace primary or secondary triflates with inversion of the configuration.[112] In the case of a leaving group in the anomeric position, *O*-trifluoromethyl glycoside is formed. However, it is also accompanied with notable quantities of the corresponding glycosyl fluoride (Figure 6.44).[113]

Nucleophilic fluoroalkylation in the anomeric position has been performed with trifluorochloroethylene,[114] or with perfluorovinyl ethers.[115] The compound obtained with trifluorochloroethylene is an irreversible inhibitor of α-glycosidases (Figure 6.44).[114] Trifluoromethylzinc bromide can be used to perform the difluoromethylation of hydroxyls in various positions, probably through a carbenic mechanism.[3c, 116]

Compounds of the S—CF_3 type have been prepared by reacting CF_3TMS with a saccharidic thiocyanate. The reactions can be performed on any of the positions, including the anomeric one.[3, 117] The reaction has been extended to β-cyclodextrine derivatives. Although the lipophilic chains are thus reduced to only one carbon, these compounds are able to form stable monolayers.[118] Radical perfluoroalkylation of thioglycosides (with dithionite as initiator) permits easy synthesis of the superior homologues.[119]

6.4.2.2 O-Fluoroalkyl Glycosides (RFn-$(CH_2)_2$-n-O-sugar) and Perfluoroalkylidene Acetals Derived from Sugars

The very low nucleophilicity of fluoroalcohols makes it difficult to substitute of a hydroxyl (anomeric or not).[120] This is the reason why this type of ether is not very common. Such ethers have only been isolated in very small quantities in solvolysis reactions, or in carben insertions, performed in fluorous alcohols.[121, 122] Preparation of these ethers has been solved by means of the Mitsunobu reaction. This reaction is known to be dependent on the pK_a of the acceptor of the glycosyl: the acidity of fluorous alcohols allows a much easier deprotonation than with non fluorinated alcohols.[123]

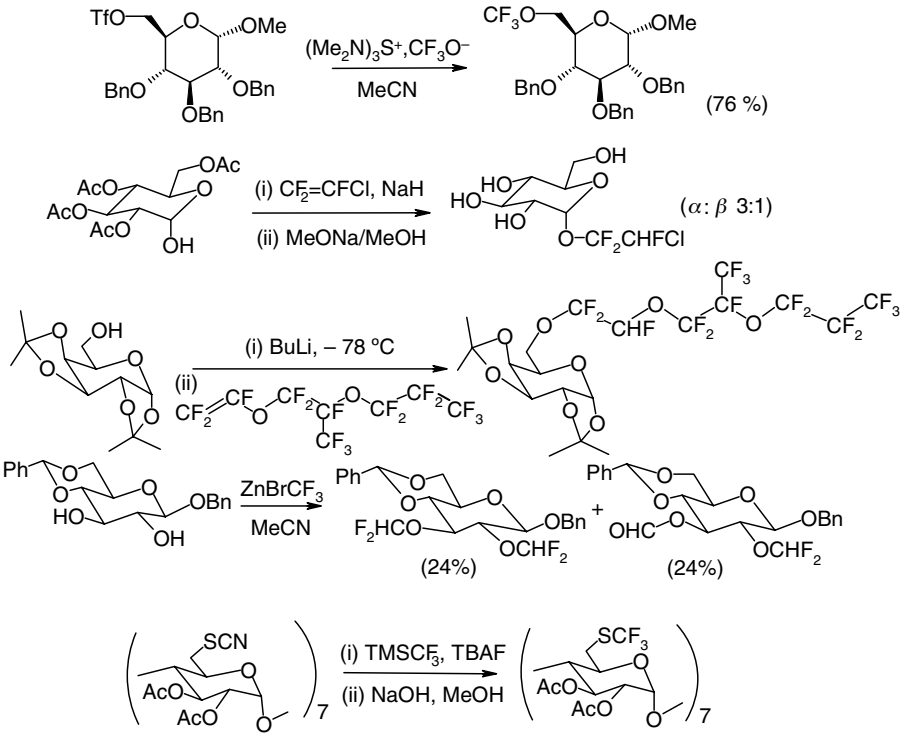
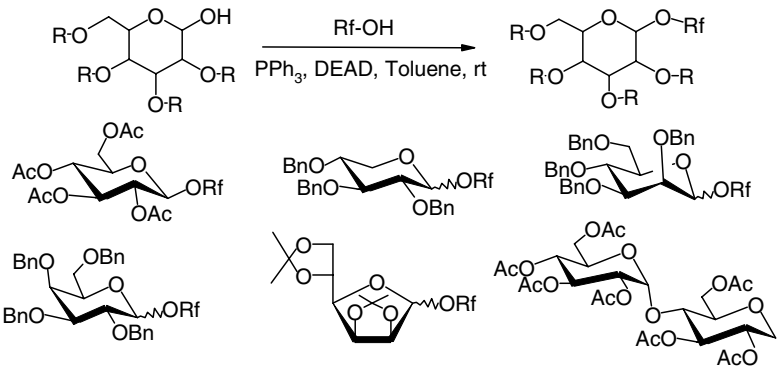


Figure 6.44 *O*- and *S*-perfluoroalkylation of sugars.

O-Fluoroalkyl and *O*-fluoroaryl glycosides have thus been prepared in good yields[124](Figure 6.45).

Perfluoroalkylidene acetals derived from sugars are not accessible via conventional methods. Indeed, the intermediate of the formation of the acetal from the hemiacetal is



R = CH_2CF_3, $CH_2CF_2CF_3$, $CH_2CF_2CF_2CF_3$, $CH(CF_3)_2$, $C(Ph)(CF_3)_2$, C_6F_5

Figure 6.45 Preparation of *O*-fluoroalkyl and *O*-fluoroaryl glycosides.[124]

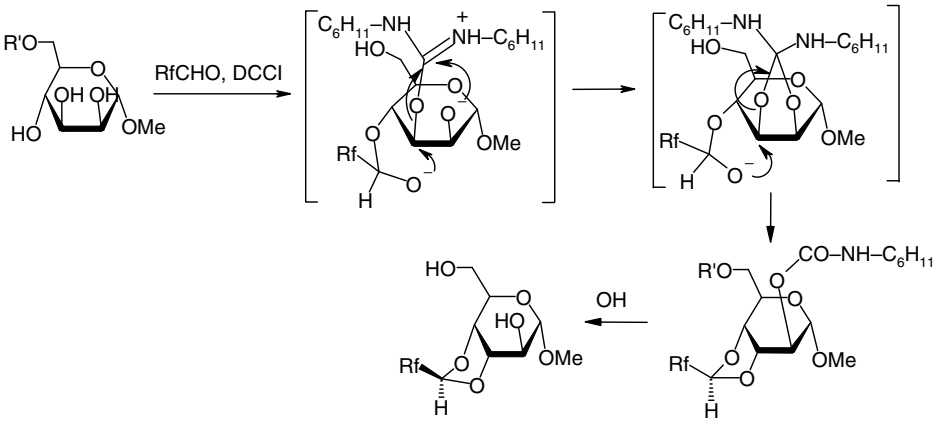


Figure 6.46 Preparation of fluoroalkyl acetals.[125]

fluoroalkyl alkoxycarbenium. This latter species is strongly destabilized due to the fluoroalkyl group. Nevertheless, it is possible to prepare these acetals from perfluoroaldehyde, by inversing the polarity (umpolung) of the reaction: the oxyanion of the fluorinated hemiacetal being the internal nucleophile that substitutes the hydroxyl of the pyranose, which is activated by DCCI (Figure 6.46).[125]

6.4.2.3 O-Fluoroalkyl Glycosides (Rf—CH_2)n—CH_2—O— *O*-Fluoroalkyl glycosides with two or even three methylenes between the Rf group and the oxygen are not accessible by direct glycosylation. The most common compounds (having three methylenes) are usually prepared by radical addition of perfluoroalkyl iodide (initiated by sodium dithionite) onto an *O*-allyl glycoside. The reaction is efficient on any position, including the anomeric one.[126]

A second method is based on the abnormal course of the Koenigs–Knorr reaction with fluoroalkyl alcohols. Indeed, when there are two or three methylenes between the Rf group and the hydroxyl, the reaction does not lead to substitution of the anomeric bromide but instead affords an orthoester. In the presence of mercuric bromide, this orthoester can undergo a rearrangement into an *O*-fluoroalkyl glycoside (Figure 6.47).

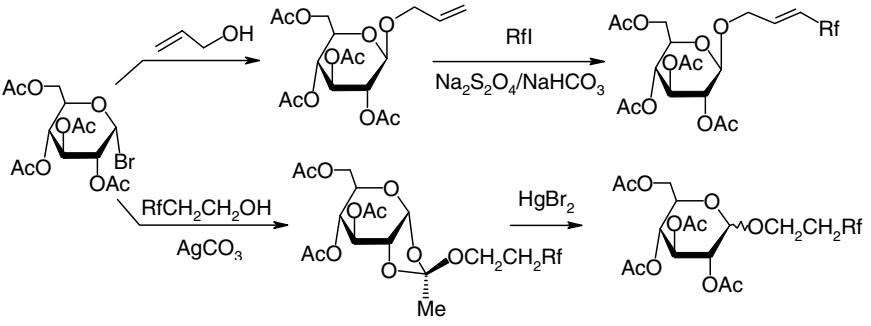


Figure 6.47 Preparation of *O*-fluoroalkyl glycosides.

Fluoroalkyl thiols do not behave like fluoroalkyl alcohols. Indeed, in the presence of a Lewis acid, they afford fluoroalkyl thioglycosides.[127]

6.4.3 Applications of Amphiphilic Fluoroalkyl Sugars

6.4.3.1 Surfactants Numerous sugars having one or several perfluoroalkyl chains (directly connected, or not, to the sugar core) have been prepared. They are used as surfactants in order to stabilize perfluorocarbon emulsions used in the biomedical and pharmaceutical fields.[128] Perfluorocarbon emulsions can be injected and have applications as oxygen-carrier fluids, as contrast agents in medical imaging, and also as systems for targeting drugs.[129] Some of these emulsions are currently in development or on the market (Fluosol®, Oxygent™, Imagent®) (cf. Chapter 8). The role of the surfactant, in the formation of an "oil-in-water" emulsion, is to facilitate the dispersion of the oil, thus stabilizing the emulsion. The surfactant forms a film that coats each drop and organizes the system: interaction between the polar heads and the external water, and insertion of the hydrophobic tails into the oil. Classical hydrocarbon surfactants have only a small affinity for the fluorous phase. Thus, hydrocarbon and fluorous phases do not mix with each other. Lowering of the superficial pressure γ_i is necessary to increase the interfacial area in order to obtain emulsification. For this purpose, a surfactant that is more fluorophilic than lipophilic is required. Thus, the surfactant must bear fluoro- or perfluoroalkyl chains.[130] If the polar head of the surfactant is polyhydroxylated, numerous hydrogen bonds can be formed: a better synergy with the other constituents of the emulsion is obtained and so stabilization is achieved.[128b] Thus, numerous surfactants have been created based on fluoroalkyl saccharide surfactants (Figure 6.48). Choice of the structures of the four elements that constitute the surfactant is important in order to optimize the bond between the phases and thus the stability of the emulsion. Some factors that allow the tuning of the fluorophilic character are the length of the perfluoroalkyl tail (C_4F_9, C_5F_{11}, C_6F_{13}, C_8F_{17}), the length of the hydrocarbon spacer and also its structure (unsaturated or not), and the nature the linking element (carbon, oxygen, nitrogen, sulfur). Moreover, the linking element can permit introduction of a charge or can be a metabolism site. Finally, choice of the saccharide (e.g., glucose, galactose, maltose, mannitol, glucitol, xylitol) is useful for tuning the hydrophilic force and the form of the molecule.

The presence of a fluoroalkyl chain renders the molecule more hydrophobic and enhances its amphiphilic character by lowering the superficial pressure and the critical micellar concentration (CMC) (Figure 6.49). On the other hand, these chains do not cause any specific toxicity, and the hemostatic activity is often lowered.[128b]

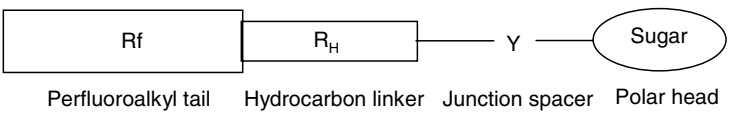
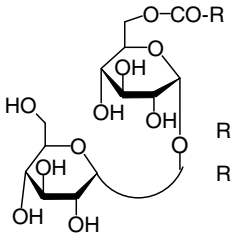


Figure 6.48 Creation of fluorinated surfactant derived from a sugar.



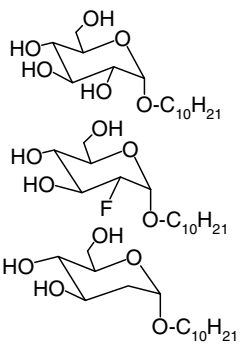
	CMC	γ_l(perfluorodecaline/H_2O)
R = $CH_2CH_2C_8F_{17}$	0.007 mM	2.6 mN/m
R = $C_{10}H_{21}$	0.39 mM	17.4 mN/m

Figure 6.49 Effect of a fluoroalkyl chain on the amphiphilic character.

6.4.3.2 Liquid Crystals The important enhancement of the hydrophobic character, due to the presence of fluoroalkyl tails, favors the auto assembly of amphiphilic fluorinated compounds when they are dispersed in water or in other solvents. They allow the formation of organized structures such a as films, membranes, vesicles, and tubules.[128b]

Thanks to this auto-organization faculty, some amphiphilic sugars have properties of liquid crystals.[131] This tendency is pronounced in the case of fluoroalkyl sugars. The asymmetry of the molecule, the van der Waals interactions between hydrophobic chains, and the hydrogen bond network's polar heads induce the formation of phases and govern their stability. This supramolecular auto-organization does not form a rigid state, but rather a system that has a variable fluidity. This system can evolve into other forms of organization. In the case of liquid crystals based on amphiphilic sugars, smectic and columnar structures are observed.

Replacement of the hydroxyl of a sugar by a fluorine atom renders the hydrogen bond network weaker, thus systematically leading to destabilization of the mesophase. The effect of the introduction of a fluorine atom on the thermal mesogen compounds is shown in Figure 6.50. However, when fluorine atoms are introduced on the hydrophobic part of the molecule, the contrast between the hydrophilic and the hydrophobic parts is increased, thus stabilizing the mesophase. Perfluoroalkyl chains are more rigid than alkyl chains, due to the great difference of energy between the *gauche* and *trans*



	Mp	Cp	
	76 °C	138 °C	(Smectic A)
	88 °C	110 °C	(Smectic A)
	112 °C	73 °C	(Smectic A)

Figure 6.50 Thermal properties of mesogenic fluoroalkyl amphiphiles.

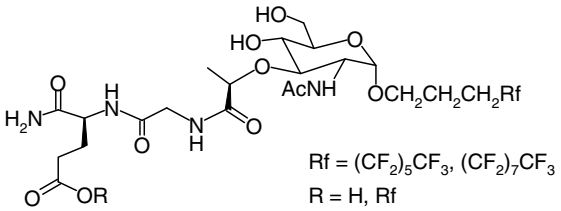


Figure 6.51 Fluoroalkyl derivatives of *N*-acetylmuramyl-L-alanyl-D-isoglutamine.

conformations. These chains exhibit *trans* conformations with lower conformational freedom degree than alkyl chains. Thus, they can adopt helical conformations. By replacing an alkyl chain by a perfluoroalkyl chain, a significant stabilization of the mesophase formed by the amphiphilic sugar is observed.[132]

6.4.3.3 Other Applications of Fluoroalkyl Sugars Other applications of fluoroalkyl sugars in the biomedical area have been reported.

1. Specific and reversible recognition of amphiphiles (with sugar as polar head) by a lectine. The concanavalin A (ConA). ConA acts on vesicles prepared with the surfactant. It provokes agglutination, which is reversible by adding glucose. The phenomenon is significantly enhanced when the lipophilic chains of the surfactant have fluoroalkyl groups. This is due to the enhancement of the hydrophobic forces that increase the stability of the membranes.[133]
2. Sugars substituted by a functionalized fluoroalkyl chain have been used to glycosylate proteins, such as albumin (BSA, HSA) and haptenes. In the latter case, the fluorine atoms can be used as probes in ^{19}F NMR to determine quantitatively the bonding of the haptene.[134]
3. Perfluoroalkyl sugars have been designed to facilitate the transport of a drug (e.g., arabinocytosine). The linking element, in this case, is a biodegradable function.[135, 136]
4. A few fluoroalkyl sugars have also been directly studied for their own biological acivity. *N*-Acetylmuramyl-L-alanyl-D-isoglutamine is the minimal structure of the peptidoglycan of the bacterial wall. Fluoroalkyl derivatives of this molecule have immunogenic activity (Figure 6.51).[137] On the other hand, sulfated oligosaccharides of the laminarin type, and also galactosyl ceramides with fluoroalkyl chains, inhibit HIV cell penetration.[128b]

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7

INHIBITION OF ENZYMES BY FLUORINATED COMPOUNDS

Enzyme inhibitors can be designed through different ways taking into account the effects of fluorine substitution on the behavior of a substrate toward the enzyme. Many fluorinated inhibitors (reversible or irreversible) have been studied. In this chapter, we only consider cases in which fluorine atoms play a determinant role in the inhibition and which are of importance in drug discovery. We successively focus on the following:

1. Fluorinated analogues of substrates in which the bond that should be cleaved in the enzymatic reaction is replaced by a nonscissile C—F bond. This category includes molecules where a leaving group (hydroxyl or hydrogen) is replaced by a fluorine atom.
2. Fluorinated analogues of substrate mimics of dipeptides or of phosphates in which the peptidic or phosphate bond is nonscissile.
3. Pseudosubstrates in which the fluorinated group is introduced to destabilize a reaction intermediate or a transition state of the enzymatic transformation. This can provoke inhibition or irreversible inactivation of the enzyme.
4. Compounds able to mimic the transition state of the enzymatic reaction, and thus to stabilize it.
5. Fluorinated substrates that are transformed into activated entities capable of reacting in an irreversible manner with the enzyme (mechanism-based inhibitors or suicide substrates). In the case of a mechanism-based inhibitor, the enzyme does not add onto the substrate itself, but onto an intermediate

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(generally an electrophilic one) generated from this substrate by the enzymatic reaction. The site of addition is not determined by the reaction mechanism, but by the proximity of this intermediate with nucleophilic residues of the active site to the enzyme.

Most of the work dealing with fluorinated inhibitors of enzymes was done in order to design new drugs and was not oriented toward basic enzymology. Research of global biological activity has therefore been privileged with regards to the pure enzymological aspect. For this reason, although the biological effect is often undeniable, a lack of clear kinetic and mechanistic data does not allow a rigorous interpretation at the enzymological level. In order to illustrate this point, this chapter begins by detailing the inhibition of the Krebs cycle by fluoroacetic acid.

The toxicity of fluoroacetic acid and of its derivatives has played an historical decisive role at the conceptual level. Indeed, it demonstrates that a fluorinated analogue of a natural substrate could have an activity profile that is far different from that of the nonfluorinated parent compound. The toxicity of fluoroacetic acid is due to its ability to block the citric acid cycle (Krebs cycle), which is an essential process of the respiratory chain. The fluoroacetate is transformed *in vivo* into 2-fluorocitrate by the citrate synthase. It is generally admitted that aconitase (the enzyme that performs the following step of the Krebs cycle) is inhibited by 2-fluorocitrate: the formation of aconitate through elimination of the water molecule is *a priori* impossible from this substrate analogue (Figure 7.1).

Although this interpretation can be found in most books, the reality is much more complex. Citrate synthase yields the sole (2*R*,3*R*)-2-fluorocitrate with a large stereoselectivity. This stereomer (and three other ones) does not inhibit aconitase, but it is a substrate of this enzyme. Aconitase cannot afford *cis*-aconitate by elimination since

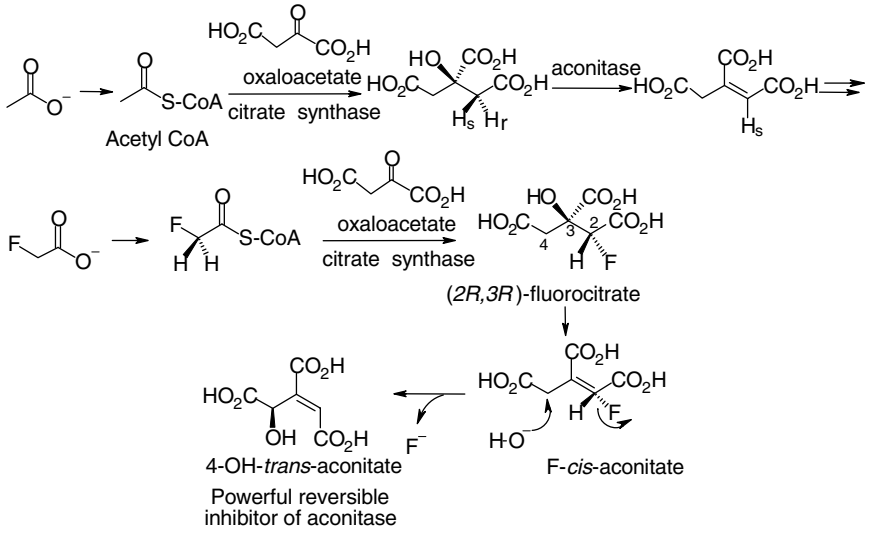


Figure 7.1 Krebs cycle and its inhibition by fluorocitrate.

the hydrogen atom (2*R*) that is eliminated in the enzymatic process is replaced by the fluorine atom (2*R*). Instead, this enzyme performs the dehydration of the (2*R*,3*R*)-2-fluorocitrate by pulling out one of the hydrogens in position 4, to afford F-*cis*-aconitate. A β-elimination reaction occurs with loss of an HF molecule, which is followed by the addition of OH^-, thus yielding 4-OH-*trans*-aconitate. This latter compound is the genuine inhibitor of aconitase (Figure 7.1).[1, 2] Inhibition by 4-OH-*trans*-aconitate is reversible, but it has a strong affinity. This mechanism has been confirmed by the X-ray structure of aconitase/4-OH-*trans*-aconitate adduct complex.[3]

Nevertheless, the toxicity of fluoroacetate seems to be only partially due to the inhibition of aconitase. The competitive nature of the inhibition, its K_i value ($K_i = 20$–$60\ \mu M$),[4] and the time-dependent nature (but reversible) of the inhibition of aconitase seem to be poorly compatible with the sharp and irreversible toxicity of fluorocitrate. Thus, it has been suggested that fluorocitrate can covalently bind with the proteins that are involved in citrate transport through the mitochondrial membrane.[5]

This example of the toxicity of fluoroacetate shows that interpreting a biological effect at the enzymological level requires long and complex studies. Thus, we must remember that explanations about the role of fluorine in the inhibition of enzymes should be considered with caution. In most cases, they must be considered as hypotheses.

This chapter successively considers the various types of inhibitors that are substrate analogues, the inhibitors that act through destabilization of an intermediate or transition state, the analogues of the transition state, the mechanism-based inhibitors, and, finally, the inhibitors that are interesting at the level of medicinal chemistry, but whose inhibition mechanisms have not been clearly elucidated.

7.1 SUBSTRATE ANALOGUES

7.1.1 Fluorine Replaces a Hydrogen Involved in the Catalytic Cycle

7.1.1.1 Inhibition of Thymidylate Synthase Discovery of the antitumor properties of 5-fluorouracil (5-FU) in the late 1950s,[6] short time after that of fluorocorticoids, had an determining impact by showing the potential of fluorinated molecules in medicinal chemistry.

Thymidylate synthase (TS) is the enzyme that converts 2-deoxyuridine monophosphate into thymidine monophosphate. This is a key step in the biosynthesis of DNA. This enzymatic reaction of methylation involves the formation of a ternary complex between the substrate, the enzyme, and tetrahydrofolic acid (CH_2FAH_4).[7a] The catalytic cycle involves the dissociation of this complex and the elimination of FAH_4. It is initiated by pulling out the proton H-5, thus generating an exocyclic methylene compound.[7b] As the release of a F^+ ion is energetically forbidden,[7a, 8a, 9] the fluorine atom that replaces the proton H-5 cannot be pulled out by the base. This leads to inhibition of the enzyme (Figure 7.2).

Although the antitumor activity of 5-fluorouracil (5-FU) is mainly due to the inhibition of thymidylate synthase (after its *in vivo* glycosylation and its phosphorylation), it

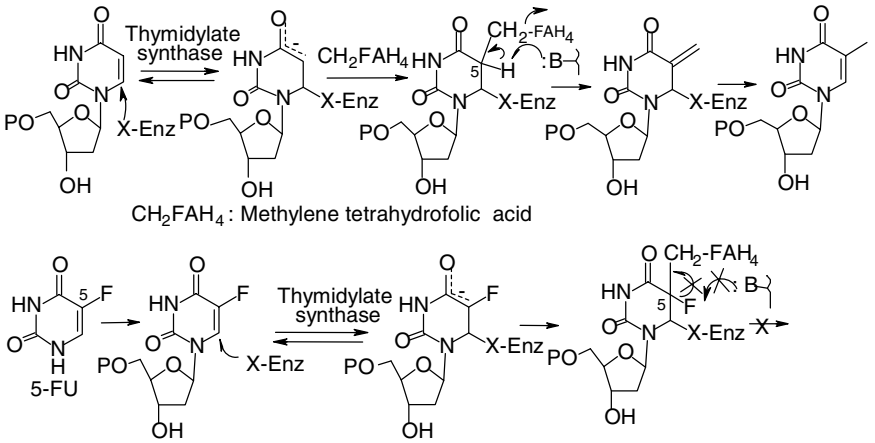


Figure 7.2 Inhibition of thymidylate synthase by 5-FU.[7]

is actually multifactorial. Incorporation of 5-FU, through F-desoxyuridine state, into various types of RNA leads to cytotoxicity. This occurs through inhibition of the methylation and of the maturation of ribosomal RNA.[9] 5-FU is also a precursor of monofluoroalanine, via metabolic degradation. Monofluoroalanine is itself toxic.

5-Fluorouracil and its derivatives are still important drugs in the chemotherapy of numerous cancers (*doxifluridine*, *tegafur*, *carmofur*) (cf. Chapter 8). Studies on the mechanism of action of 5-FU had great influence on the development of other antitumor drugs that are derived from pyrimidine and purine. 5-FU is industrially prepared by fluorination of uracil with elemental fluorine (cf. Figure 2.6, Chapter 2).

Trifluridine, a trifluoromethylthymidine, inhibits the thymidylate synthase (TS) with a mechanism different from that of 5-FU. It is a mechanism-based inhibitor (see Figure 7.52).

7.1.1.2 Inhibition of 2-Desoxycytidine-5-Methyltransferase 2-Desoxycytidine-5-methyltransferase (DCMTase) is the enzyme responsible for methylation of 2′-desoxycytidine (dC), thus affording 5-methyl-2-desoxycytidine. On the same basis as previously (i.e., replacement of a labile hydrogen by a fluorine atom), 2′-deoxy-5-fluorocytidine (5-F-dC) has been designed as an inhibitor of DCMTase. In the catalytic cycle, a thiol group from the enzyme adds onto position 6 of pyrimidine. This reaction is followed by the transfer of a methyl (stemming from *S*-adenosyl methionine) onto position 5 of dC. The presence of the fluorine atom renders impossible the β-elimination that normally allows regeneration of the catalytic thiol of the enzyme (Figure 7.3).[8a, 10]

7.1.1.3 Inhibition of Chorismate Synthase Shikimic and quinic acids are used by microorganisms, fungi, and superior plants for the synthesis of essential aromatic amino acids from acyclic sugars. Fluorinated analogues of substrates and reaction intermediates have been synthesized in order to inhibit enzymes involved in

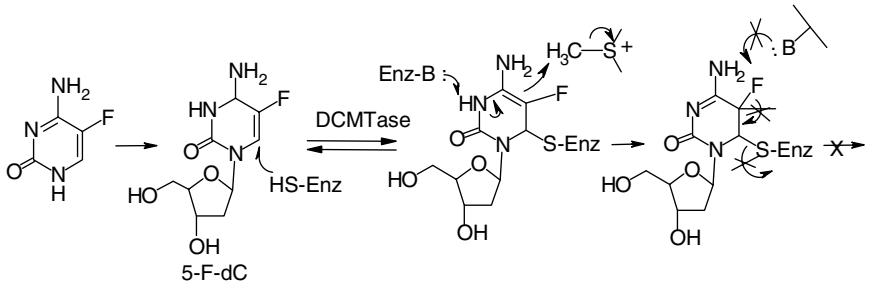


Figure 7.3 Inhibition of 2′-desoxycytidine-5-methyltransferase (DCMTase).

these biosyntheses. Chorismate synthase catalyzes the seventh step of the shikimic path: transformation of 5-enol-pyruvylshikimate 3-phosphate (EPSP) into chorismate. This reaction is formally a 1,4-*trans*-elimination of the pro-(*R*)-6 hydrogen and of the phosphate in position 3.[11a] In order to examine the mechanism, 6-(*R*)- and 6-(*S*)-F-EPSP have been prepared through enzymatic synthesis from 6-fluoroshikimic acids. These latter are themselves prepared from shikimic acid.[11b, 12] Introduction of fluorine occurs by opening of an epoxide with the HF/Py complex or by treatment of the protected diol with DAST (see Figure 7.4).[13, 14a] Inhibition of chorismate synthase by the two 6-F-EPSP is strong (0.2 μM for the 6-(*R*)-F and 2.2 μM for 6-(*S*)-F) and competitive. However, lack of supplementary data, in particular, for the possible transformation of 6-F-EPSP by the enzyme, does not allow to confirm this mechanism. Conversely, it has recently been shown that 6-(*S*)-F-EPSP can be a substrate for chorismate synthase, and thus can be transformed into 2-fluorochorismate. 2-Fluorochorismate is a powerful inhibitor of 4-amino-4-deoxychorismate synthase (ADCS). ADCS is an enzyme involved in the pathway yielding *p*-aminobenzoic acid from chorismate (Figure 7.4). The antibacterial activity (*Escherichia coli*) of 6-fluoroshikimic acids, especially of the (*S*) isomer, should be due to this irreversible inhibition of the ADCS.[14c]

Applications of the inhibition of enzymes of the shikimic pathway have given rise to the synthesis of numerous fluorinated derivatives of shikimic acid, especially for applications in crop sciences (bactericides, fungicides, herbicides).[14, 15] Due to the lack of precise data on the inhibition mechanism, these examples are not considered here.

7.1.2 Fluorine Replaces a Hydroxyl

The van der Waals radii of oxygen and fluorine atoms and the polarity of the C—F and C—O bonds are close. It can be assumed that replacement of a hydroxyl by a fluorine atom in a substrate of an enzyme does not impede recognition by the enzyme and can eventually transform the substrate into a potential inhibitor.

Despite the analogy of the structural data, this frequently validated hypothesis (*vide infra*) is more questionable in the case of a vinyl fluoride as an enol mimic (Figure 7.5),

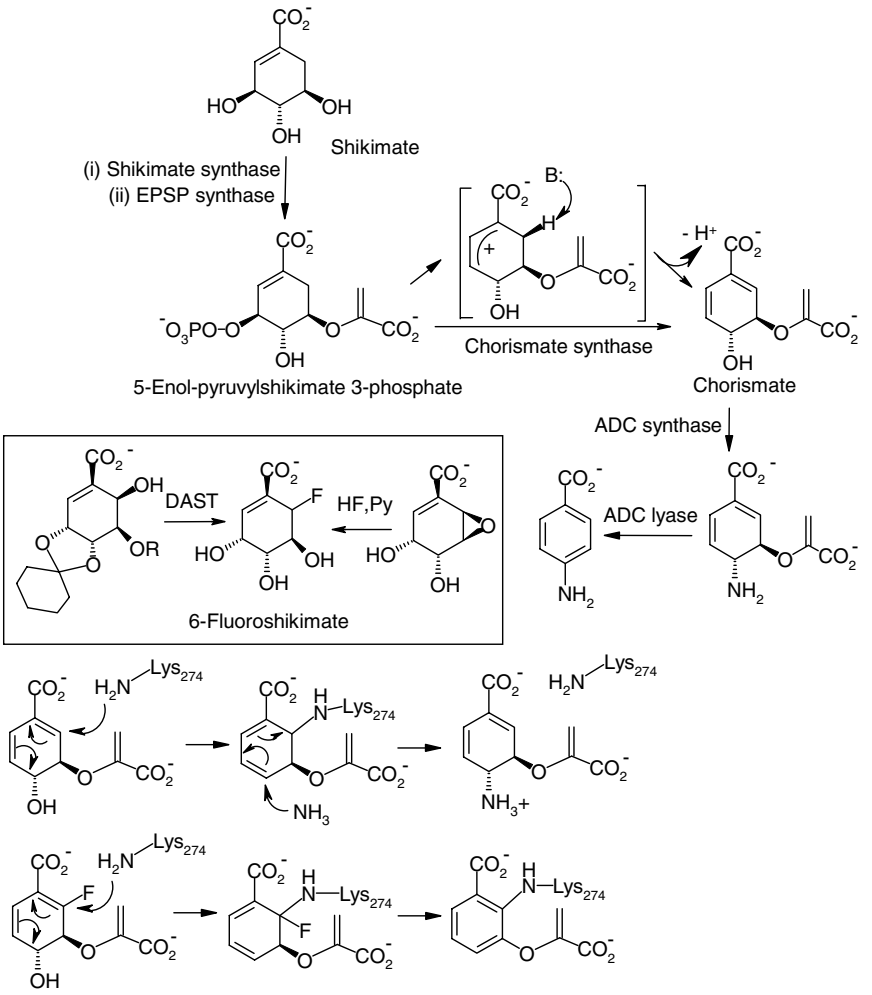


Figure 7.4 Inhibition of chorismate synthase by 6-fluoroshikimate.

	OH	F
$R_{C\text{-}C}$ (Å)	1.35	1.35
$R_{C\text{-}X}$ (Å)	1.36	1.325
E_{HOMO} (eV)	– 9.3	– 10.2
μ(D)	1.72	1.702

Figure 7.5 Comparison between an enol and a vinyl fluoride (MNDO).[16]

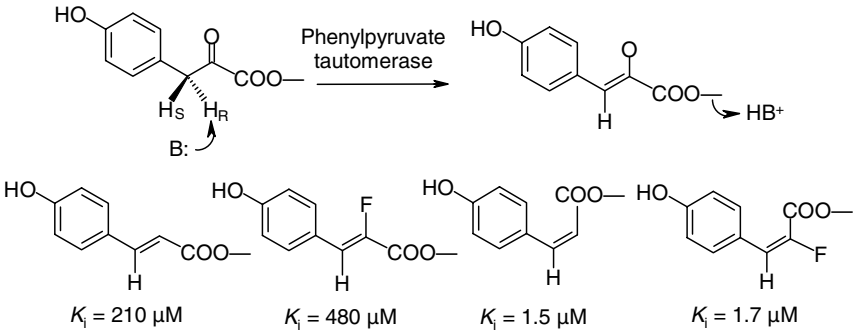


Figure 7.6 Inhibition of phenylpyruvate tautomerase.[16]

since inhibition K_i values of phenylpyruvate tautomerase by vinylic fluoride or by nonfluorinated substrate are close (Figure 7.6).[16] This approach also failed in the case of the inhibition of the steroid 5α-reductase.[17] When good inhibition is observed, as with the steroid C17(20) lyase (see Figure 7.62), the mechanism is probably different.

7.1.2.1 Inhibition of Dehydroquinase Type II Dehydroquinase type II is an important enzyme in the shikimic and quinic routes. It ensures the reversible conversion of 3-dehydroquinate (DHQ) into 3-dehydroshikimate (DHS). Elimination of the hydroxyl is assisted by an acid/base catalysis that is associated with a residue of the active site.

The enolate involved in the conversion of 3-dehydroquinate into 3-dehydroshikimate can be sterically and electronically mimicked by a vinyl fluoride. However, the ketonization process is impossible. This vinyl fluoride is a competitive inhibitor of dehydroquinase II that is 20 times more powerful than the nonfluorinated analogue (Figure 7.7). Moreover, it is very selective toward dehydroquinase I, while it acts according to a different mechanism.[18]

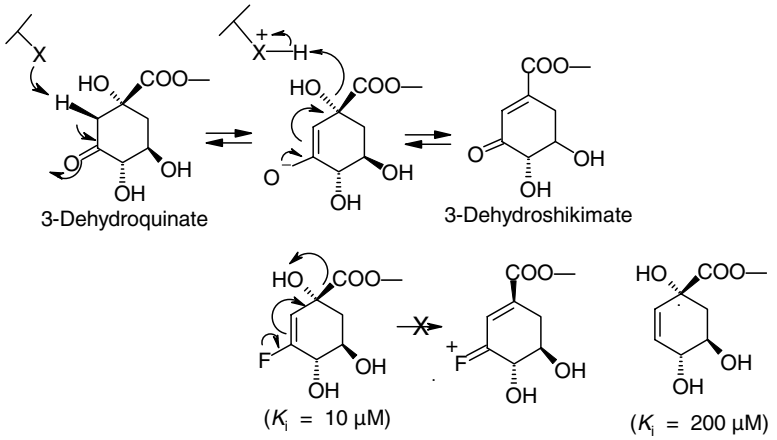


Figure 7.7 Inhibition of dehydroquinase II.

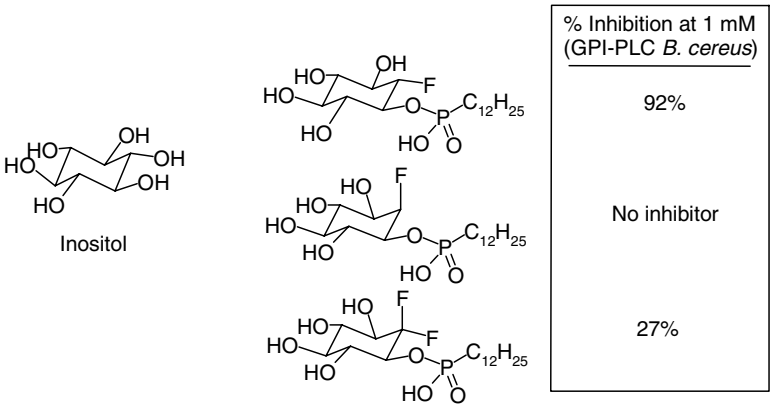


Figure 7.8 Inhibition of glycosyl phosphatidylinositol phospholipase C (GPI-PLC).[19b]

7.1.2.2 Inhibition of Glycosyl Phosphatidylinositol Phospholipase C (GPI-PLC) Glycosyl phosphatidylinositol phospholipase C (GPI-PLC) is a key enzyme in the metabolism of membrane phosphatidylinositols that are involved in signal transduction. GPI-PLC plays an important role in the release of phosphatidylinositols from their linking at the protein surface. Among the described fluoroinositols,[19b] the phosphonates of 2-fluoro-2-deoxyinositols deserve attention. The compound in which an equatorial fluorine replaces the hydroxyl of inositol is an inhibitor with a submillimolar inhibition constant. Conversely, when the fluorine is axial, the compound is a poor inhibitor. However, the difluorinated compound has a comparable inhibition to the compound with the equatorial fluorine (Figure 7.8).[19b]

7.1.3 Fluorinated Analogues of Substrates in Which Fluorine is Not Directly Involved in Inhibition

In the substrate analogues previously reported, fluorine replaces a leaving group (e.g., a hydrogen) or mimics a hydroxyl group that is directly involved in the enzymatic process. This section deals with substrate analogues in which a C—Y bond (Y = O, N) that is normally broken during the enzymatic process is replaced by a nonscissile carbon–carbon bond. For instance, replacement of the peptidic bond by a C—C bond in a dipeptide substrate of a protease could transform this dipeptide into an inhibitor of this protease. This approach concerns proteases and esterases, but also other families of enzymes: kinases and phosphatases, sulfatases, glycosidases, and glycosyltransferases. It is obvious that the environment of this bond must be sterically and electronically mimicked as well as possible. Fluorine atoms are often introduced to enhance the mimicking qualities of these substrate analogues. Indeed, they allow one to modify the electronic distribution, the geometry, and the pK_a and to reinforce the hydrogen bonds.

In contrast with previous examples (cf. Sections 7.1.1 and 7.1.2), fluorine atoms are not directly involved in the enzymatic reaction. They are useful to improve the inhibitor properties of the substrate analogue.

7.1.3.1 Fluorophosphonates as Mimics of the Phosphate Group A phosphate group has a pronounced charged character and is unstable toward hydrolysis. For these reasons, it is difficult to utilize molecules bearing such a group in medicinal chemistry, and the search for nonscissible mimics, such as phosphonates, is the focus of numerous investigations. In this context, Blackburn has introduced fluorophosphonate compounds,[20] and numerous synthetic studies have followed in order to produce kinase and phosphonate inhibitors.[21] Replacement of the oxygen atom of a phosphate by a methylene, leading to a phosphonate, induces a decrease in the electronegativity. Thus, by introducing fluorine atoms onto a phosphonate, this electronegativity is recovered, and the acidity of the phosphonate becomes close to that of a phosphate (cf. Chapter 3, Figure 3.21).

Phosphonates that do not undergo cleavage by phosphatases can also be used as stable analogues of phosphorylated molecules, and thus they can be considered as substrates. Various applications are given at the end of this section.[22]

(a) Preparation of Fluorophosphonates Difluorophosphonates are generally prepared by condensation of a metallated difluoromethane phosphonate (Li, Ce, etc.) with an electrophile (displacement of a triflate, addition of an aldehyde followed by a deoxygenation step).[23] Monofluorophosphonates are also prepared in this organometallic way. However, they are also prepared using other approaches: electrophilic fluorination of phosphonate carbanions, nucleophilic fluorination of hydroxyphosphonate with DAST, Peterson or Horner–Emmons olefination of fluorophosphonate anions, radical addition, or metal-catalyzed cross-coupling (Figure 7.9).[21–23]

(b) Fluorophosphonates as Kinase and Phosphatase Inhibitors

(i) PHOSPHOTYROSINE PHOSPHATASE PROTEIN 1B Phosphotyrosine phosphatase protein 1B (PTP1B) downregulates the signaling pathways of insulin and of leptin. Consequently, PTP1B is a promising target for the treatment of diabetes type II and of obesity.[24a]

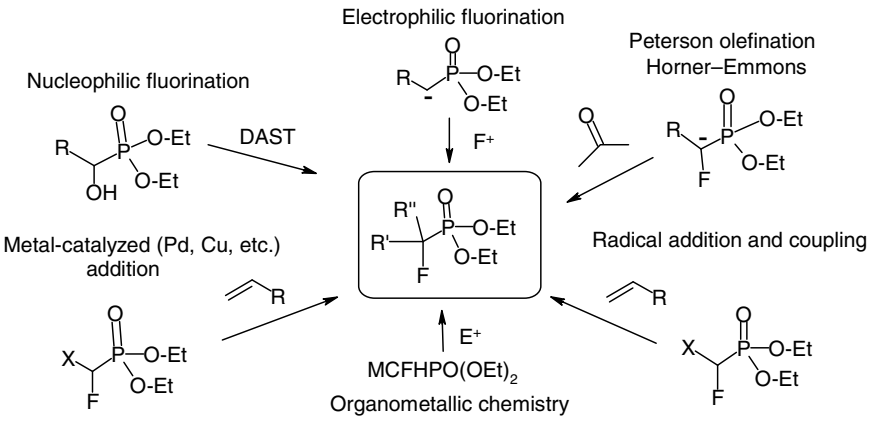


Figure 7.9 Main preparation routes for ethyl monofluorophosphonates.[23]

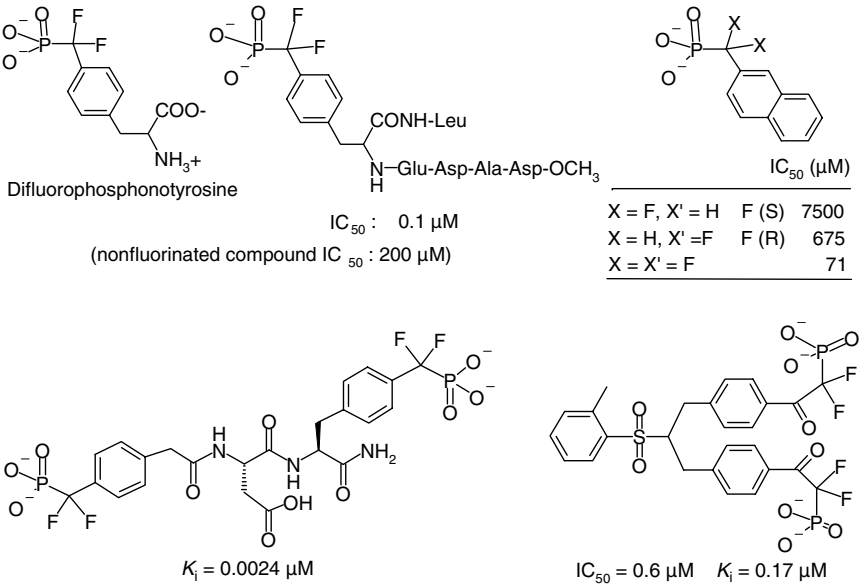


Figure 7.10 Inhibition of the PTP1B by phosphonotyrosine analogues.

The difluoro analogue of phosphonotyrosine has been incorporated into various peptides in order to inhibit phosphatases. Thus, a difluorophosphonotyrosine-containing hexapeptide is an excellent inhibitor of phosphotyrosine phosphatase protein 1B (PTP1B): it is 2000 times more powerful than its nonfluorinated analogue (see Figure 7.10).[25] This peptide is able to lower the overexpression of the insulin receptor associated with the overexpression of PTP1B in some forms of diabetes.[24b] Other difluorophosphonotyrosine-containing peptides specifically inhibit the processes of signal transduction between phosphatidylinositol-3 kinase and the β receptor of PDGF.[26] Some simpler compounds, such as naphthyldifluoromethyl phosphonates, are also good inhibitors of PTP1B. They are far better inhibitors than the corresponding monofluorophosphonates (Figure 7.10).[27a]

Numerous structural modifications have been done on these compounds, affording PTP1B inhibitors that are more powerful and more selective toward other phosphatases. Among them, some bis(difluorophosphonates)[27b, 28] and bis(difluoro-β-ketophosphonates)[27c] deserve particular attention (Figure 7.10).

The strong affinity of peptidyl fluorophosphonates for the PTP1B enzyme is very surprising compared to that of nonfluorinated parent peptides. In order to explain this phenomenon, the existence of a hydrogen bond has been suggested between one of the fluorine atoms of the difluorophosphonate and the NH moiety of the phenylalanine-182 (C—F···H—N(Phe182)). According to theoretical molecular dynamic studies, this hydrogen bond could contribute 4.6 kcal/mol of the interaction energy.[29] This bond could be reinforced by the anomeric effect of both geminal fluorine atoms. Computational studies show that a 0.05 Å shortening of this bond could be expected (Figure 7.11).[21]

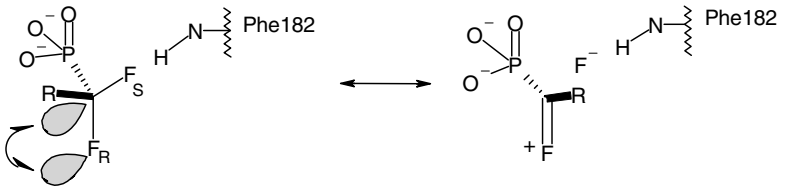


Figure 7.11 Increase of the hydrogen bond acceptor ability of fluorine through the anomeric effect of geminal fluorinated atoms.

(ii) PURINE NUCLEOSIDE PHOSPHORYLASE Purine nucleoside phosphorylase (PNP) is a key enzyme in the recycling pathway of purines. PNP catalyzes the reversible phosphorylation of nucleosides or of deoxynucleosides (guanosine, inosine) into free base and phosphate ribose (or phosphate deoxyribose). This transformation goes through a ternary complex: enzyme, nucleoside, and orthophosphate. This enzyme constitutes a good target for designing immunosuppressor agents and antivirals and for treating some leukemias (T cell leukemia). PNP inhibitors also enhance the plasma half-life of drugs such as 2′,4-dideoxyinosine (ddI).

A bisubstrate analogue, which is made up of a nucleoside covalently linked to a phosphate, should be able to inhibit PNP. This approach has been successfully accomplished with acyclovir, a classical antiviral. When this latter is phosphorylated, it becomes a powerful PNP inhibitor. It is phosphorylated *in vivo* only by a specific kinase of the herpesvirus, and thus it exhibits low toxicity. Replacement of a phosphate by a phosphonate is accompanied by a diminution of the inhibition. In contrast, difluorinating the phosphonate restores the inhibition.[30] Incorporation of an aromatic ring does not modify the affinity but, surprisingly, incorporation of one more fluorine atom gives a one order-of-magnitude gain (Figure 7.12).[31]

(iii) PHOSPHOGLYCERATE KINASE Phosphoglycerate kinase (PGK) is a glycolytic enzyme found in erythrocytes. PGK catalyzes phosphate transfer from ATP to position 1 of 1,3-diphosphoglycerate.

When erythrocytes circulate in underoxygenated tissue, release of 2,3-diphosphoglycerate (2,3-DPG) is increased. This release of 2,3-DPG lowers the affinity of hemoglobin for oxygen (2,3-DPG is an allosteric effector of hemoglobin). As a consequence, extraction of oxygen from blood by tissues is increased. Thus, PGK inhibition is a possible approach for treating cardiac and respiratory disorders.

Bis(difluorophosphonates), mimics of 1,3-diphosphoglycerate, have been suggested as PGK inhibitors. Some of these compounds have millimolar K_i values. The presence of a polar function at the molecule center is indispensable.[32] On the other hand, studies on the dissociation constants of the enzyme complexes with diphosphonates have shown that the relative values of pK_a of both phosphonic acids are important for the affinity. This explains the interest in the incorporation of fluorine (Figure 7.13).[33a]

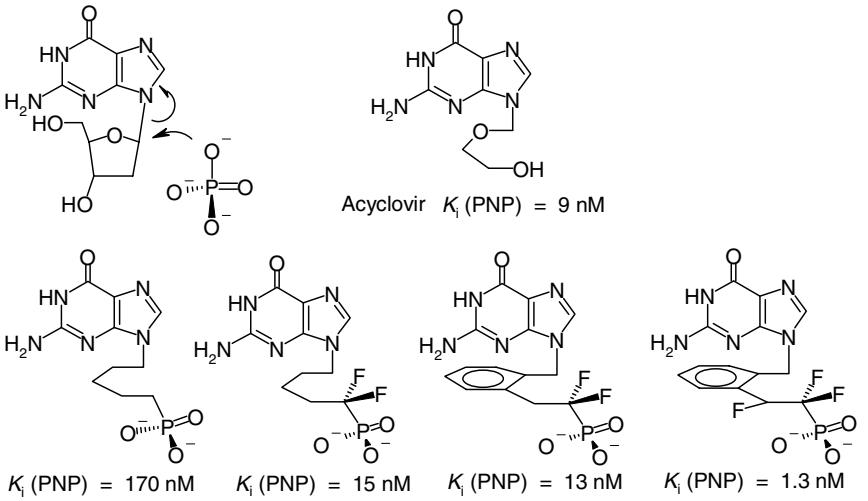


Figure 7.12 Bisubstrate analogues as PNP inhibitors.

Remark: *Inhibition of sulfatase by difluorosulfonates.* A similar approach to that of fluorophosphonates has been developed with difluorosulfonamides (nonhydrolyzable analogues of sulfates) for the inhibition of steroid sulfatases (STS), which could be an attractive target in the treatment of steroid dependent cancers. Difluorosulfonamide is a more powerful inhibitor than the corresponding sulfonamide for the reversible inhibition of estrone sulfatase (Figure 7.14).[33b, c] Inhibition of carbonic anhydrase by difluorosulfonamides follows a different mechanism.[34]

(c) Enzyme Substrates with a Fluorophosphonate Moiety Although this chapter is dedicated to fluorinated inhibitors, examples where fluorophosphonates act as substrates are also given. These examples highlight the influence of fluorination

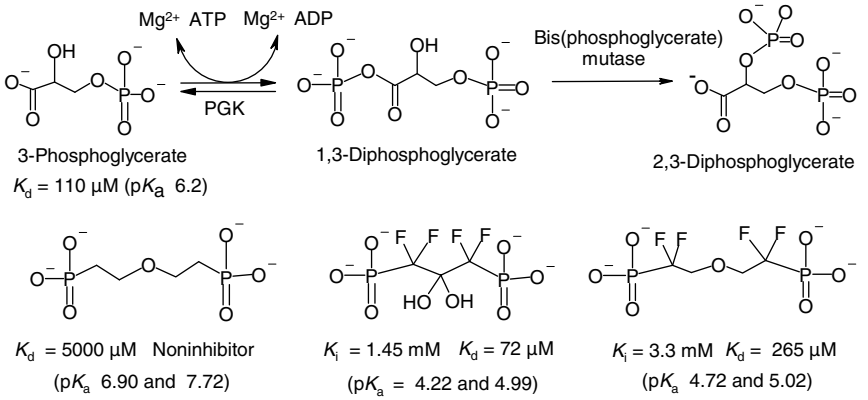


Figure 7.13 Inhibition of phosphoglycerate kinase by fluorinated diphosphonates.[32]

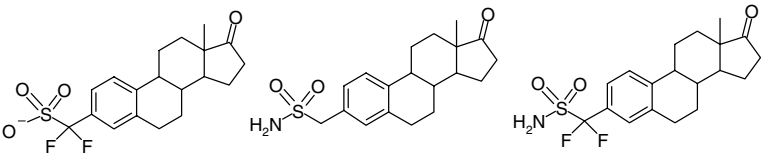


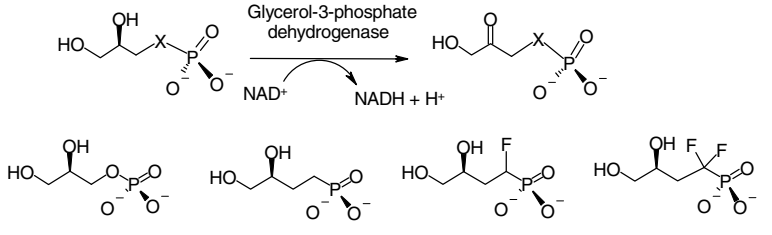
Figure 7.14 Inhibition of the steroid sulfatase by fluorinated sulfonamides.[33c]

on recognition and affinity and also display the possible use of these compounds as stable analogues of substrates.

(i) Influence of Fluorination on Affinity

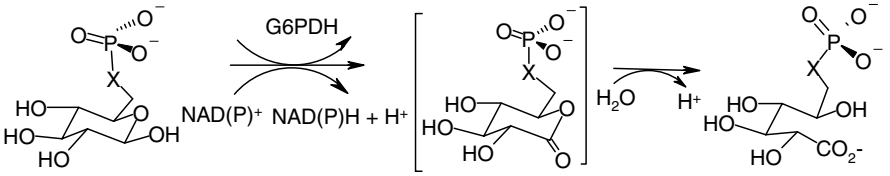
Glycerol-3-Phosphate Dehydrogenase The influence of fluorination on the affinity of phosphonates toward glycerol-3-phosphate dehydrogenase (G3PD) has been studied. Phosphonate analogues of glycerol phosphate are substrates of the enzyme and the kinetic data are close to that of the natural substrate of the enzyme. These data show that the difluorophosphonate is the poorer substrate, and that the enzyme is able to discriminate the two diastereomers of monofluorophosphonate (Figure 7.15).[35]

Glucose-6-Phosphate Dehydrogenase (G6PDH) Phosphonate (fluorinated or not) analogues of glucose-6-phosphate are accepted as substrates by glucose-6-phosphate dehydrogenase (G6PDH) and are oxidized into acids with concomitant reduction of $NADP^+$ (Figures 7.16 and 7.17). Monofluorophosphonate has almost the same acidity as that of phosphate ($pK_{a2} = 6.2$ vs. $pK_{a2} = 6.6$). Conversely, pK_{a2} of difluorophosphonate is significantly lower (5.4). Variations of K_{cat} are not significant, while variations of the K_m of the two diastereomers of monofluorophosphonate differ by one order of magnitude (0.23 mM vs. 2.26 mM). This difference of affinity can be due to an ion-dipole favorable interaction between the fluorine with (*S*) configuration and



K_m (mM)	0.20	0.18	0.17	0.73
V_{rel}	1.0	0.8	0.9	0.8

Figure 7.15 Phosphonates as substrates of G3PD of mammals.



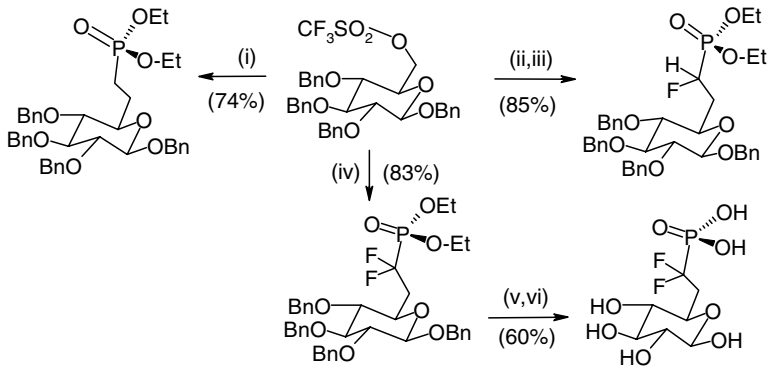
X	pK_{a2}	K_m (mM)	k_{cat} (s^{-1})	K_m/k_{cat}
O	6.6	0.12	241	2010
CH_2		0.49	224	457
CHF(7*R*)	6.2	0.23	212	922
CHF (7*S*)		2.26	195	86
CF_2	5.4	1.35	248	184

Figure 7.16 Phosphonates as substrates of the G6PDH (*L. mesenteroids*).

the ammonium of lysine 148 of the active site (distance N···F = 3.4 Å).[21] This study shows the absence of correlation between the affinity and the pK_{a2}. It also illustrates the important role of the configuration of the fluorine atom for the binding interaction.

(ii) Fluorophosphonates as Stable Analogues of Phosphate

Fluoro Analogues of Lysophosphatidic Acids Lysophosphatidic acids (LPAs) are diacylglycerol phosphates that are produced by activated platelets. The activity of these mediators is exerted through specific receptors (LPA receptors). Their role in the signal transduction offers opportunities in cancer chemotherapy. The search for more stable analogues of endogenic ligands under physiological conditions has led



(i) $LiCH_2P(O)(OEt)_2$; (ii) $KCF(SO_2Ph)P(O)(OEt)_2$; (iii) Na(Hg), NaH_2PO_4, MeOH, THF; (iv) $LiCF_2(O)OEt)_2$; (v) TMSBr, CH_2Cl_2; (vi)H_2, $Pd(OH)_2/C$

Figure 7.17 Preparation of protected glucose-6-difluorophosphonates.[21]

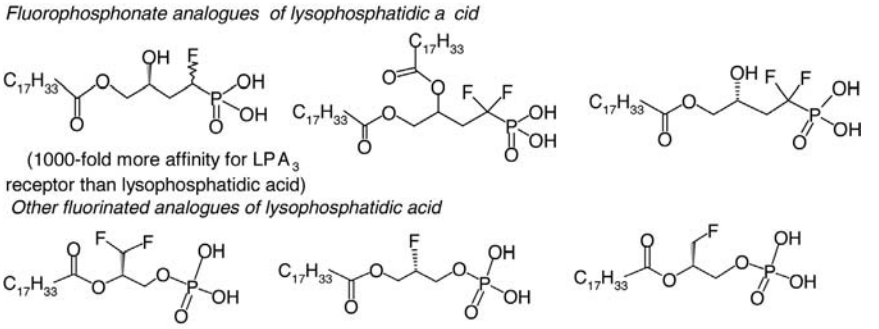
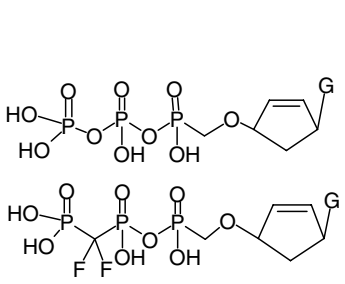


Figure 7.18 Fluorinated analogues of lysophosphatidic acids.[36]

to the synthesis of mono- and difluorophosphonates that are analogues of acids (Figure 7.18). Preliminary results show cell activities close to that of endogenic ligands.[36] Other monophosphonate fluorinated analogues have also been studied (where the fluorine atom replaces the hydroxyl or the O-acyl).[31] They induce platelet aggregation.[36b–d].

Inhibitors of HIV Reverse Transcriptase (RT-HIV) Replacement of the oxygen by a difluoromethyl in triphosphate analogues of carbovir, is accompanied by a one order-of-magnitude loss in anti-RT activity, while the plasma half-life is fifty times enhanced (Figure 7.19).[37]

Preparation of Antibodies Directed Toward Phosphorylated Proteins Considering the ability of fluorophosphonates to mimic the phosphate group and their good stability in biological media, phosphonate-based antibodies directed toward phosphorylated proteins have been prepared. In order to study the regulation of suppressive tumor protein p53, a difluorophosphonoserine-containing peptide has been used to obtain antibodies directed toward the phosphorylated form of the serine of p53 protein.[38] These polyclonal antibodies recognize protein p53 only when serine-6 is phosphorylated (Figure 7.20).[39] This type of antibody has not been prepared successfully by other approaches.



	RT-HIV		
	IC_{50}	K_m	Plasma half-life
	1.3 μM	1.1 nM	65 min
	16.5 μM	7.8 nM	45 h

Figure 7.19 Inhibitors of RT-HIV.[37]

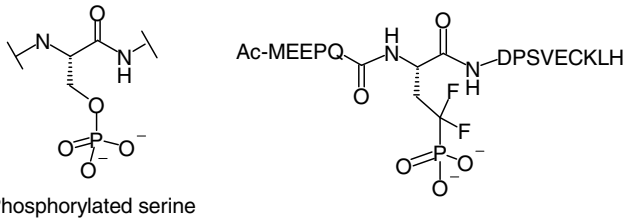


Figure 7.20 Examples of haptens for the creation of antibodies directed toward the 6-phosphorylserine tumor suppressive protein p53.[39]

7.1.3.2 Difluoro-C-Disaccharides as Mimics of the Glycosidic Bond

Replacement of the osidic bond of glycosides and of saccharides by a C—C bond has also been the focus of many investigations. This has been done in order to prepare analogues that are nonhydrolyzable, stable, and resistant to glycosidases. Although a number of difluoro-*C*-glycosides, difluoro-*C*-disaccharides, and difluoro-*C*-glycopeptides have already been synthesized (cf. Chapter 6),[40, 41] this approach does not seem to have been the focus of biological or enzymatic studies, unlike for fluorophosphonates.

7.1.3.3 Vinyl Fluorides as Protease Inhibitors The replacement of the peptidic bond of a dipeptide by a carbon–carbon bond leads to substrate analogues that are able to inhibit a protease, if the isosteric and isoelectronic character allows an efficient recognition by the enzyme. The mimic of the peptidic bond can be a double bond with a *trans* configuration. The geometry, stemming from the rotation barrier of the amide bond, is retained. However, at the electronic level, the presence of a polar substituent on the double bond is required to mimic the peptidic bond. A double bond substituted by a fluorine atom is therefore a better mimic. Indeed, beyond the steric aspect, calculations show that the dipolar moment, the charge distribution, and the electrostatic potentials are close to that of an amide (Figure 7.21).

Some peptides that contain peptidomimetic units Ψ[CF = C] have been studied.[8c] Among them, prolylamides have exhibited the most striking results. The differences in the inhibition properties between the tetrapeptides with Ψ[CF = C]Pro and those with Ψ[CH = C]Pro as peptidomimetic units are significant.[8b] The *trans* conformation of the amide bond of a peptide is generally considered to be more stable than the *cis*

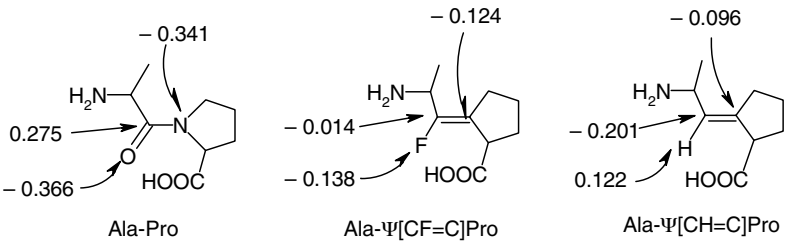


Figure 7.21 Charge distribution of fluoroolefins as dipeptide mimics.[8b]

conformation (difference = 5 kcal/mol). Conversely, for prolylamides, the *trans* and *cis* conformations have close stabilities: the activation barrier of the equilibrium is ca. 20 kcal/mol. However, the *trans* and *cis* conformations of the prolylamide bonds are crucial for the folding and the secondary structure of the peptides that contain this motif. Moreover, the regulation of enzymatic activities by prolyl isomerases (PIases) is sometimes controlled by the *cis–trans* isomerization of the prolylamide units.

Dipeptidyltransferase IV (DPT IV) is a transmembrane serine protease found in various human tissues. It is also used as a label of lymphocyte activity, and it is a well-validated target in the treatment of diabetes type II. DPT IV operates a specific amino terminal cleavage of polypeptides when there is a proline or an alanine on the penultimate position P_1. Any other amino acid can occupy position P_2 (Figure 7.22). Nitriles with a (*Z*)-Ala-Ψ[C = C]-Pro moiety inhibit very efficiently dipeptidyl peptidase IV (DPP IV): the nitrile function is electrophilic and interacts in a reversible manner with the OH from the serine of the active site. It then forms an imidate intermediate with the enzyme.[42c] Fluorinated analogues (*Z*)-Ala-Ψ[C = C]-Pro with a nitrile group or a hydroxamate function have been synthesized. They are good inhibitors of DPP IV and are more stable in aqueous solution (pH 7.6) than the nonfluorinated dipeptide analogues (Ala-Pro-NHO-Bz(4-NO_2) ($t_{1/2} = 8$ min) (Figure 7.22).[42a,b] Conversely, it appears from more detailed studies performed with the corresponding (*Z*)-Gly-Ψ[CF = C]-Pro nitriles that the presence of a fluorine atom on the double bond lowers the inhibition of DPP IV in a more pronounced manner than that of DPP II. In this latter case, it can be explained by the minor role of hydrogen bonds with the enzyme residues.[42c]

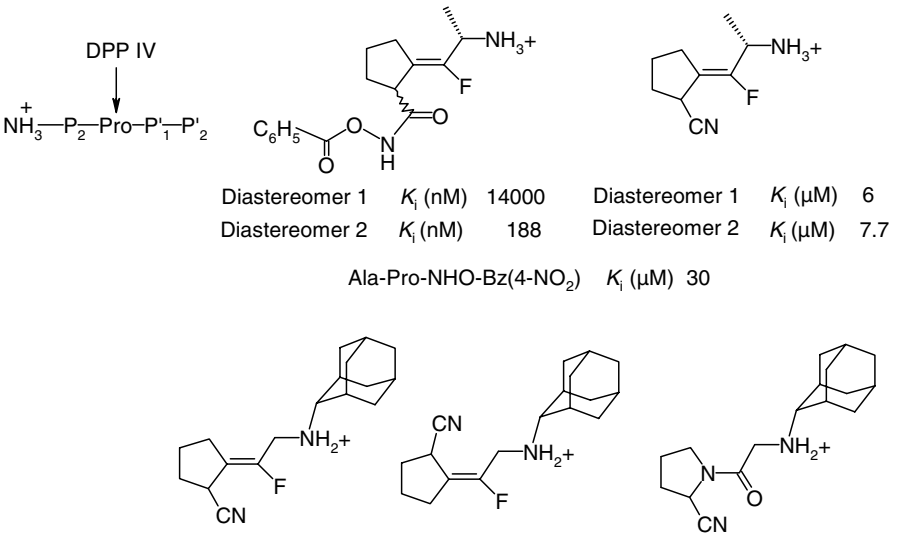


Figure 7.22 Inhibition of DPP IV by prolylamide analogues.[42]

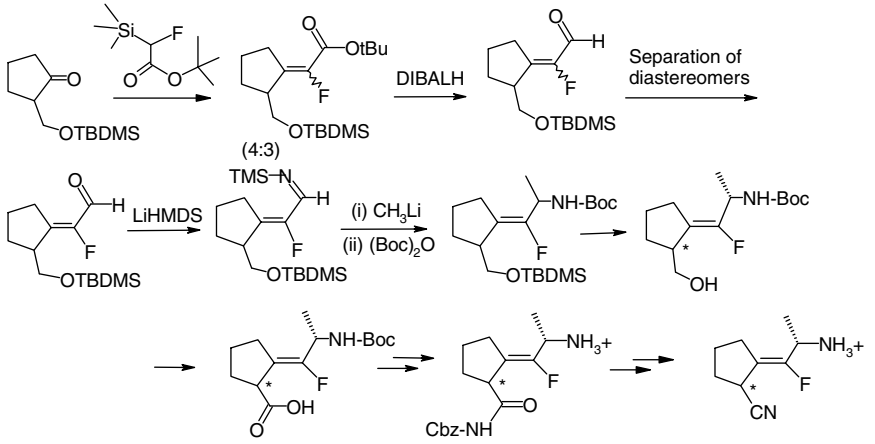
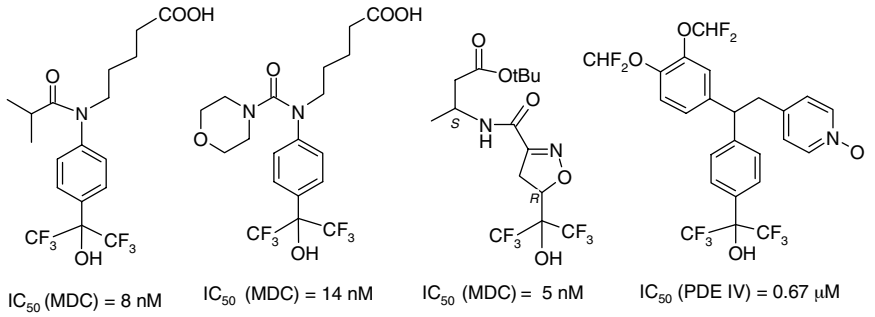


Figure 7.23 Preparation of a fluorinated pseudopeptide as DPP IV inhibitor.[8b]

Synthesis of these prolylamide mimics is based on the Peterson olefination between *tert*-butyl α-fluoro-α-trimethylsilyl acetate and a protected hydroxypentanone. Further introduction of the amino group is rather difficult. This step has been accomplished through conversion of the ester into aldehyde, followed by the formation of the silylated aldimine with LiHMDS, and then the addition of methyl lithium (Figure 7.23).[8b]

7.1.3.4 Fluorinated Alcohols and Amino Alcohols Replacement of an alkyl group of an alcohol by a trifluoromethyl group strongly enhances the acidity of the neighboring hydroxyl, as shown by the pK_a values (minus 3 units) (cf. Chapter 1). The hydroxyl also becomes a better hydrogen bond donor and a poorer acceptor (cf. Chapters 1 and 3). Due to the reinforcement of the acidic character, trifluoromethyl alcohols are generally better ligands than the parent nonfluorinated alcohols.

As an example, bis(trifluoromethyl) carbinols have been described as strong inhibitors of malonyl-CoA decarboxylase, an enzyme involved in the metabolism of fatty acids, a possible target for the treatment of ischemic heart disease and diabetes (Figure 7.24).[43] Although few enzymological data are available, it is reasonable to



IC_{50} (MDC) = 8 nM IC_{50} (MDC) = 14 nM IC_{50} (MDC) = 5 nM IC_{50} (PDE IV) = 0.67 μM

Figure 7.24 Bis(trifluoromethyl) carbinol containing inhibitors.

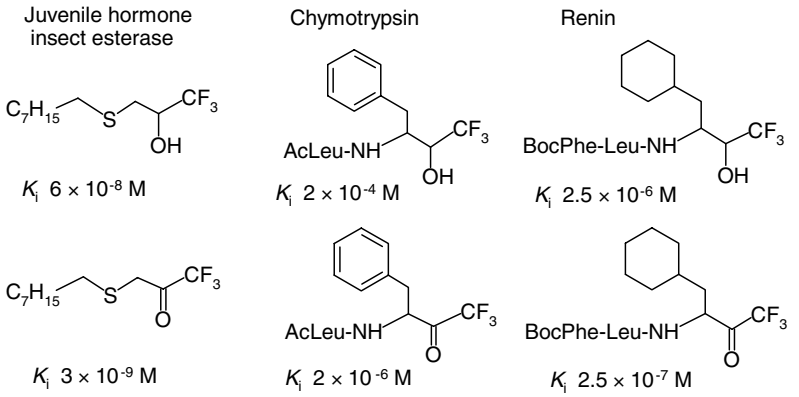


Figure 7.25 Inhibition of proteolytic enzymes by trifluoromethyl alcohols and ketones.

hypothesize that a histidine residue of the active site of the enzyme could form a strong hydrogen bond with bis(trifluoromethyl) carbinol moiety of the MCD inhibitors and thus facilitate the decarboxylation process.[44] Similar observations regarding bis(trifluoromethyl) carbinol pharmacophore have been reported for the liver X receptor-α (LXR) agonists and phosphodiesterase IV (PDE4) inhibitors.[45]

Trifluoromethyl β-thioalkyls and β-amino alcohols are often good reversible inhibitors of esterases and proteases, respectively. Depending on the enzymes (serine or aspartyl enzymes), fluorinated alcohols are often less efficient inhibitors than the corresponding ketones, which act as analogues of the transition state (*vide infra*). Nevertheless, fluoroalcohols inhibit hydrolytic enzymes with high inhibition constants (Figure 7.25).[46, 47]

Considering serine proteases (HLE, PPE, cathepsin G), it is difficult to draw clear conclusions about the influence of the absolute and relative configurations on the respective affinity of peptidyl ketones and trifluoromethyl alcohols. In some cases, it is rather surprising to state that alcohols can be better inhibitors than the corresponding ketones.[8d, 48] Some β-peptidyl fluorinated alcohols are also good inhibitors of aspartyl proteases (renin, PR-HIV, etc.).[8e] Thus, β-trifluoromethyl-β-amino alcohols (e.g., trifluoromethyl isoserines) are peptidomimetic central units of inhibitors of aspartic acid-containing proteases, such as HIV proteases[49] and plasmepsins.[50] The pseudosymmetric β-amino difluoroalcohol represented in Figure 7.26 is a nanomolar inhibitor of HIV protease. However, the corresponding ketone is a better inhibitor (cf. Section 7.3).[51]

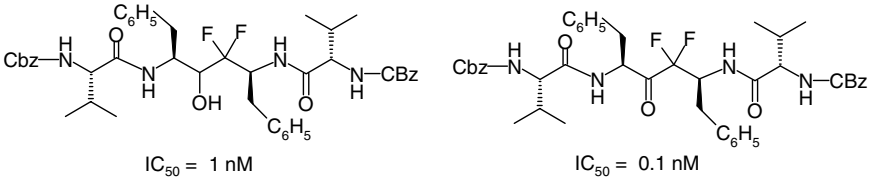


Figure 7.26 Pseudosymmetric inhibitor of HIV protease.[51]

7.2 DESTABILIZATION OF REACTION INTERMEDIATES (OR OF TRANSITION STATES) OF ENZYMATIC PROCESSES BY FLUORINATED GROUPS

The ability of fluorinated substituents to prevent the development of a positive charge on the α position has been used to slow down or even inhibit enzymatic processes involving positively charged transition states. According to the case, the observed result can be (1) slowing down the reaction, (2) reversible inhibition, or (3) irreversible inhibition. Various examples are now given.

7.2.1 Prenyl Transfer

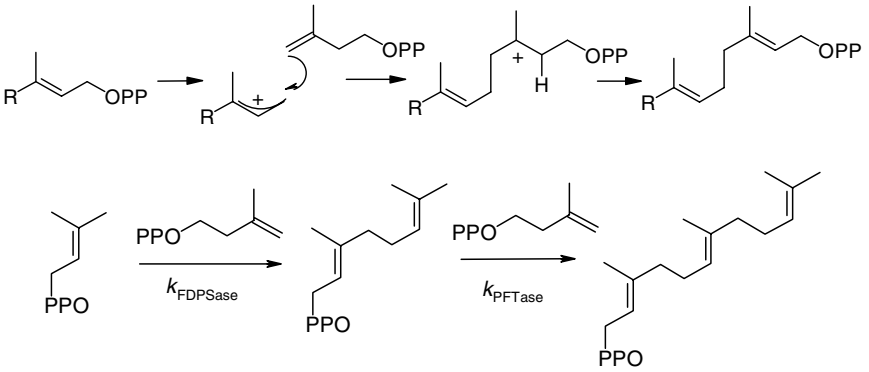
Prenylation, the key step in terpene biosynthesis, is catalyzed by prenyltransferases. These enzymes are responsible for the condensation of isopentenyl pyrophosphate (IPP) with an allyl pyrophosphate, thus yielding isoprenoids. Numerous studies have been performed with fluorinated substrates in order to determine the mechanism of the reactions that involve these enzymes: prenyltransferases, farnesyl diphosphate synthase (FDPSase), farnesyltransferase (PFTase), and IPP isomerase.[11a] These studies are based on the potential ability of fluorine atoms to destabilize cationic intermediates, and then slow down S_N1 type processes in these reactions.[11a]

To illustrate this, we give as an example investigations on the prenyl transfer catalyzed by FDPSase and by PFTase. These studies show that, with a fluorinated substituent, the reaction is significantly slowed down (Figure 7.27).[8f]

7.2.2 Inhibition of Glycosidases and Glycosyltransferases

Glycosidases are responsible for the cleavage of the glycosidic bond in carbohydrates. These enzymes are involved in numerous biological processes. The transition state of the reactions catalyzed by glycosidases and by glycosyltransferases involves an intermediate in which the anomeric carbon has a very pronounced alkoxycarbenium character. Such a cationic transition state is destabilized by the presence of an electron-withdrawing substituent: a fluorine atom in β or a CF_3 group in α, for example. Thus, the formation of this intermediate requires a high activation energy. However, if the substrate bears an excellent leaving group, the formation of an intermediate bonded to the enzyme is possible. In this case, the formed bond is strong enough not to be further cleaved. Indeed, the presence of a fluorinated substituent renders the carboxylate of an aspartic acid of the enzyme less effective as a leaving group (Figure 7.28).[8g] This leads to accumulation of the intermediate, and thus inactivation of the enzyme. According to the localization of the fluorinated substituent, this latter has a variable effect on the strength of the glycosidic bond that is formed with the enzyme. The fluorinated analogue can behave in different manners: as a slow substrate, as a competitive inhibitor, or as an irreversible deactivator.[8g, 52]

Since mechanisms for the cleavage of glycosidic bonds by α- and β-glycosidases are different, a fluorosugar has a different behavior when it is the substrate of the two



	$k_{FDPSase}$, s^{-1}	k_{PFTase}, s^{-1}
PPO	1	1
PPO, H	4.0×10^{-8}	6.3×10^{-3}
PPO, CF_2H	$7.7 \times 1 0^{-9}$	7.6×10^{-4}
PPO, CF_3	2.3×10^{-4}	1.5×10^{-2}

Figure 7.27 Relative rates of prenyl transfer catalyzed by FDPSase and PFTase.

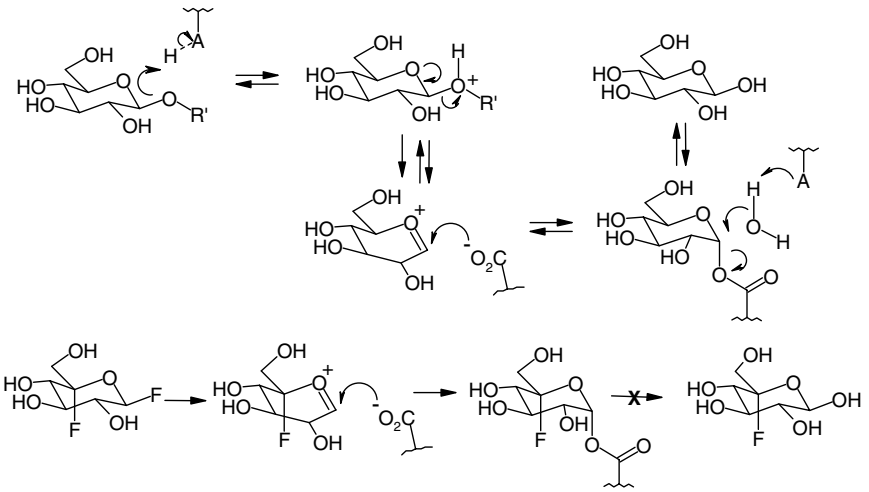
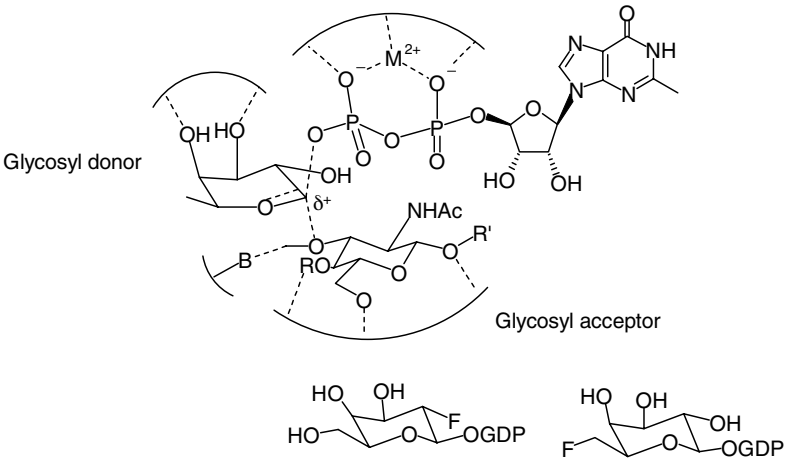


Figure 7.28 Cleavage of the glycosidic bond by a glycosidase with inversion of configuration. Inhibition by 5-fluoroglycosyl fluoride.[8g]



GDP-Fucosyltransferases	K_M (μM)	K_i (μM)	K_i (μM)
FucT-III	33.6	38	22
FucT-V	18.8	4.0	3.4
FucT-VI	9.0	10	1.0
FucT-VII	8.0	21	11

Figure 7.29 Mechanism and inhibition of human fucosyltransferases by fluoro-GDP-fucoses.[53]

enzyme types. This is the reason why fluorosugars are also used as probes for studying the mechanisms of glycosidases.[8g, 52]

Fucosyltransferases (glycosyltransferases) promote the transfer of fucose from GDP-fucose onto a saccharidic acceptor. This transfer occurs with inversion of the configuration of the anomeric carbon. The inhibition has been studied with fluorinated substrates. GDP-2-fluoro-2-deoxyfucoses (GDP-2F-fucose) and GDP-6-fluoro-6-deoxyfucoses (GDP-6F-fucose) are competitive inhibitors. The K_i values are close to or less than that of K_M (Figure 7.29).[53] The very close K_i values of GDP-2F-fucose and of GDP-6F-fucose show that the fluorine atoms in positions 2 and 6 (equidistant from the oxygen of the cycle) do not hinder the approach and have close electronic effects (Figure 7.29).[53] Similar results have been obtained with sialyltransferase and with β-galactosyltransferase.[53]

7.2.3 Inhibition of UDP-GlcNAC Enolpyruvyltransferase (MurZ)

UDP-GlcNAC enolpyruvyltransferase (MurZ) catalyzes the reaction between the phosphate of the enol pyruvate and the UDP-GlcNAC to form the corresponding enolpyruvate. This reaction is the first stage of the biosynthesis of the peptidoglycan of the bacterial wall. Phosphates of mono- and difluoroenolpyruvates are substrates of MurZ (Figure 7.30).[11a, 54] The tetrahedral intermediates formed after incubation

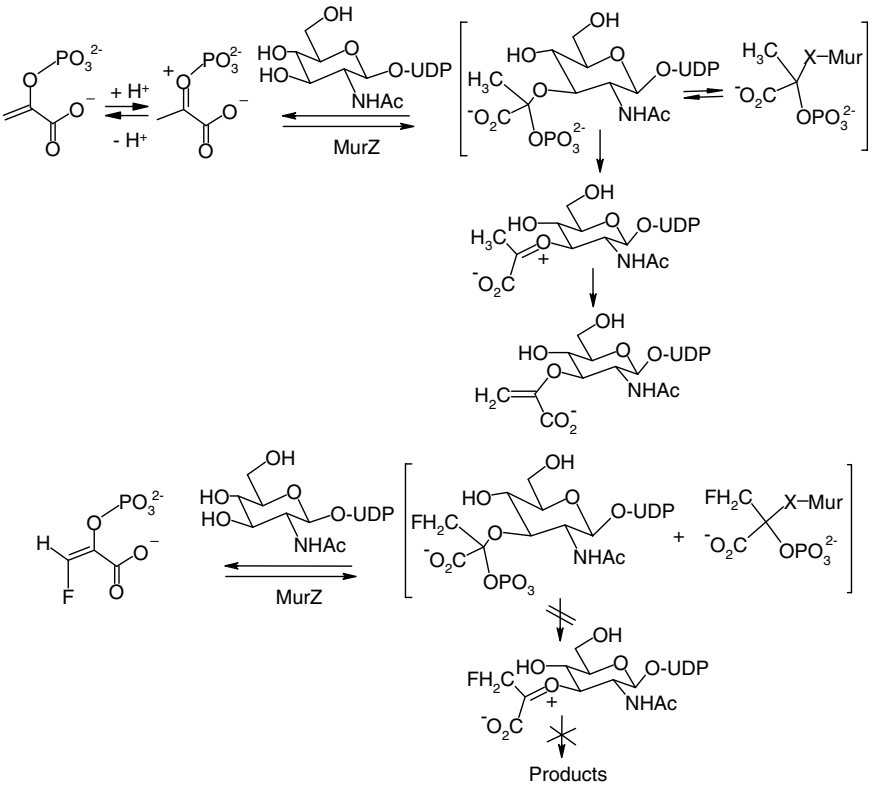


Figure 7.30 Inhibition of UDP-GlcNAC enolpyruvyltransferase (MurZ) by phosphofluoroenolpyruvate.[54b]

of UDP-GlcNAC with MurZ, in the presence of fluoroenolpyruvate, cannot eliminate in a normal way the phosphate anion. Indeed, the alkoxycarbenium ion that should result from this reaction would be highly destabilized by the presence of the fluorine group. The inhibition is irreversible ($K_i = 36\,\mu M$). These tetrahedral adducts have been isolated. However, their formation from fluorinated substrates is much slower (10^{-4}) than that of nonfluorinated substrates. This can be explained by the destabilization of the oxonium ion by a fluorine atom: it renders the protonation of the double bond more difficult.[11a]

7.2.4 Enolpyruvate Shikimate Phosphate Synthase (EPSPS)

Enolpyruvate shikimate-3-phosphate synthase (EPSPS) is the enzyme that catalyzes the condensation of shikimate-3-phosphate with phosphoenolpyruvate. The corresponding difluorophosphonate (phosphoenolpyruvate analogue) irreversibly inhibits EPSPS. The mechanism of the inhibition by difluorophosphonate is similar to that reported for MurZ inhibition (Figure 7.31).[54, 55]

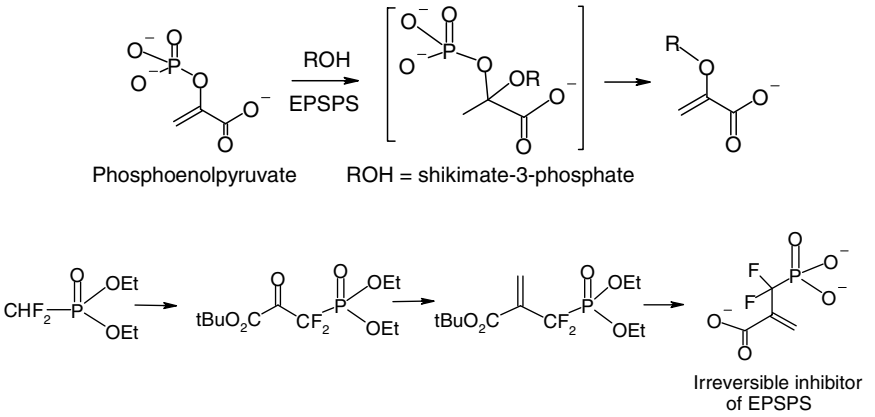


Figure 7.31 Synthesis of 2-difluorophosphomethyl acrylate, an EPSPS inhibitor.

7.3 INHIBITORS THAT ARE ANALOGUES OF THE TRANSITION STATE: DI- AND TRIFLUOROMETHYL KETONES

Due to the strong electron-withdrawing effect of the CF_3 group, the carbonyl function of trifluoromethyl ketones is very reactive toward nucleophiles.[56] Thus, a catalytic nucleophilic residue of an enzyme, such as the hydroxyl of a serine, can add onto the activated carbonyl, thus affording a stable tetrahedral intermediate that mimics the transition state of the hydrolysis reaction (cf. Chapter 3). Although this addition is reversible, the inhibition is generally time dependent. This is due to the strong affinity of the tetrahedral intermediate for the enzyme, and also to the time needed for the equilibrium to provide of the tetrahedral adduct (slow- and/or tight-binding inhibition). This mechanism has clearly been demonstrated for serine enzymes (X-ray structures of the tetrahedral adducts with the enzyme and ^{19}F NMR data).

Without recalling the fundamental aspects of this type of inhibition (cf. Chapter 3), we illustrate it with examples of inhibition of various types of esterases and proteases by trifluoromethyl ketones.

7.3.1 Serine Enzymes

7.3.1.1 Acetylcholinesterase Acetylcholinesterase (AchE) is a serine esterase that hydrolyzes acetylcholine (Ach). This neurotransmitter is involved in the transmission of the nervous influx. It is supposed to be strongly involved in degenerative diseases of the central nervous system. Trifluoromethyl ketones are extremely powerful inhibitors of AchE (Figure 7.32).[57] Optimization of the structure of the inhibitors has shown that noncharged bulky groups (e.g., *tert*-butyl or TMS) are excellent mimics of the trimethyl ammonium group. Surprisingly, the lack of charge has no dramatic unfavorable effect on the affinity. The presence of an aromatic ring led to femtomolar inhibitors. This very strong affinity can be explained by the conformational rigidity brought about by the aromatic ring, which mimics the *anti* conformation

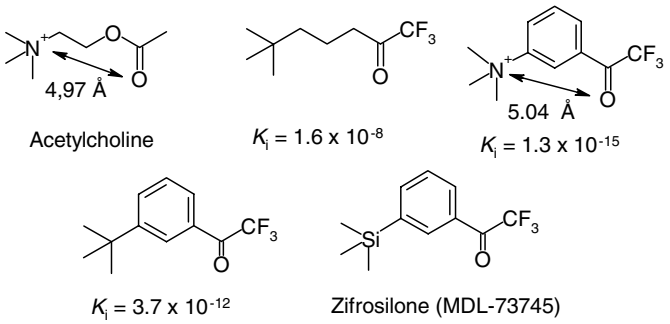


Figure 7.32 Fluoroketones as AchE inhibitors.

of the carbon chain of the substrate.[58] *Zifrosilone* (MDL-73745) has been developed in preclinical tests for the treatment of Alzheimer disease.[59]

7.3.1.2 Esterases of the Juvenile Hormone of Insects Many works have been dedicated to the inhibition of esterases of the juvenile hormone of insects. The purpose of these works is to control insect populations by eliminating their metamorphosis.[60] Among the numerous trifluoromethyl ketones that have been synthesized, thioalkyl derivatives of trifluoroacetone have been shown to be the most active ones. Curiously, the corresponding alcohols are also excellent inhibitors.[61] Trifluoromethyl ketones can also inhibit other insect esterases: antenna esterases[62] and esterases that are involved in the release of pheromones (Figure 7.33).[63] The inhibition of these latter ones can also be interesting for insect control purposes.

Ab initio calculations have been performed to evaluate the ease of hydration and the charge densities of the carbonyl of fluoroketones that are carboxyesterase

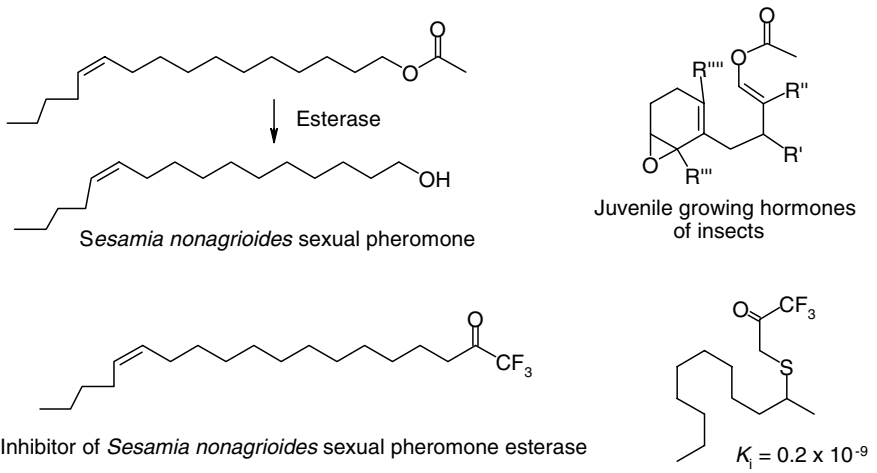


Figure 7.33 Inhibition of insect esterase.

inhibitors. The value mainly correlates with inhibition activity. In the case of α-thioalkyl trifluoromethyl ketones, the possibility of a hydrogen bond between the sulfur atom and the *gem*-diol hydroxyl has been suggested on the basis of crystallographic data of ketone hydrates. However, this hypothesis must still be proved to explain the strong inhibitor power of α-thioalkylfluoroketones compared to that of nonthioalkylfluoroketones.[64]

The α-thioalkyl trifluoromethyl ketones are also selective inhibitors of mammalian carboxyesterases. These enzymes are involved in the liver detoxification processes.[65]

α-Thioalkyl ketones are easily accessible through substitution of the bromotrifluoroacetone by a thiolate. In contrast, synthesis improvements have been required to access other trifluoromethyl ketones.[66] In this context, the excellent method based on the addition of an alkyl lithium onto ethyl trifluoroacetate deserves attention.[67]

7.3.1.3 Phospholipase A_2 Arachidonic acid is precursor of "arachidonic cascade" metabolites. Phospholipase A_2 catalyzes release of this acid from the pool of membrane phospholipids and is therefore an obvious therapeutic target. While it still remains uncertain that phospholipase A_2 is a serine enzyme,[68] it is considered in this section. Introduction of a CF_2 group in a ketone analogue of a phospholipid enhances the inhibiting power 300 times ($K_i = 50\,\mu M$) (Figure 7.34).[69] Trifluoromethyl ketone derived from arachidonic acid is far more powerful than difluoroketone.[70a] In most cases, inhibitions with CF_2Cl and C_2F_5 ketones are weaker. This fact correlates with the lower aptitude of these compounds to be hydrated, probably due to steric reasons.[70b]

7.3.1.4 Serine Proteases

(a) Human Leukocyte Elastase (HLE) Inhibition of serine proteases by fluorinated peptidyl ketones has been the focus of research in medicinal chemistry.[71, 72] Pioneer work by Abeles[57] has demonstrated the efficiency of this approach and has determined the kinetic determinants of the inhibition, particularly on α-chymotrypsin.[73] Human leukocyte elastase (HLE) is an enzyme involved in inflammatory phenomena such as pulmonary insufficiency and rheumatoid arthritis. This enzyme has been a special target of study.[72] The triad Val-Pro-Val-CF_3 gives the best results for inhibition as well as for selectivity and has led to nanomolar inhibitors. Other structural modifications have afforded compounds that have, moreover, a good oral bioavailability (Figure 7.35).[72]

Trifluoromethyl ketones are also powerful inhibitors of proteases of the trypsin family (trypsin, thrombin, enzymes of blood coagulation).[74, 75]

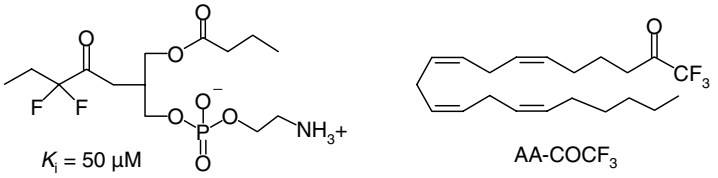


Figure 7.34 Fluorinated inhibitors of phospholipase A_2.

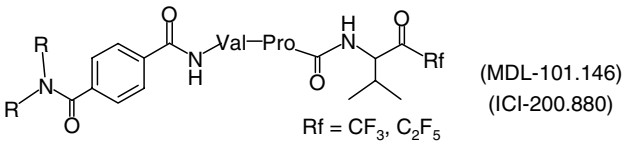


Figure 7.35 Examples of HLE inhibitors.

(b) Chimase Human cardiac chimase is a serine protease of the chymotrypsin family, which converts angiotensin I into angiotensin II. As in the previous example, difluoromethyl ketones are stronger and more selective inhibitors of this enzyme than the corresponding trifluoromethyl ketones. The choice of substituent at the P_3 site ensures a high specificity for the chymase toward α-chymotrypsin. Substitution of the valine in P_1 by a glutamic acid enhances spectacularly (a factor of 10^4) this selectivity (Figure 7.36).[76]

(c) Inhibition of Viral Proteases: Human Cytomegalovirus (HCMV) Cytomegalovirus is a widespread herpesvirus. Among others, it is responsible for opportunistic infections of immunosupressed patients. Fluoroketones are good inhibitors of this protease. A pentafluoroketone has been shown to be the most efficient (submicromolar) and the most selective inhibitor (Figure 7.37).[77]

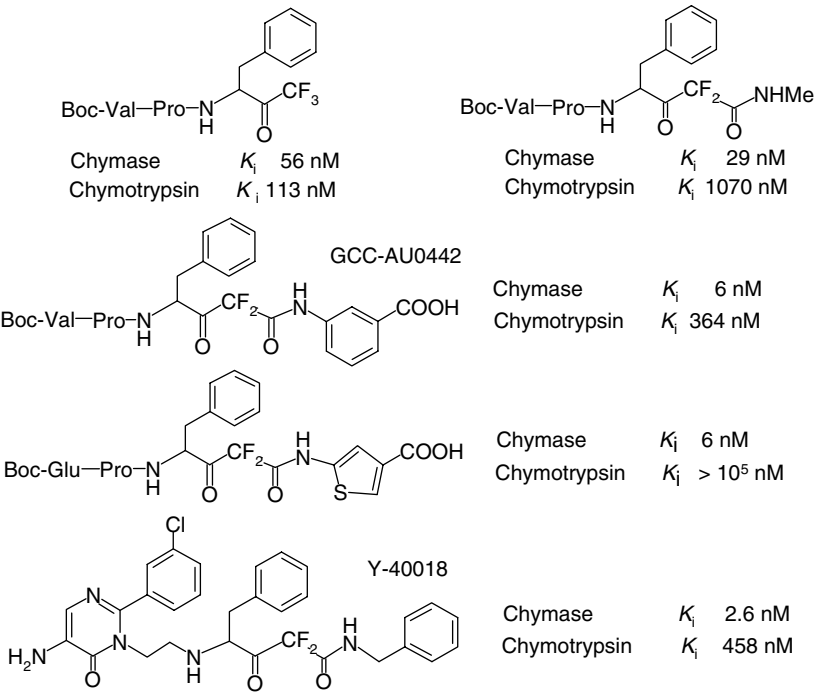


Figure 7.36 Inhibition of human cardiac chymase.

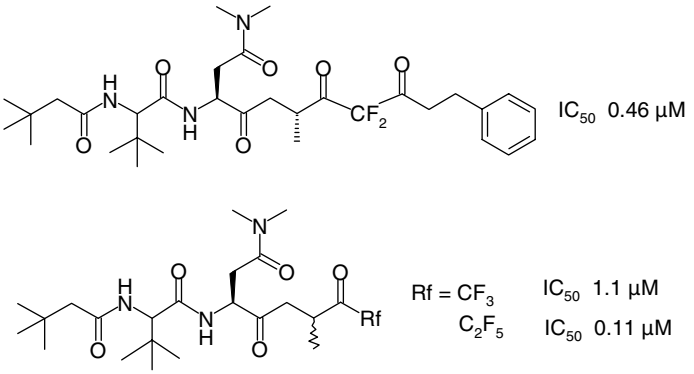


Figure 7.37 Inhibition of the protease of human cytomegalovirus.[77]

7.3.2 Inhibition of Aspartyl Enzymes

7.3.2.1 Inhibition of Aspartyl Proteases Inhibition of aspartyl proteases has given rise to a great number of studies, due to the therapeutic importance of enzymes such as renin or HIV protease. Peptidyl fluoroketones occupy a significant position in this research. For aspartyl proteases, the concept of transition state differs slightly from that invoked for serine proteases. Indeed, in the former case, the catalytic nucleophile is not a nucleophilic entity of the enzyme but is a water molecule that is chelated by both the aspartic acids of the active site (Figure 7.38). Conversely to serine proteases, the tetrahedral transition state (or the tetrahedral intermediate formed with the inhibitor) is then not covalently bonded to the enzyme. The hydrate oxyanion of the fluoroketone is a mimic of the tetrahedral transition state of the hydrolysis of the peptidic bond. For this reason, "acidic" alcohols (such as α-fluoroalkyl alcohols) can also mimic the transition state and thus they can act as inhibitors. This is illustrated by peptidyl fluoroalcohols, which are excellent aspartyl protease inhibitors. In this case, the difference between the concepts of substrate analogue and transition state analogue becomes rather narrow.

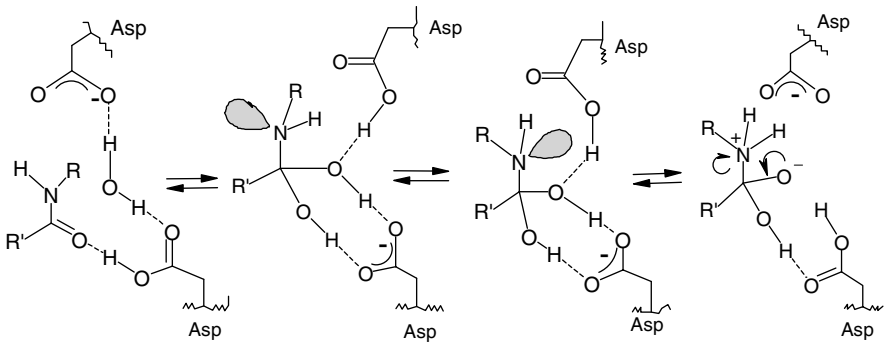


Figure 7.38 Catalytic mechanism of aspartyl proteases.

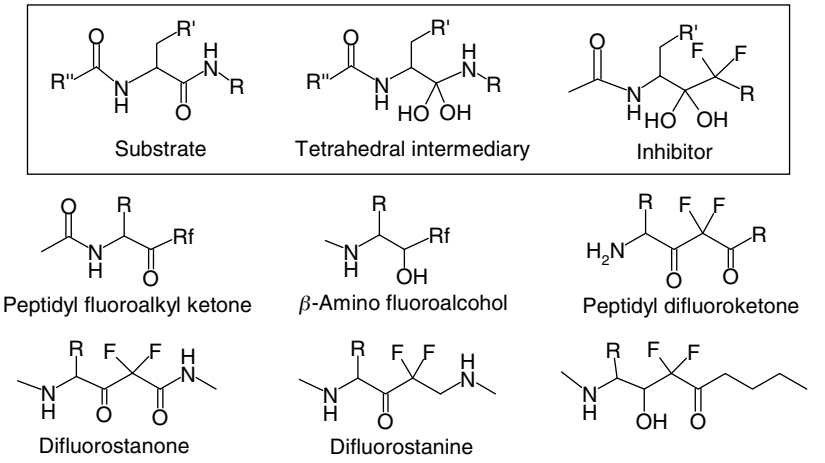


Figure 7.39 Inhibition of aspartyl proteases by fluorinated inhibitors.

α-Peptidyl perfluoroalkyl ketones, β-peptidyl-α-trifluoromethyl alcohols, difluorostanones, and difluorostanines with various general structures reported in Figure 7.39 have been synthesized and evaluated as inhibitors of aspartyl proteases.

(a) Inhibition of Renin In the frame of research on hypertension, a relatively large number of nanomolar inhibitors of renin that contain either the fluoroketone or fluoroalcohol moiety have been prepared. Some of these inhibitors are very selective and have good solubility in water (Figure 7.40). A series of peptidyl fluoroalkyl

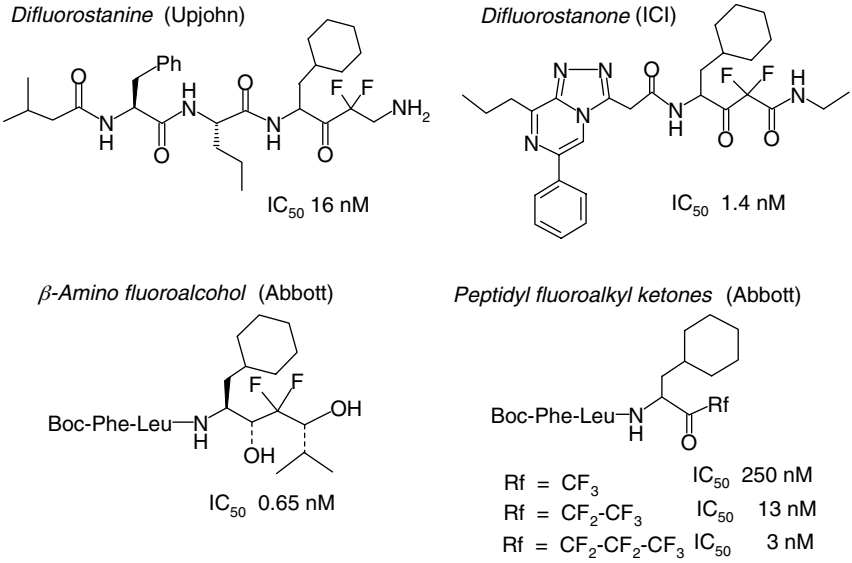


Figure 7.40 Examples of fluorinated inhibitors of renin.

ketones exhibit disconcerting and unexplained increasing inhibition values (×200) when the fluorinated chain is longer (CF_3 to C_3F_7) (Figure 7.40).[8e, 78]

(b) Inhibition on HIV Protease In spite of their potency and selectivity, renin inhibitors have never become drugs. However, the huge volume of knowledge that has been acquired in this field has permitted consequent advances in the search for inhibitors of other aspartic acid proteases, such as HIV protease. These advances have led to decided improvements in AIDS chemotherapy and to the inversion of vital prognoses.[79] In this context, fluoroketones have been excellent drug candidates.

HIV protease is an homodimer of C_2 symmetry. This enzyme specifically cleaves the precursor polyprotein and affords the proteins required for maturation of the virion and for virus replication. Some pseudosymmetric inhibitors have been conceived on this basis. For example, pseudosymmetric difluoroketones exhibit subnanomolar inhibitions and are active toward infected lymphocyte MT-4 cell lines. Nevertheless, simpler α-peptidyl fluoroketones are also good inhibitors (Figure 7.41). The difluorostanones developed by Merrell–Dow were very efficient toward infected cells.[8e, 8h]

(c) Inhibition of γ-Secretase Secretases are proteolytic enzymes involved in the constitution of amyloid fibrils, which are connected to appearance of the Alzheimer disease. Among this enzyme family, γ-secretase is an important therapeutic target. γ-Secretase is an aspartyl protease that catalyzes the final step of the biosynthesis of β-amyloid protein. Inhibitors have been designed using the potential of fluoroketones as inhibitors of proteases, although at this time the enzymatic mechanism of γ-secretase was not known. Along this line, selective inhibitors that contain the

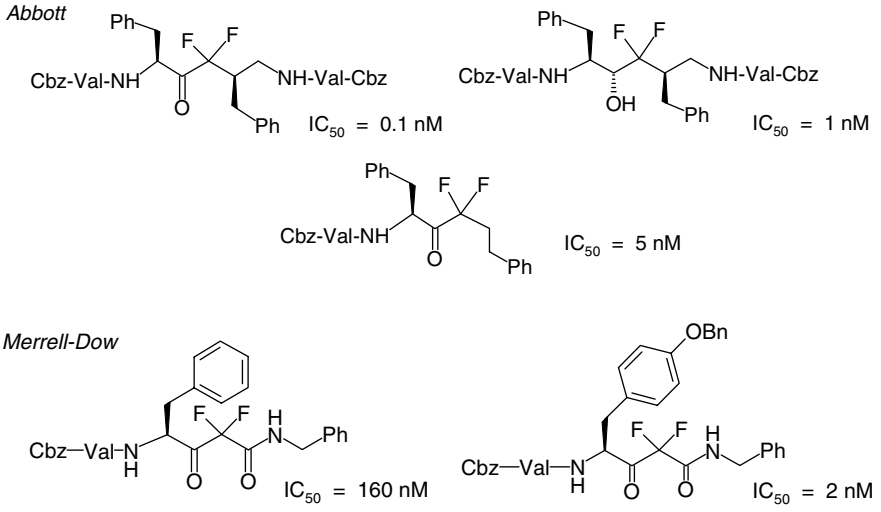


Figure 7.41 Fluorinated inhibitors of HIV protease.

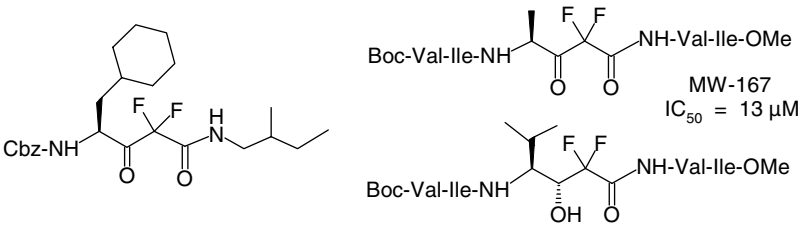


Figure 7.42 Fluorinated inhibitors of γ-secretase.

difluoroketone motif have been found. This work has also led to comprehension of the catalytic mechanism of this enzyme (Figure 7.42).[80]

7.3.2.2 Inhibition of Glycinamide Ribonucleotide Transformylase

Glycinamide ribonucleotide transformylase (GAR Tfase) is a folate-dependent enzyme essential to the *de novo* purine biosynthetic pathway. It utilizes the cofactor 10-formyl tetrahydrofolic acid (10-formyl-THF) to transfer a formyl group to the primary amine of its substrate α-glycinamide ribonucleotide. Potent, and potentially selective, inhibitors of GAR Tfase and *de novo* purine biosynthesis have been shown to be promising as antitumor drugs.

By replacing N10 with a carbon, the cofactor analogue, such as 10-formyl-DDACTHF bearing a nontransferable formyl group, precludes formyl transfer and yet can competitively bind to the folate binding site.[81] X-ray data revealed that the inhibitor binds as the hydrated aldehyde (*gem*-diol) in the enzyme active site, mimicking the formyl transfer tetrahedral intermediate. Based on this finding, a trifluoromethyl ketone, 10-CF_3CO-DDACTHF, has been introduced to replace the aldehyde of 10-formyl-DDACTHF (Figure 7.43). Similarly, X-ray structures indicate that there are extensive interactions with the formyl transfer region, especially with Asp144 and His108, two essential residues in the formyl transfer reaction. Asp144 carboxylate forms hydrogen bonds (2.5 and 2.7 Å) to each of the hydroxyl groups of the *gem*-diol. His108 also forms hydrogen bonds with both hydroxyls of the *gem*-diol.[81] As expected with aspartyl enzymes, the corresponding 10-CF_3CHOH is less potent (60 times).[82]

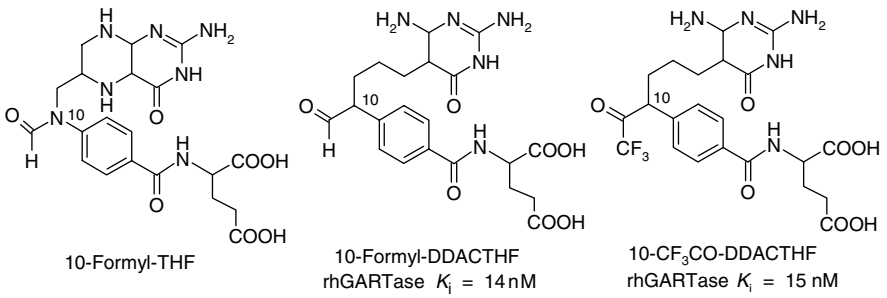


Figure 7.43 Inhibition of the GAR Tfase by trifluoromethyl ketone.

7.3.3 Inhibition of Metalloproteases

Zinc metalloproteases can be inhibited by fluoroketones. This inhibition should stem from complexation of the monoanion of the fluoroketone hydrate with zinc. Thus, β-amido and peptidyl fluoroketones inhibit carboxypeptidase A[83] and microbial metallo-β-lactamases with micromolar K_i.

HDACs are zinc metalloproteases involved in the acetylation of histone. Inhibition of HDACs represents a new strategy in human cancer therapy since these enzymes play a fundamental role in regulating gene expression and chromatin assembly. Along this line, inhibition of HDAC by fluoroketones has been studied.[84] The inhibition power of fluoroketones toward HDACs is comparable to that of hydroxamates, which are the classical inhibitors of metalloproteases. These fluoroketones exhibit antiproliferative activities on tumor cell lines (Figure 7.44).[85]

7.3.4 Cysteine Protease and Thiol Enzymes

It could be expected *a priori* that fluoroketones may be potent inhibitors of cysteine proteases, since the nucleophilicity of the thiol of a cysteine is indeed greater than that of the hydroxyl of a serine. However, studies performed with papain and cathepsin B have shown that fluorinated ketones are only modestly reversible inhibitors of cysteine proteases ("slow-binding" inhibition).[86, 87] Although the inhibiting power of a trifluoromethylketone toward a serine protease is at least 10 times superior to that of the corresponding aldehyde, the opposite occurs with cysteine proteases: the inhibiting power of aldehydes is 10^4 times superior to that of trifluoromethylketones.[87] Fluoroketones have thus been disappointing in inhibiting cysteine proteases.[88]

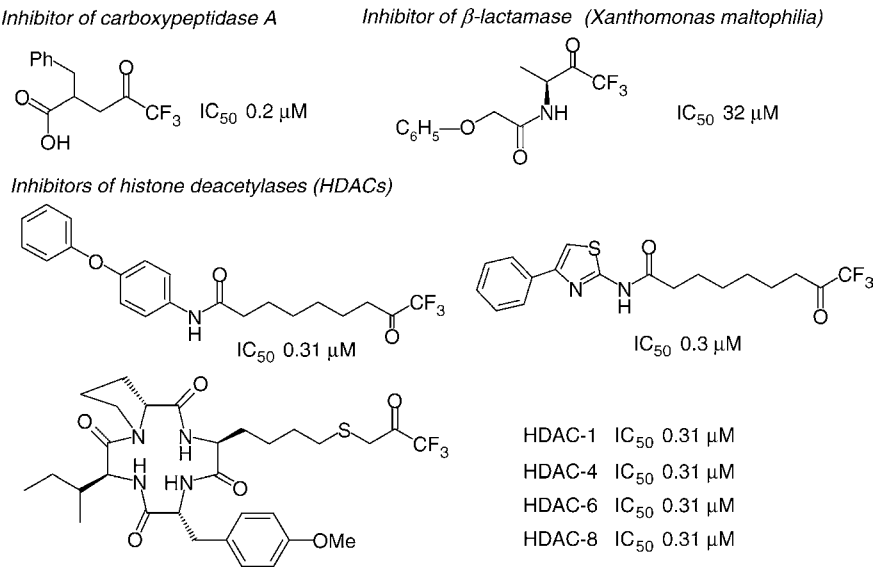


Figure 7.44 Fluorinated inhibitors of metalloproteases.

Theoretical studies have been done in order to understand this behavior difference. Semiempirical calculations (AM1, MNDO) of formation energy (of the hemithioketal–hemiketal interconversion) have shown that hemithioketals are less stable than the corresponding hemiketal (from 10 to 15 kcal/mol). This difference can be due to steric factors, connected to the respective sizes of sulfur and oxygen. Stereoelectronic factors can also be evoked: stabilization that is brought about by the anomeric effect is *a priori* more important for a *gem*-dihydroxylated compound than for the hemithioketal.[89] Moreover, at the kinetic level, displacement of the water molecule of the inhibitor (under aqueous conditions, the inhibitor is hydrated) by the thiol of the enzyme is a slow and disfavored reaction. In contrast, the same reaction is favored with the hydroxyl of a serine. Experimentally, equilibrium occurs very slowly with the enzyme as well as with model molecules.[87]

7.3.4.1 Aspartate Semialdehyde Dehydrogenase Aspartate semialdehyde dehydrogenase (ASA-DH) bears a catalytic cysteine. This enzyme is involved in the biosynthesis of lysine and of its precursor, diaminopimelic acid. These latter molecules are important elements of the biosynthesis of peptidoglycan of the bacterial wall, and of some other essential amino acids. Inhibitors of ASA-DH stop the synthesis of proteins and that of peptidoglycan, two key processes of bacterial metabolism. A difluoroketone analogue of the ASA-DH substrate, in which a —CF_2— replaces the oxygen of the γ-aspartyl phosphate, has been prepared. After pre-incubation of the inhibitor with the enzyme, a reversible inhibition ($K_i = 95\ \mu M$) has been observed. The data seem to indicate that inhibition would be the "slow-binding" type via interaction of the thiol of the active site with the carbonyl of the hydrate form of the difluoroketone (Figure 7.45).[90]

Syntheses of amido- and peptido-fluoroketones have been reviewed (Figure 7.46).[8, 49] The main problems concern enantio- and diastereoselectivity, and also the oxidation step of a fluorinated amino alcohol, which is generally required. Indeed, the peptidic couplings required for the edification of parts P_1, P_2, etc. cannot be

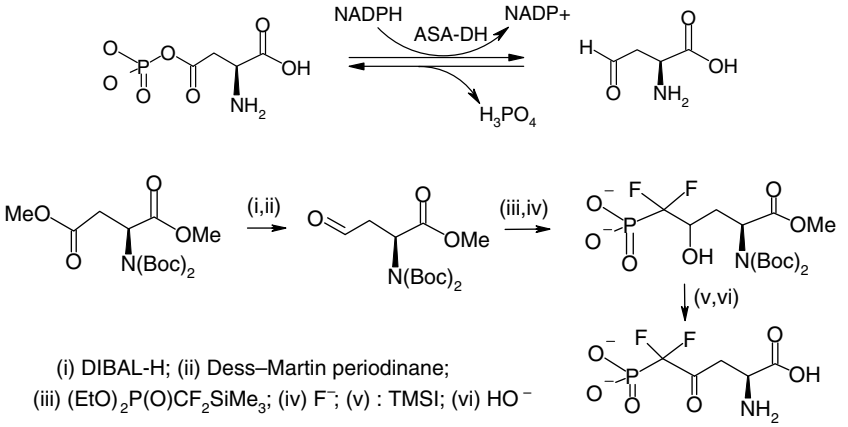


Figure 7.45 ASA-DH and the difluorinated analogue of aspartyl phosphate.

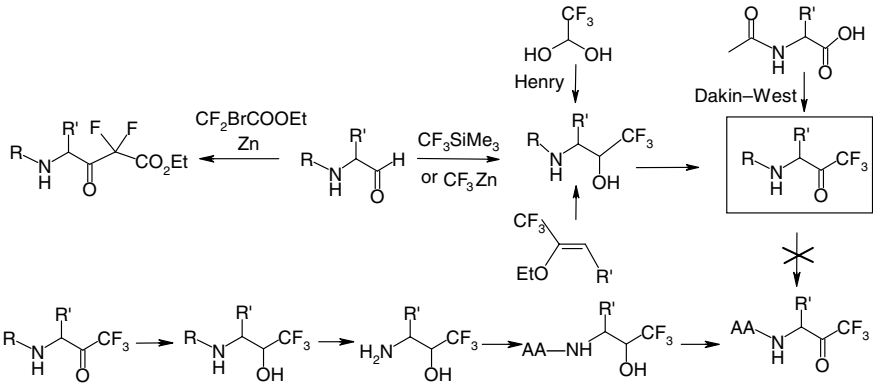


Figure 7.46 Main methods for the synthesis of amido trifluoromethyl ketones.

performed directly on the amino ketone. These are realized after reduction of the amino ketone into amino alcohol. After coupling, it is then necessary to perform the difficult oxidation of the fluorinated alcohol. The fluorostanine-type derivatives generally come from the addition of the Reformatsky reagent of the bromodifluoroacetate onto an aldehyde or onto an α-peptidyl aldehyde (Figure 7.46) (cf. Chapter 2).

7.4 MECHANISM-BASED INHIBITORS

The term "mechanism-based inhibitors" is ambiguous and not really explicit because most of the inhibition concepts are based on the enzymatic mechanism. The mechanism-based inhibitor concept rests on the transformation by the enzyme of a pseudosubstrate into a reactive molecule. This latter can further react with this enzyme by forming a covalent bond that is fatal for catalytic activity. It is then essential that the formed intermediate is reactive enough to react on the enzyme before diffusion outside the active site. This concept requires (1) an irreversible and time-dependent inhibition, (2) the formation of covalent and stoichiometric adducts, and of course (3) a reactive entity stemming from an enzyme-catalyzed reaction. Such pseudosubstrates, which are transformed by the enzyme itself, are sometimes named "suicide substrates."[91]

The reactive entities that are used in this type of approach are often electrophiles with a Michael acceptor structure. These species are frequently generated by a β-elimination process when the reaction involves the development of a negative charge in β of a leaving group. The presence of an electron-withdrawing group is required in order to ease the development of the negative charge in α (more acidic hydrogen), and also to obtain a reactive conjugated system after the β-elimination. The electrophilic species that is then generated must be able to react with a nucleophilic entity of the catalytic site of the enzyme. This alkylation generally leads to the irreversible inhibition of the enzyme. While this concept was first developed for inhibition of pyridoxal phosphate enzymes, it has also been used to obtain inhibitors of

other enzymes: for example, flavin-dependent enzymes (monoamine oxidases), reductases (nucleoside phosphate reductases), and proteases.

The efficiency of the inhibition by a mechanism-based inhibitor depends on the selective addition of the electrophilic entity on a nucleophile of the catalytic site, and not on the other numerous nucleophilic sites of the enzyme. Factors leading to a lack of selectivity are the insufficient reactivity of the electrophilic entity (a long half-life is often accompanied by the diffusion of the species outside the active site) and a large distance between the electrophile and the nucleophile of the active site of the enzyme.

Fluorinated compounds occupy an important position in this type of approach, since they easily undergo β-elimination reactions with the release of a fluoride ion, when there is an electron-withdrawing group in β. Moreover, they are poor electrophiles and, consequently, they are stable in protic or nucleophilic media. This is a major advantage with regard to chlorinated and brominated derivatives. These latter compounds are unstable or promote nonspecific alkylations under physiological conditions. Moreover, when the pseudosubstrates are di- or trifluoromethylated, reactivity of the formed Michael acceptor is largely enhanced by the presence of fluorine atoms on the conjugated double bond.

7.4.1 Inhibition of Pyridoxal Phosphate Enzymes

Among the numerous enzymes that utilize pyridoxal phosphate (PLP) as cofactor,[7b] the amino acid racemases, amino acid decarboxylases (e.g., aromatic amino acids, ornithine, glutamic acid), aminotransferases (γ-aminobutyrate transaminase),[92] and α-oxamine synthases,[93] have been the main targets in the search for fluorinated mechanism-based inhibitors. Pharmaceutical companies have played a very active role in this promising research (control of the metabolism of amino acids and neuroamines is very important at the physiological level).

The first step of the enzymatic process is the transaldimination of the Schiff base lysine-PLP by the amino acid. The pulling out of the proton in α of the fluorinated amino acid is accompanied by elimination of a fluorine atom of the CX_2F group, thus affording a very reactive quinonic species. This latter one can further react with a nucleophilic entity of the enzyme (e.g., the lysine of the active site) ("Michael addition inactivation process") (Figure 7.47).[7b, 93, 94]

Very detailed studies on the inhibition of alanine racemase by fluoroalanines have been conducted. This enzyme catalyzes the racemization of alanine to provide D-alanine, which is required for synthesis of the bacterial wall. This work has demonstrated that a more complex process than that represented in Figure 7.47 could intervene. For instance, in the case of monofluoroalanine, a second path (Figure 7.48, path b) occurs: lysine-38 of the active site can also attack the Schiff base PLP-aminoacrylate that comes from the elimination of the fluorine atom. This "enamine inactivation" process (path b) has been confirmed by isolation and identification of the alkylation compound, after denaturation of the enzyme (Figure 7.48).[95]

Inhibition processes can highly depend on the number of fluorine atoms. Thus, while mono- and trifluoroalanine are good inhibitors of alanine racemase,

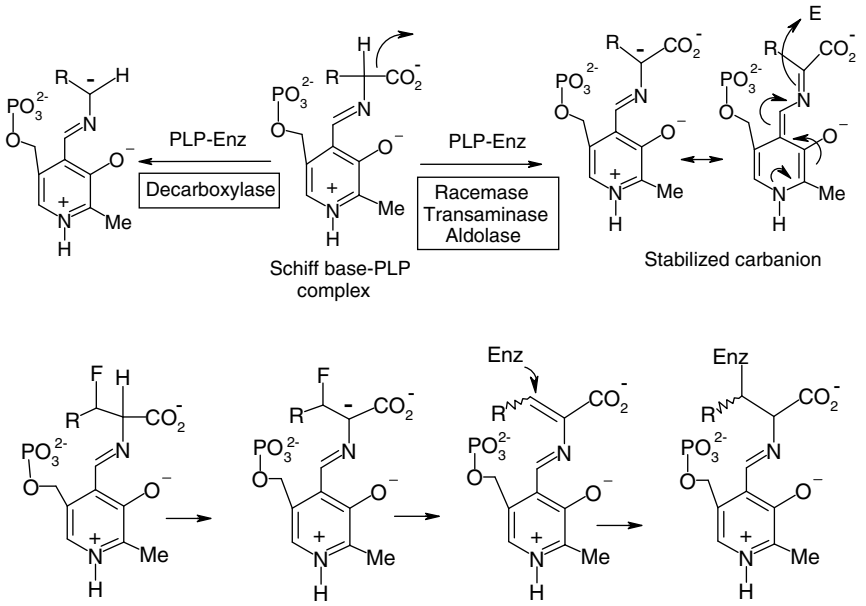


Figure 7.47 Inhibition of pyridoxal phosphate-dependent enzymes by a fluorinated amino acid.

difluoroalanine is a good substrate for this enzyme. In this latter case, the adduct formed with the enzyme is hydrolyzed in the medium and the enzyme is regenerated (Figure 7.49). In contrast, difluoroornithine is a good inhibitor of ornithine decarboxylase.[96]

Complexity of inhibition of PLP-dependent enzymes is highlighted by detailed investigations on the inhibition of γ-aminobutyric acid aminotransferase (GABA-AT), the enzyme responsible for the degradation of γ-aminobutyric acid (GABA), one of the major inhibitory neurotransmitters in the mammalian central nervous system. Inhibition of GABA-AT results in an increased concentration of GABA in the brain and could have therapeutic applications in neurological disorders (epilepsy, Parkinson disease, and Alzheimer disease).

A number of conformationally restricted fluorinated inhibitors have been synthesized and evaluated.[97] These studies show that (1) subtle conformational differences of the substrates affect the inhibition (potency, reversible or irreversible character) (Figure 7.50), (2) a third inhibition process involving an aromatization mechanism could take place (Figure 7.51). When the Michael addition and enamine pathways lead to a covalently modified active site residue, the aromatization pathway produces a modified coenzyme able to produce a tight binding complex with the enzyme, responsible for the inhibition (Figure 7.51).[98]

Ornithine decarboxylase catalyzes the conversion of ornithine into putrescine. Like other polyamines, the latter is involved in the regulation of cell development. Inhibition of this enzyme has been an important goal in medicinal chemistry. In this context, difluoroornithine has been shown to be an excellent inhibitor

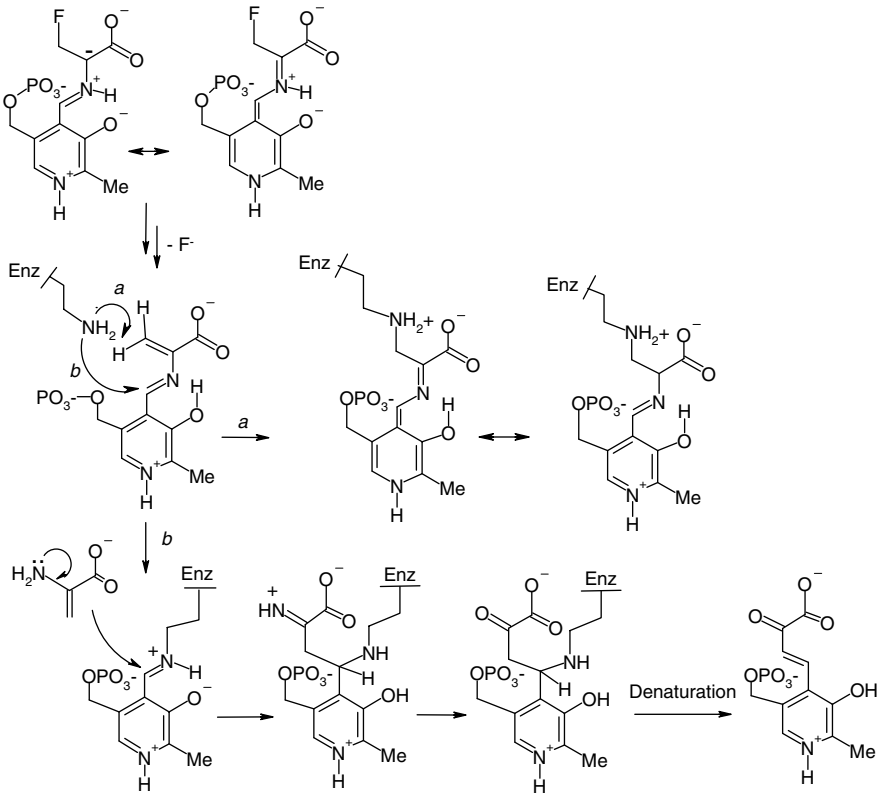


Figure 7.48 Inhibition of the alanine racemase by monofluoroalanine.

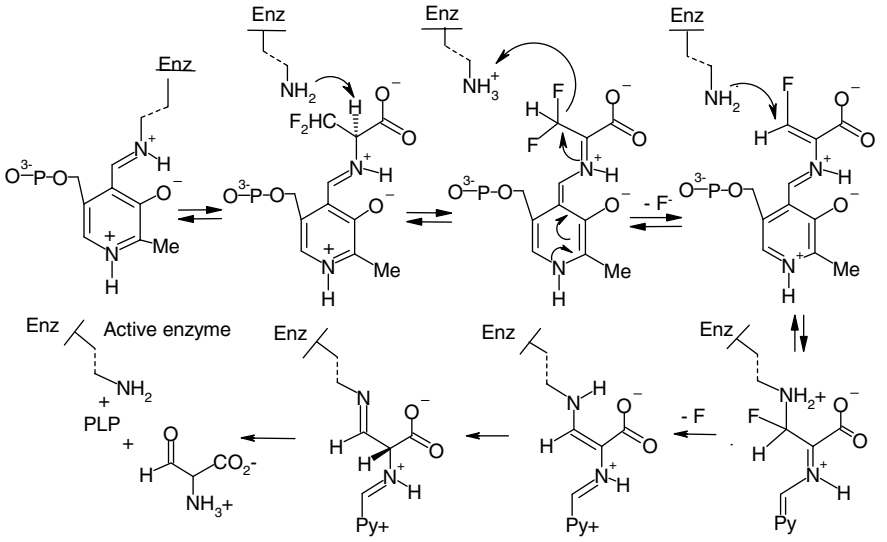


Figure 7.49 Difluoroalanine as substrate of alanine racemase.

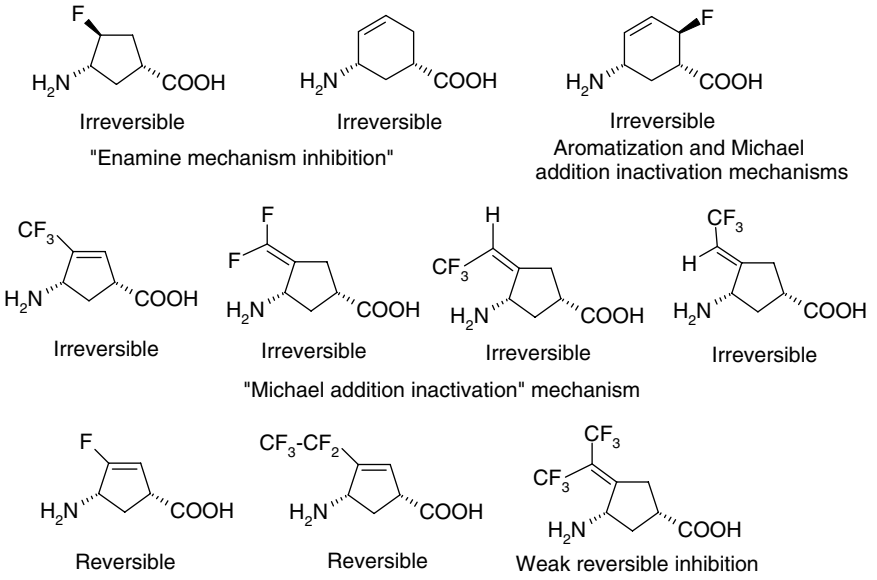


Figure 7.50 Conformationally restricted fluorinated inhibitors of GABA-AT.[97–99]

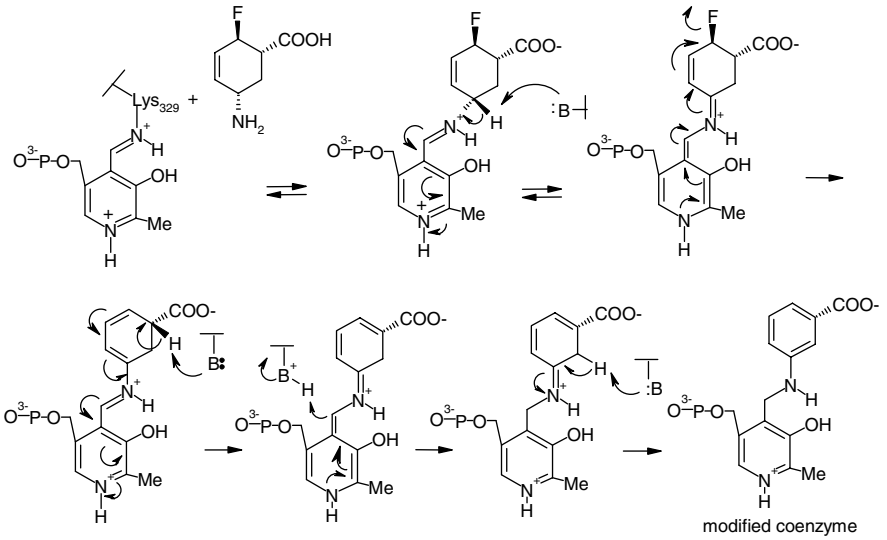


Figure 7.51 Mechanism of aromatization inactivation of GABA-AT.[98]

in vitro.[100] While development of this compound failed as an application for cancer chemotherapy, it is currently the best drug available for treating sleeping sickness (trypanosomiasis), even if its bioavailability is rather poor (cf. Chapter 8).[101] Preparation of difluoroornithine (*eflornithine*) is described in Chapters 4 and 8.

7.4.2 Thymidylate Synthase

Trifluridine, a trifluoromethylthymidine, is a mechanism-based inactivator of thymidylate synthase (TS), with a mechanism different from 5-FU (Figures 7.2 and 7.52). Trifluridine is marketed for the topical treatment of herpes simplex virus infection in eyes.

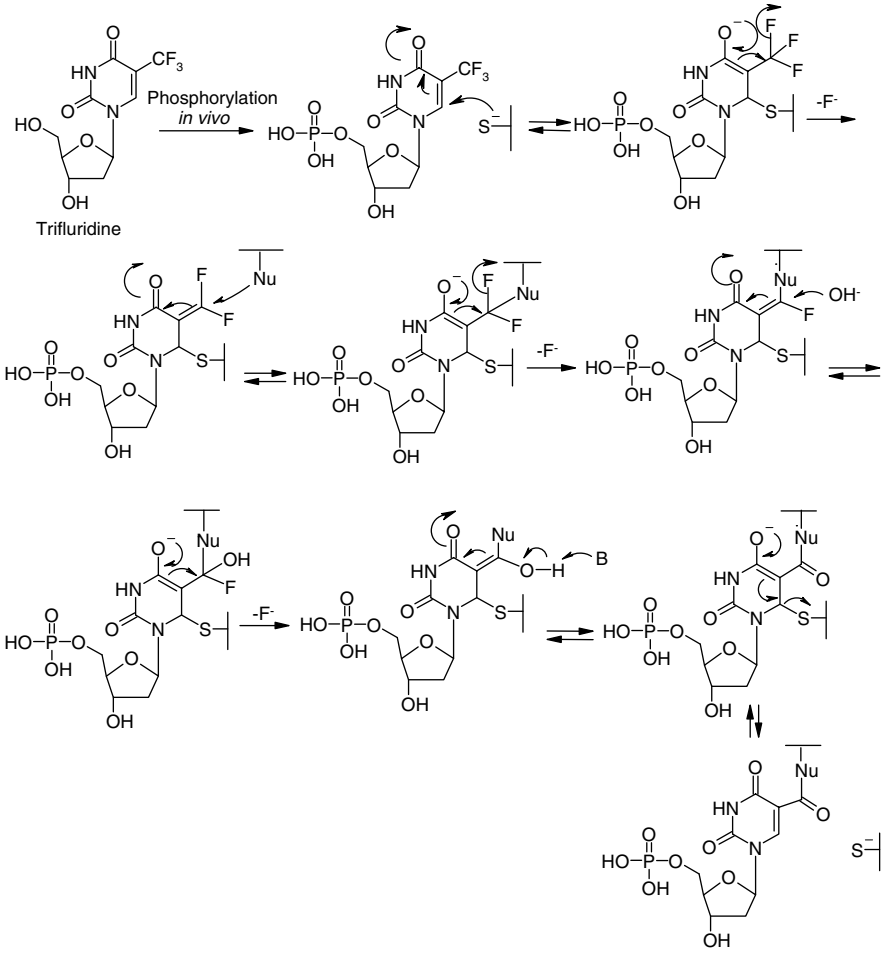


Figure 7.52 Inhibition of thymidylate synthase by trifluridine.

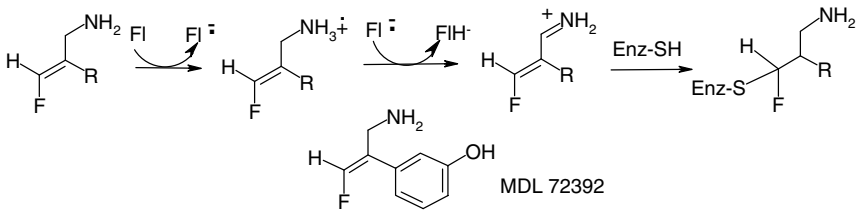


Figure 7.53 Postulated mechanism for the inhibition of MAOs by fluoroallyl amines.

7.4.3 Inhibition of Monoamine Oxidases

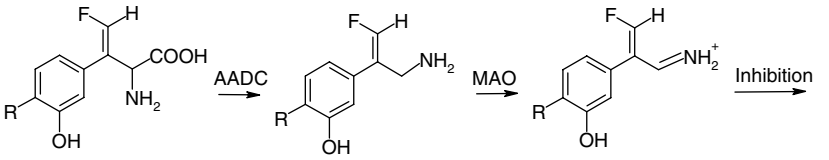
Monoamine oxidases (MAOs) are mitochondrial membrane enzymes. These flavin-dependent enzymes are responsible for the oxidative deamination of numerous endogenic and exogenic amines (norepinephrine, serotonin, dopamine, etc.). MAO A and B take part in the regulation of these amines in many organs, such as the brain. The essential physiological role of these amines, especially in the central nervous system, has motivated the search for inhibitors of their catabolism in order to enhance the synaptic concentration of neuroamines.

Propargylic, cyclopropyl, and fluoroallyl amines are powerful and irreversible mechanism-based inhibitors of MAOs. Oxidation by the enzyme affords a very active entity onto which a nucleophile of the enzyme, or of the cofactor, can be added (Figure 7.53).

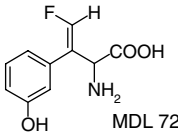
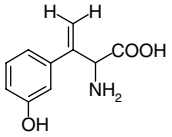
Neuroamines are biosynthesized in the central nervous system by decarboxylation of the corresponding amino acids by the amino acid decarboxylases (AADCs), which are present in nerve endings. In consequence, inhibition of the AADCs could be a means to regulate concentration in neuroamines. Research has been based on the hypothesis that a β-fluoromethylene amino acid could be used as a precursor of the inhibitor. If this fluorinated amino acid was a substrate for the AADC, it would then be transformed *in situ* into a β-fluoromethylene amine, which is an irreversible inhibitor of MAOs (Figure 7.54).[102]

Considering the important implications of L-dopa in Parkinson disease, studies have mainly been dedicated to tyrosine derivatives. The starting hypothesis has thus been verified: β-fluoromethylenetyrosines are not substrates of MAOs but are recognized by the AADC, and then decarboxylated into fluoroallyl amines. These latter are indeed inhibitors of MAO A and B.[103, 104]

A detailed study of the inhibition of MAOs by fluorophenyl cyclopropyl amines shows that the presence of fluorine has very important effects on this inhibition. While some of the regioisomers are inhibitors of the CAO (copper-containing amine oxidase),[105a, b] some other ones, such as 2-fluoro-1-arylcyclopropyl amines, are excellent selective and irreversible inhibitors of MAO A. In this latter case, the nonfluorinated parent compound is a poor inhibitor of MAO B (Figure 7.55).[105b, c]

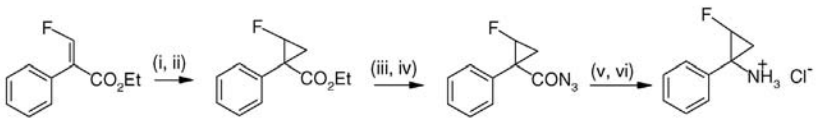


AADC : Amino acid decarboxylase; MAO : Monoamine oxidase

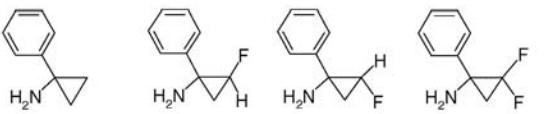
	Relative rate of decarboxylation into allylic amine[a]	MAO inhibition Type A $t_{1/2}$ (min)	Type A K_i (M)	Type B $t_{1/2}$ (min)	Type B K_i (M)	Selectivity for type A
 MDL 72394	54	2	$1x10^{-7}$	15	$1x10^{-7}$	10
	20	5	$5x10^{-5}$	5	$2.5x10^{-4}$	5

[a] Percentage (%) relative to the rate of decarboxylation of L-dopa into dopamine.

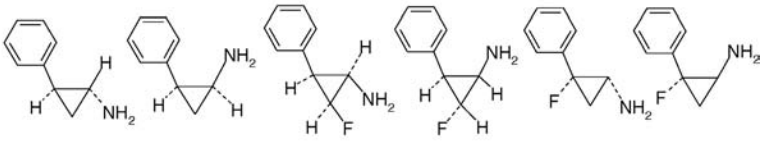
Figure 7.54 Schematic representation of the inhibition of MAOs by β-fluoromethylene tyrosines.[104]



(i) CH_2N_2; (ii) hν; (iii) NH_2NH_2; (iv) HCl, $NaNO_2$; (v) tBuOH, reflux; (vi) HCl (2 N/Et_2O)



IC_{50} (μM) MAO A	730	1.1	0.9	110
IC_{50} (μM) MAO B	190	290	72	NI
IC_{50} (μM) CAO	NI	NI	NI	NI



IC_{50} (μM) CAO	35	33	3.6	190	3.6	190
	(Competitive)	*(Irreversible)*	*(Competitive)*	*(Irreversible)*	*(Competitive)*	*(Irreversible)*

Figure 7.55 Inhibition of the monoamine oxidases CAO, MAO A, and MAO B by fluorophenyl cyclopropyl amines.[105]

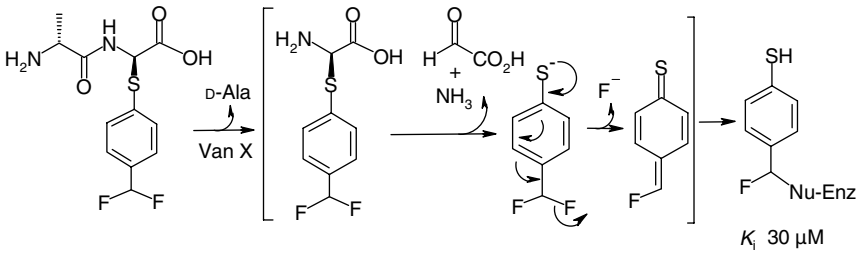


Figure 7.56 Mechanism-based inhibition of VanX.[106]

7.4.4 D-Ala-D-Ala Dipeptidase (VanX)

The VanX enzyme is a zinc amino dipeptidase. It is responsible for the degradation of D-Ala-D-Ala dipeptide, and it is associated with a high level of resistance to vancomycin. A dipeptidic mechanism-based inhibitor has been designed: this compound is recognized as a substrate by the enzyme and it undergoes enzymatic hydrolysis and affords D-Ala and a hemithioaminal, which spontaneously decomposes into *p*-difluoromethyl thiophenol. Then, this latter species quickly loses a fluoride anion to yield fluoromethylene thioquinone (Figure 7.56). This compound is reactive enough to undergo the addition of a nucleophile at the active site of the enzyme. All the criteria that are required for a mechanism-based inhibition are fulfilled: irreversible and time-dependent inhibition, covalent and stoichiometric adduct, reactive entity stemming from an enzyme-catalyzed reaction, and a life time that is short enough to react without diffusing outside the active site of the enzyme.[106]

7.4.5 Inhibition of Ribonucleotide Diphosphate Reductase

Ribonucleotide diphosphate reductase (RDPR) is a homodimeric enzyme that catalyzes the crucial step of the biosynthesis of DNA: the conversion of nucleotides into deoxynucleotides (Figure 7.52). Its inhibition constitutes an interesting target for antiviral and antitumor therapies. The mechanism of reduction of the nucleotide catalyzed by RDPR is complex. The subunit R_1 contains the active site for the binding and reduction of the substrate, while the subunit R_2 contains the essential tyrosyl radical cofactor. The reduction process involves the abstraction of the hydrogen 3′ by a radical generated from cysteine-439 of R_1, generated itself by the radical tyrosyl of the subunit R_2. The hydroxyl in 2′ is then eliminated as a water molecule and the reduction of the α-keto radical by cysteines-225 and -462, followed by the transfer of hydrogen Ha to the radical, provides the deoxynucleotide and regenerates the sulfur radical (Figure 7.57).[8i]

Fluoromethylene deoxycytidines have been rationally designed as bioprecursors, after phosphorylation *in vivo* by the deoxycytidine kinase, of the mechanism-based inhibitors of RDPR. Among these, *tezacitabine* (MDL-101731) has been shown to be an excellent irreversible inhibitors of various RDPRs.[8i] It has a high antiproliferative activity and is currently in Phase III clinical trials for the treatment of solid tumors. Synthesis of *tezacitabine* is reported in Chapter 8.

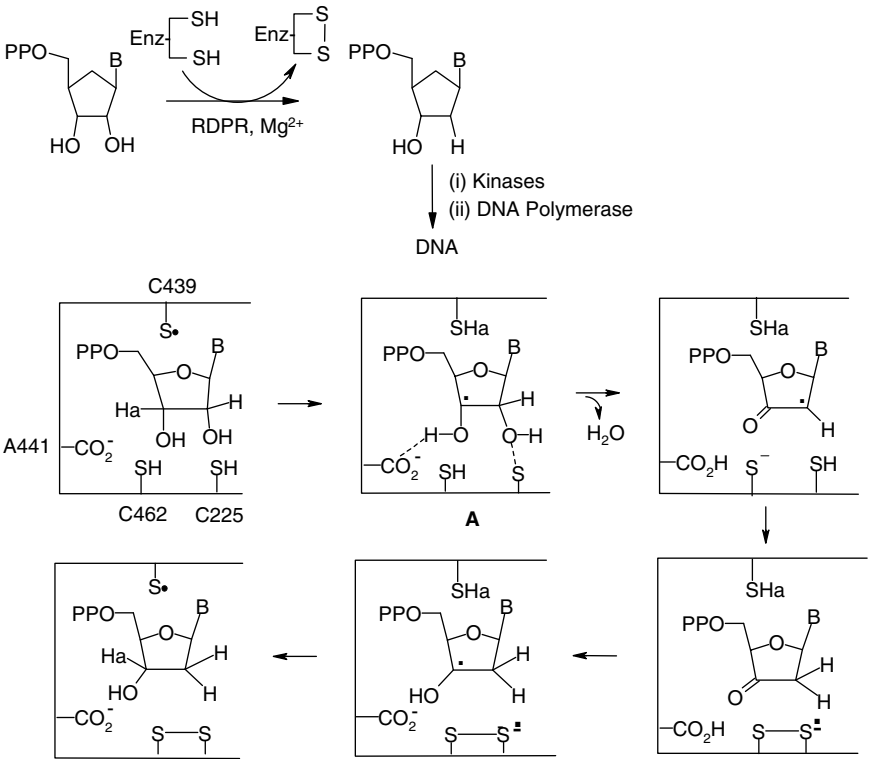


Figure 7.57 Mechanism of reduction by RDPR.[8i]

The proposed mechanism for the inactivation of RDPR by tezacitabine is detailed in Figure 7.58. Conversely to the radical A generated from the cytidine phosphate, the radical A′ formed from the 2′-fluoromethylene-2-deoxycytidine cannot eliminate a water molecule (Figures 7.57 and 7.58). It undergoes an isomerization into a new radical B′ centered on the fluorine-substituted carbon. This latter finally provides, after several steps, a high electrophilic entity D′ able to add the subunit R_1 of the enzyme. The resulting covalent adduct of D′ with the enzyme has been identified.[8i]

7.4.6 Inhibition of *S*-Adenosylhomocysteine Hydrolase

S-Adenosylmethionine (SAM) is a donor of a methyl group in numerous biological methylations. It is first transformed into *S*-adenosylhomocysteine (SAH), then into adenosine and homocysteine by SAH hydrolase.

SAH that is produced by SAH hydrolase regulates back the methylase that generates it. By regulating the level of SAH, SAH hydrolase indirectly controls the potential of methylation. This is the reason why inhibitors of SAH hydrolase may exhibit antiviral activity: they allow the accumulation of SAH. As a consequence, methylation of messenger RNAs that are required for virus replication is inhibited.

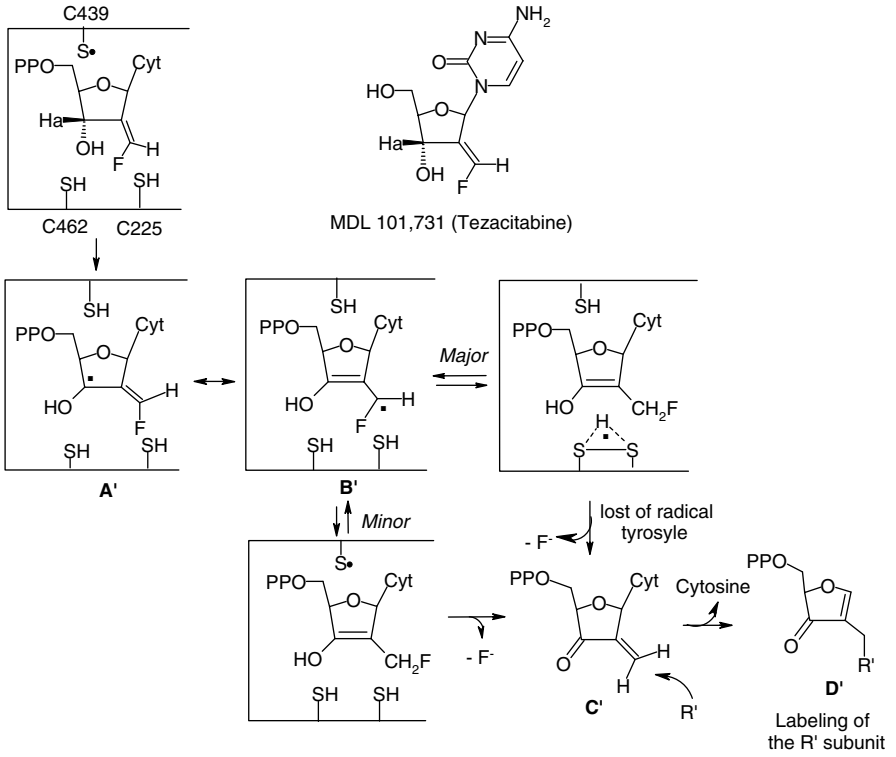


Figure 7.58 Proposed mechanism for the inactivation of RDPR by MDL-101731 (*tezacitabine*).[8i]

On the basis of a similar approach used with MDL 101731, irreversible inhibitors of SAH hydrolase have been designed.[107] However, the supposed addition–elimination mechanism of a nucleophile of the enzyme onto the Michael acceptor has been ruled out: the hydrolysis of the vinyl fluoride into aldehyde is responsible for the irreversible inhibition (Figure 7.59).[108]

7.4.7 Inhibition of Cytidine-5′-diphosphate-D-Glucose 4,6-Dehydratase (CDP D-Glucose 4,6-Dehydratase)

This enzyme catalyzes, via several steps, the transformation of cytidine-5′-diphosphate-D-glucose into cytidine-5-diphosphate-6-deoxy-6-*threo*-D-glycero-4-hexulose (Figure 7.60). These reactions involve the transfer of a hydrogen of carbon 4 to carbon 6 of the glucose molecule, via the substrate/NAD^+ complex. 6,6-Difluoro-6-deoxyglucoses are irreversible inhibitors of this enzyme. Alkylation of the protein comes from the addition of a nucleophile of the enzyme onto the Michael acceptor (stemming from the elimination of fluorine atoms) as demonstrated by the characterization of the covalent adduct between the difluoroglucose and the enzyme (Figure 7.61).[109]

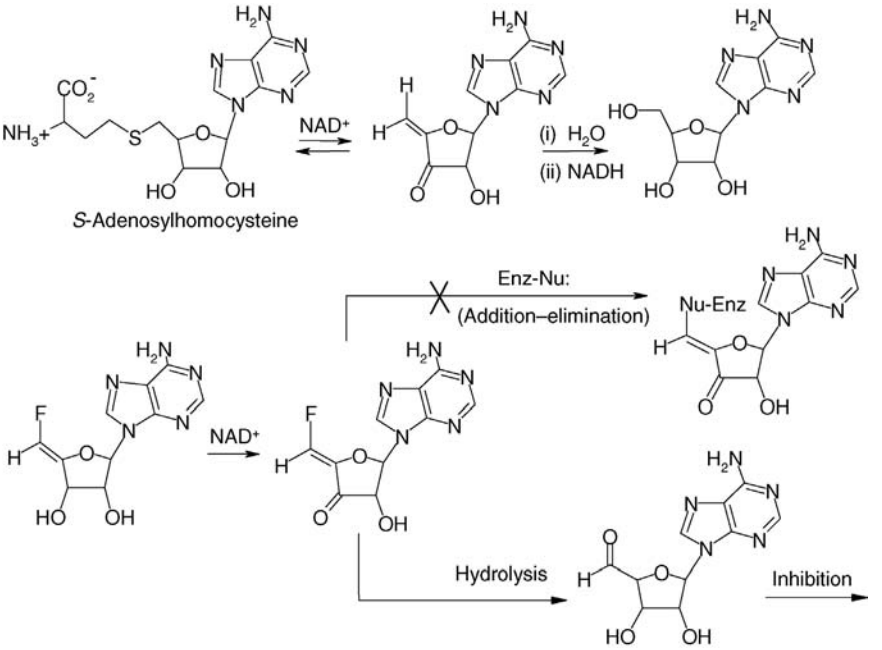


Figure 7.59 Inhibition of SAH hydrolase.

7.4.8 Other Irreversible Inhibitors

We only report here on the fluorinated compounds that act as phosphorylating or acylating agents, such as phosphonofluoridates (affinity labelers)[110] and acyl fluorophosphates (e.g., fluorophosphate of arachidonic acid, an inhibitor of phospholipase A_2.[111]) We can also cite alkylating agents, such as monofluoromethyl peptidyl ketones, which are inhibitors of serine and cysteine proteases (caspase, SARS-CoV protease, etc.).[112] The lowered reactivity of monofluoromethyl ketones, compared to bromo or chloro ones, constitutes an advantage at the level of selectivity and toxicity:

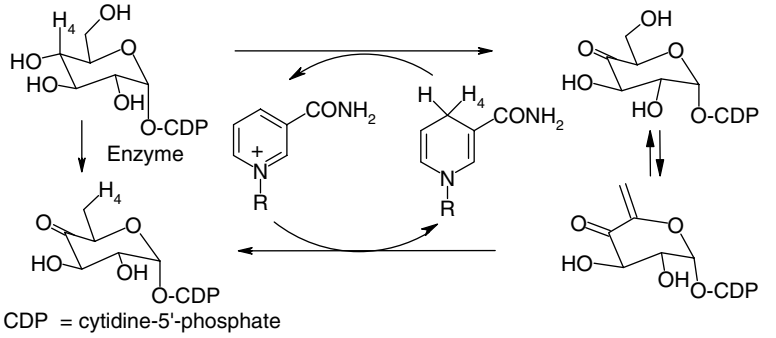


Figure 7.60 Reaction of CDP-D-glucose-4,6-dehydratase.

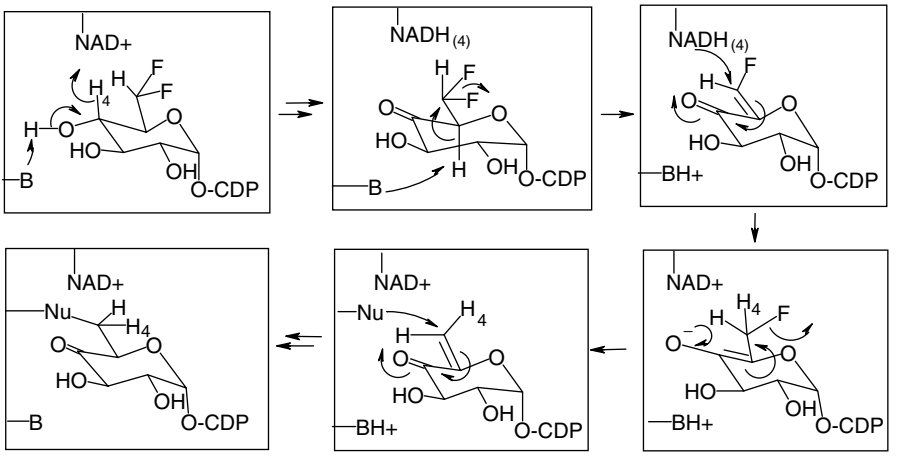


Figure 7.61 Inhibition of CDP-D-glucose-4,6-dehydratase by deoxy-6,6-difluoroglucose.[109]

they are more stable in physiological media. This can limit nonspecific alkylations, which are a source of toxicity.[113]

7.5 FLUORINATED INHIBITORS INVOLVING A STILL UNKNOWN MECHANISM

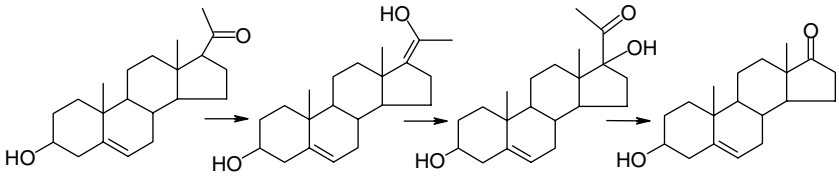
7.5.1 Inhibition of the Steroid $C_{17(20)}$lyase

The steroid $C_{17(20)}$lyase is an enzyme that is involved in the biosynthesis of androstenedione and of dehydroepiandrosterone from progesterone and pregnenolone, respectively. As androgen and estrogen hormones are necessary for the growth of tumors, this enzyme is a potential therapeutic target for the treatment of prostate cancer and in hormone-dependent breast cancers.

Synthesis of inhibitors of the steroid $C_{17(20)}$lyase is based on the use of a vinylic fluoride that is able to mimic the enol intermediate of the reaction. This enol is supposed to be involved in the first stage of the enzymatic reaction: the hydroxylation at C-17. The synthesized vinyl fluorides are good inhibitors but, surprisingly, the inhibition is time dependent. This fact suggests that the real mechanism of inhibition is different from that expected for an analogue of the transition state—implying very strong affinity constants (Figure 7.62).[114]

7.5.2 Phosphatidylinositol Phospholipase C (PI-PLC)

Hydrolytic cleavage by phosphatidylinositol phospholipase C (PI-PLC) of the cyclic *myo*-inositol-1,2-phosphate (cIP) at C-2 is faster than that at C-1. A cyclic monofluorophosphonate has been prepared as a stable analogue of the substrate in



Concentration (μM)	Preincubation time (min)	(% inhibition)
10	0	78
1	0	49
10	40	94
1	40	72

Figure 7.62 Inhibition of the steroid $C_{17(20)}$lyase by vinyl fluorides.[114]

order to inhibit this PI-PLC enzyme. It has been proposed that the fluorine atom could possibly stabilize the pentacoordinated transition state of hydrolysis of the cyclic phosphate by the enzyme. This fluorophosphonate could then behave as a substrate analogue as well as a transition state analogue. Indeed, the fluorophosphonate is an inhibitor. However, surprisingly, the inhibition does not occur during the hydrolysis step of the cyclic phosphate, but during its formation (which is the first step). The inhibition mechanism remains unknown (Figure 7.63).[115]

7.5.3 Inhibition of the Protein of Transfer of Cholesteryl Esters

The protein of transfer of cholesteryl esters (CEPT) is a plasma glycoprotein that plays an important role in the control of the circulating rates of high and low density cholesterol (HDC and LDC, respectively). This is now a therapeutic target in the

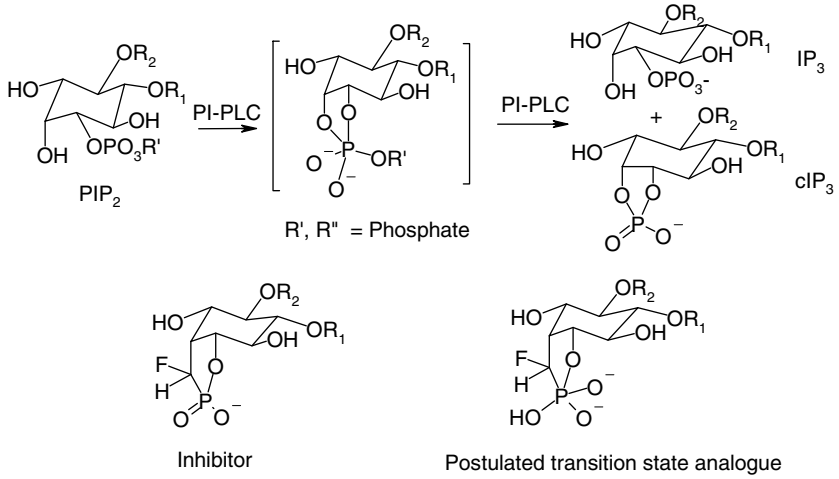
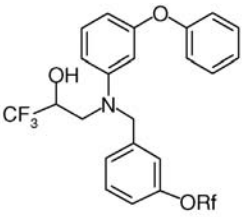
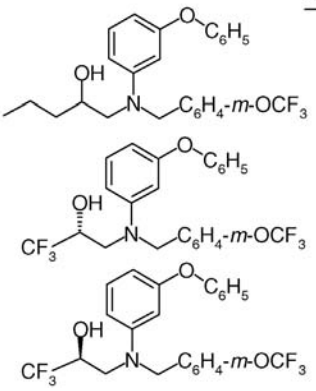


Figure 7.63 Inhibition of phosphatidylinositol phospholipase C.



	IC_{50} (μM) in buffer	IC_{50} (μM) in plasma
Rf = 3-OCF_3	1.0	40
3-OCH_3	5	>200
3-OCF_2CF_2H	0.014	5.6
3-$C(CF_3)_2OH$	0.42	4.9



IC_{50} (μM) in buffer	IC_{50} (μM) in plasma
3.6	
0.02	0.6
0.8	20

Figure 7.64 Inhibition of the protein of transfer of cholesteryl esters (CEPT) by fluorinated amino alcohols.[117]

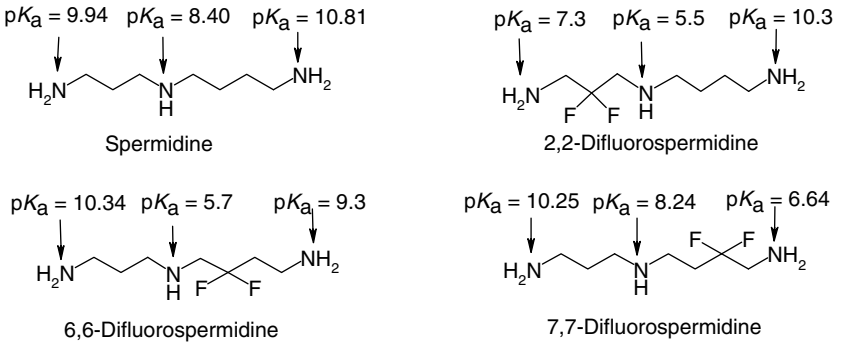
prevention of vascular coronary pathologies. The enzyme seems to involve a catalytic cysteine, but neither its structure nor its mechanism is known.[116]

Trifluoromethyl-3-amino-2-propanols are powerful (submicromolar) and reversible inhibitors of CEPT in human plasma. Reversibility of the inhibition seems to indicate that the inhibitor acts as a substrate analogue (Figure 7.64). Three important factors for the gain of affinity must be underlined: (1) replacement of the propyl group by a trifluoromethyl (affinity 30×), (2) the *R* configuration at the hydroxyl (affinity 40×), and (3) the presence of a fluoroalkyl substituent on the third aromatic ring (affinity 40×).[117]

7.5.4 β-Fluoropolyamines as Inhibitors of the Biosynthesis of Polyamines

Metabolism of polyamines has a direct action on cell proliferation. Thus, it is a therapeutic target for the design of antitumor agents. However, inhibition of ornithine decarboxylase (ODC) by specific inhibitors does not completely cancel the activity. This is due to the existence of other biosynthetic pathways (i.e., SAM-DC). These pathways are themselves regulated by polyamines.

The aminopropylation of spermidine into spermine by spermine synthase (SPM synthase) is favored by a higher basicity (ease of protonation) of the nitrogens N-1 and N-4, but also by a lower basicity of N-8 of the butylamino terminal group (more difficult protonation). This last factor enhances the affinity of the substrate for the enzyme.[118] Fluorospermidines could then appear as potential inhibitors of SPM synthase. Indeed, the presence of fluorine atoms in β of an amino group lowers the basicity of the amine: the pK_a value of N-4 is lowered by 2.70 units for 6,6-difluorospermidine derivatives, and it is lowered by 3.17 units in the case of 7,7-difluorospermidine (Figure 7.65).[119] Although 2,2-difluorospermidine is not a



		Cell polyamines synthesis (% of control)			
	SPM synthase K_m (μM)	Spermidine	Spermine	*F*-Spermidine	*F*-Spermine
Spermine	88				
6,6-Difluorospermine	458	99	111	76	17

Figure 7.65 Inhibition of spermine synthase (SPM synthase) by fluorospermidines, and related pK_a values.

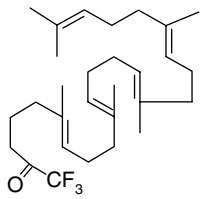
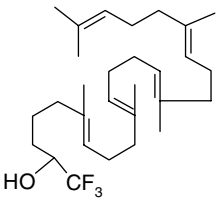
	Inhibition of cholesterol biosynthesis (human hepatocyte cells)	Cellular activity of HMG-CoA (% of control)	
		10^{-5} M	10^{-4} M
Epoxysqualene	IC_{50} = 0.5 μM)		
	IC_{50} = 0.56 μM	30 %	14 %
	IC_{50} = 1.6 μM	33 %	18 %

Figure 7.66 Trifluoromethyl alcohols and ketones as inhibitors of the biosynthesis of cholesterol.

substrate of SPM synthase and 6,6-difluorospermidine is a poor substrate, this has no consequences on the cellular synthesis of spermine. In contrast, 7,7-difluorospermidine is an excellent substrate of SPM synthase, even better than the natural substrate. When 7,7-difluorospermidine is converted into 6,6-difluorospermine, it lowers cellular transformation of spermidine into spermine by 90%. Thus, it is a powerful inhibitor of spermine synthesis in cell culture as well as *in vivo*.[119]

7.5.5 Inhibition of the Biosynthesis of Cholesterol

Trifluoromethyl ketones and alcohol derivatives of squalene have been prepared in order to inhibit squalene epoxycyclase. This important enzyme regulates the biosynthesis of cholesterol. It bears a cysteine in its active site. Although these compounds have been shown to be good inhibitors, the involved mechanism is different from what was expected. Indeed, they do not inhibit squalene epoxycyclase, but they are substrates of this enzyme and are transformed into fluorohydroxysterols. The repression of the expression of HMG-CoA reductase is responsible for the observed inhibition of cholesterol biosynthesis. This repression comes from the back-regulation that is exerted by fluorohydroxysterols. Indeed, these compounds induce an important diminution of the cell activity of HMG-CoA reductase (Figure 7.66).[120]

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8

FLUORINATED DRUGS

This chapter deals with fluorine-containing molecules that are currently clinically used as pharmaceuticals or are at an advanced stage of their development (i.e., registered by the administration or under clinical trials I, II, or III). These compounds are found in almost all therapeutic classes and stem from very diverse chemical families. In most cases, they are inhibitors of enzymes (anti-infectious, antitumor, antiviral drugs) or are ligands of various receptors (membraneous receptors coupled to protein G, ionic channels, or nuclear receptors).

More than 150 fluorinated compounds are used as pharmaceuticals. The reasons for introducing fluorine atoms into these drug are diverse. We classify these reasons into three categories:

1. Compounds in which the presence of fluorine atoms enhances the efficiency and selectivity of the biological activity with respect to the nonfluorinated parent compounds. These fluorocompounds should have fewer unfavorable effects. Due to these features (safety of use, better bioavailability, reduced dose, minor toxicity, etc.), these compounds have replaced, sometimes entirely, the nonfluorinated compounds of the same class. Volatile anesthetics and fluoroquinolones can be cited as examples of this category.
2. Drugs in which fluorine atoms bring a specific biological activity to molecules that previously had no therapeutic activity. Most of the examples are enzyme inhibitors (difluoroornithine, gemcitabine, 5-fluorouracil). Synthesis of these drugs often comes from a rational approach that is based on the action mechanism.

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3. This last category is the largest one. It contains compounds in which the fluorine atom(s) play(s) an important role albeit nonessential for the activity. The introduction of fluorine atoms occurs during lead optimization and has allowed the drug candidate to overcome more easily the various stages of clinical and preclinical development. In this category, the positive effects of the presence of fluorine atoms are generally difficult to rationalize. They can act at the level of affinity, as well as at that of pharmacokinetic properties (metabolism and bioavailability). On the other hand, commercial strategy or industrial protection can also strongly influence the choice of the molecule that will be developed.

There are many years between the search for a hit, development of a lead, and then its launch as a drug. Thus, the inventory of currently marketed drugs gives only an imperfect view of the synthetic challenges that medicinal chemists have to face. For this reason, this chapter ends with exemples of fluorinated moieties recently introduced in medicinal chemistry. These functional structural patterns, which are present on new drugs or on molecules at an early stage of development, will possibly have a strong impact in medicinal chemistry in the future.

In order to give a clear overview, this chapter classically introduces pharmaceuticals according to their respective therapeutic class. Their chemical synthesis is given only when it has a specific interest in fluorine chemistry. The reader will appreciate the marketed names of the cited pharmaceuticals reported under INN names (International Non-proprietary Names) in the appendix. General references about marketed products (or under development) can be found in the Chemical Abstracts by using the INN (*italic* in the text).

8.1 ANTITUMOR AND ANTIVIRAL FLUORINATED DRUGS

8.1.1 Fluoronucleosides

Fluorinated analogues of nucleosides are drugs that interact with enzymes involved in the synthesis of DNA and RNA (cf. Chapter 7). They are developed for treatment of cancer and viral infections. Fluorine atoms can be present either on the base moiety or on the sugar one.

5-Fluorouracil inhibits thymidylate synthase (the mechanism is reported in Chapter 7). It is clinically used for the treatment of numerous cancers either directly or in prodrug form (*carmofur*, *tegafur, doxifluridine*, *capecitabine, fosfluridine, tidoxil*) (Figures 8.1 and 8.2).[1] For instance, *capecitabine* is transformed *in vivo* into 5′-deoxy-5′-fluorocytidine (*doxifluridine*). The transformation goes through hydrolysis by a hepatic carboxylesterase, followed by deamination by cytidine desaminase. Finally, phosphorylation occurs by the nucleoside phosphorylase (mainly present in tumor tissues).

Gemcitabine is a 2′,2′-difluoro-2′-deoxycytidine that is used in the treatment of numerous cancers (breast, NSCLC, pancreas, etc.). Its market is wide: more than $500 million (U.S.) and 2.5 tons produced in 2001. Synthesis of gemcitabine is

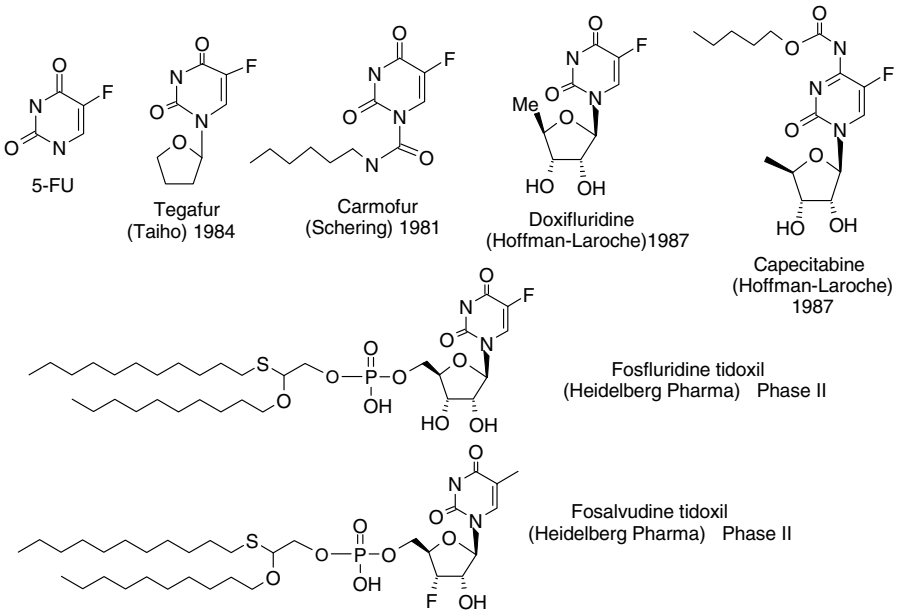


Figure 8.1 5-FU derivatives used in cancer therapy.

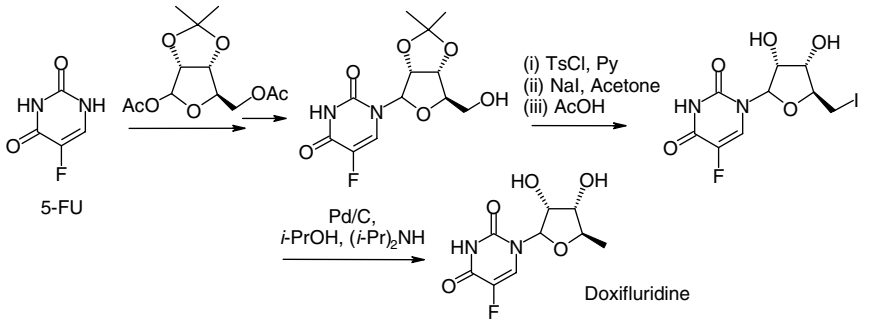


Figure 8.2 Synthesis of doxifluridine.

reported in Chapter 6. Gemcitabine, after metabolic phosphorylation, inhibits ribonucleotide diphosphate reductase (RNDR). However, it also interacts with other enzymes involved in DNA biosynthesis. This explains the great efficiency of gemcitabine (Figure 8.3).[2]

Tezacitabine is also an inhibitor of RNDR and it is currently undergoing Phase III development for cancer. Its inhibition mechanism is detailed in Chapter 7. Tezacitabine is synthesized from the cytidine protected at 4′-OH, 5′-OH, and 4-NH_2. The Swern oxidation provides a ketone that is converted to a *gem*-fluoro-sulfonyl olefin with the anion of sulfonylfluorophosphonate. Reduction of the sulfonyl group was realized with Bu_3SnH (Figure 8.4).[3]

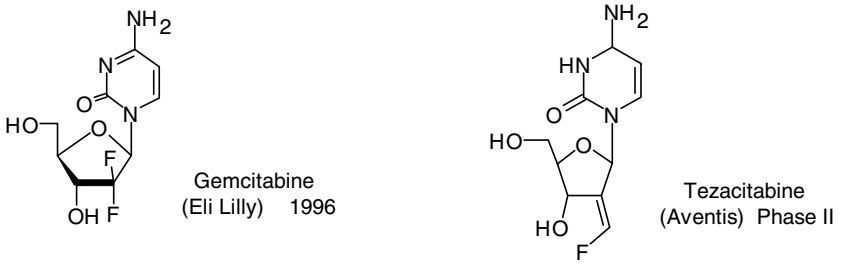


Figure 8.3 Antitumor fluorinated drugs, inhibitors of RNDR.

Fludarabine (Fludara®) is a 2-fluorocytarabine (Figure 8.5) that inhibits DNA biosynthesis via inhibition of DNA polymerase α and of RNDR. It is used clinically for the treatment of leukemia (chronic lymphocytic leukaemia—CLL).

The structurally close *clofarabine* is also marketed for the treatment of leukemia (Figure 8.5).[4] The fluorine substitution at 2′ increases the hydrolytic stability of the drug. Due to its electronegative character, fluorine disfavors development of a positive charge on the anomeric carbon, involved in the hydrolytic cleavage of nucleosides (cf. Chapter 6)

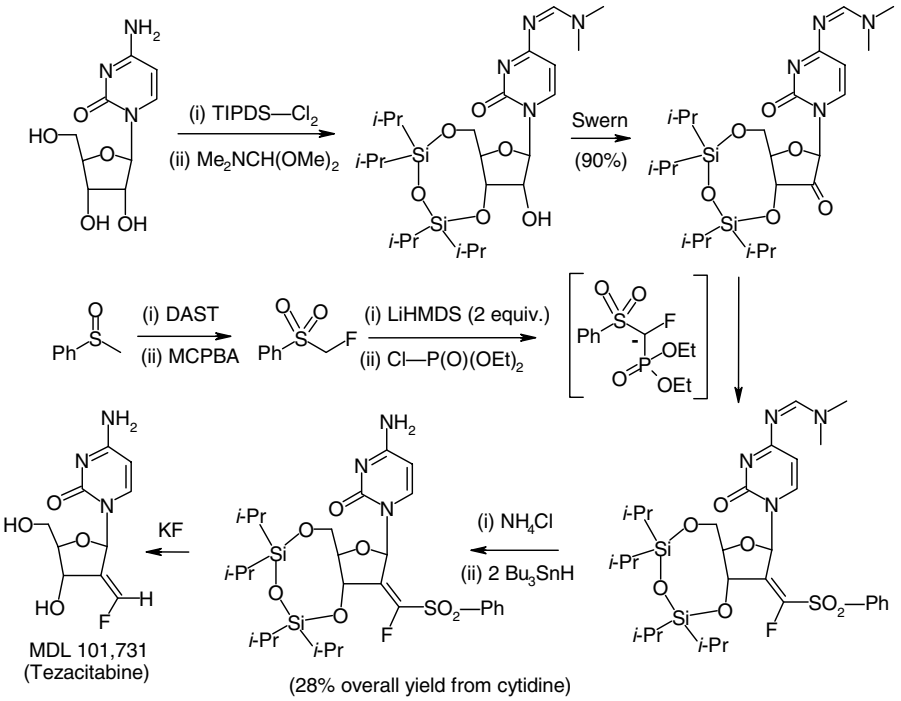


Figure 8.4 Synthesis of tezacitabine.[3]

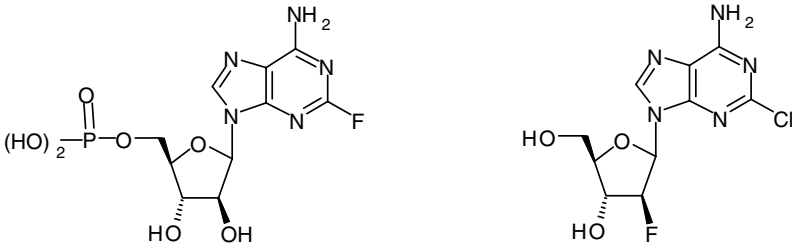


Figure 8.5 Fludarabine and clofarabine.

The antifungal ***flucytosine*** (5-fluorocytosine) is an inhibitor of the sterol *C*-14 demethylase. This latter is an enzyme involved in ergosterol biosynthesis, an element of the fungal wall. It is marketed as an antifungal, while the nucleoside derivatives of 5-fluorocytosine (*emtricitabine, elvucitabin, and FdCyd* (*287220*)) are used for treatment of viral infection and cancer (Figure 8.6).

Emtricitabine is a nucleoside reverse transcriptase inhibitor (NRTI), launched for the treatment of HIV infection (Figure 8.6). It is currently in Phase III trials for the treatment of hepatitis B virus (HBV) infection.[5] A prodrug of the NRTI *alovudine—fosalvudine tidoxil*—is currently in Phase II (Figure 8.1).

Elvucitabine is an L-cytosine nucleoside in phase III development for treatment of HIV and HBV infections (Figure 8.6). Its antiviral activity has been shown to result

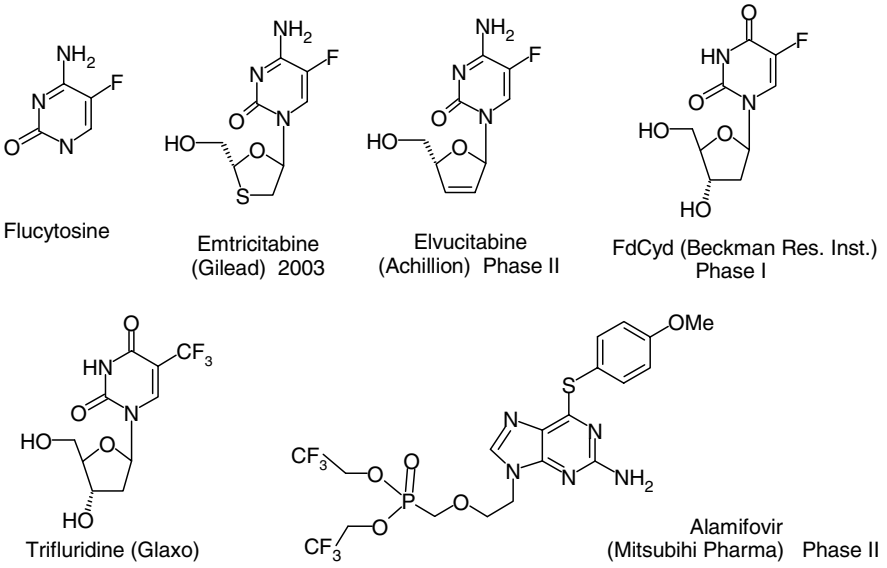


Figure 8.6 Antiviral fluoronucleosides.

from inhibition of the HIV reverse transcriptase and of the HBV DNA polymerase inhibitor.[6]

FdCyd is an inhibitor of DNA methyltransferase (DNMT) currently in Phase I.[7]

Trifluridine (5-trifluoromethyl-2′-deoxyuridine) (Viroptic®) is marketed for the topical treatment of herpes simplex virus infection in the eyes. This antiviral drug is a mechanism-based inactivator of thymidylate synthase. The mechanism of inhibition and synthesis of *trifluoridine* are reported in Chapter 7.

Alamifovir is a purine nucleotide in early clinical development as a potential therapy for hepatitis B virus (HBV) infection. It is a ditrifluoroethoxy phosphonate.

8.1.2 Other Antitumor and Antiviral Drugs

8.1.2.1 Fluoro Analogues of Antitumour Natural Products *Valrubicin* (trifluoroacetyladriamycin valerate) (Valstar®), an ester of adriamycin trifluoroacetylated on the aminoglycosidic fragment, is marketed for the treatment of resistant bladder cancer (Figure 8.7) (cf. Chapter 4).

Vinflumine (Javlor®) is a second-generation *Vinca alkaloid*. It is more active than the nonfluorinated parent compound *(vinorelbine)* in several cancers (Figure 8.7). *Vinflumine* is currently in Phase III clinical trials as a chemotherapeutic agent against a variety of cancers (metastasic breast cancer, small cell lung cancer, and bladder cancer).[8c] This drug inhibits mitotic assembly, via inhibition of tubulin polymerization in microtubules, a major element of the cytoskeleton. Effects of fluorine substitution on tubulin affinity or on metabolism are not responsible for the increased efficiency and decreased toxicity.[8] The synthesis of *vinflumine* is reported in Chapter 4.[8b]

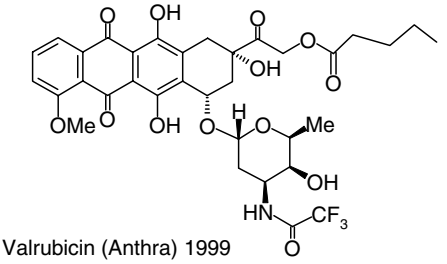
Camptothecin, an alkaloid isolated from a Chinese tree (*Camptotheca acuminate*), is a potent cytotoxic agent, acting by the inhibition of DNA topoisomerase I.[9] Derivatives that are fluorinated on the aromatic ring A have been studied, leading to two drug candidates for cancer therapies (Figure 8.7)[10]: *exatecan* is in Phase III development,[10b] and *diflomotecan* is an E-homocamptothecin currently in Phase II trials for several solid cancers.[10c]

Tafluposide (F 11782) is an *epotoside* (epipodophyllotoxin) derivative[11] (cf. Chapter 4) where the two hydroxyls of the glycosidic moiety are acylated with pentafluorophenoxyacetic acid (Figure 8.7). It has been demonstrated that tafluposide does not act as a prodrug of epotoside, but it has a unique mechanism of interaction with both topoisomerases I and IIα.[12]

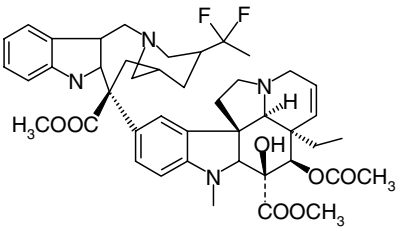
Tesetaxel (DJ-927) is a fluoro analogue of Taxol currently undergoing Phase I clinical testing for oral treatment of tumors (cf. Chapter 4).[13]

The first epithilone, a highly potent microtubule stabilizer, in advanced clinical development (Phase II) is *ZK-EPO* (ZK-219447), while *fludelone* is still in preclinical trials (cf. Chapter 4).

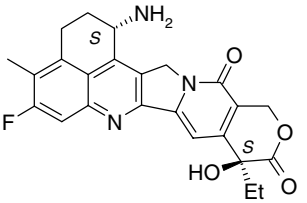
8.1.2.2 Other Fluorinated Antitumor Drugs in Development A number of totally synthetic fluorinated molecules are also in clinical development for cancer therapies. There are numerous inhibitors of kinases, some apoptosis inductors, and antifolates.



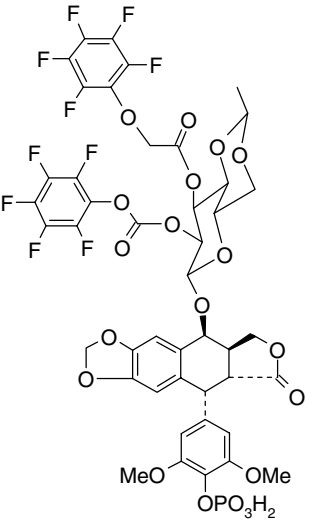
Valrubicin (Anthra) 1999



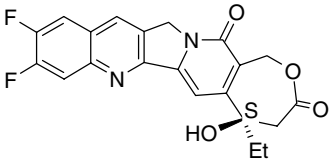
Vinflunine (Fabre) Phase III



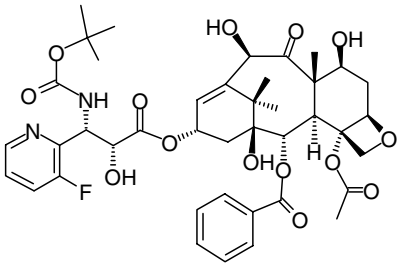
Exatecan (Daiichi) Phase III



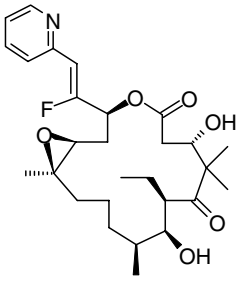
Tafluposide (Fabre) Phase I



Diflomotecan (Ipsen) Phase II



Tesetaxel (DJ-927) (Daiichi) Phase I



ZK-EPO (ZK-219477)
(Schering) Phase II

Figure 8.7 Fluoro analogues of antitumor natural compounds.

(a) Kinase Inhibitors (Figure 8.8) *Gefitinib* (Iressa®) was the first in a new class of anticancer drugs—the EGFR (epidermal growth factor receptor) tyrosine kinase inhibitors. Gefitinib was launched in 2002 in Japan for the treatment of NSCLC. However, it was withdrawn in the United States after disappointing results.

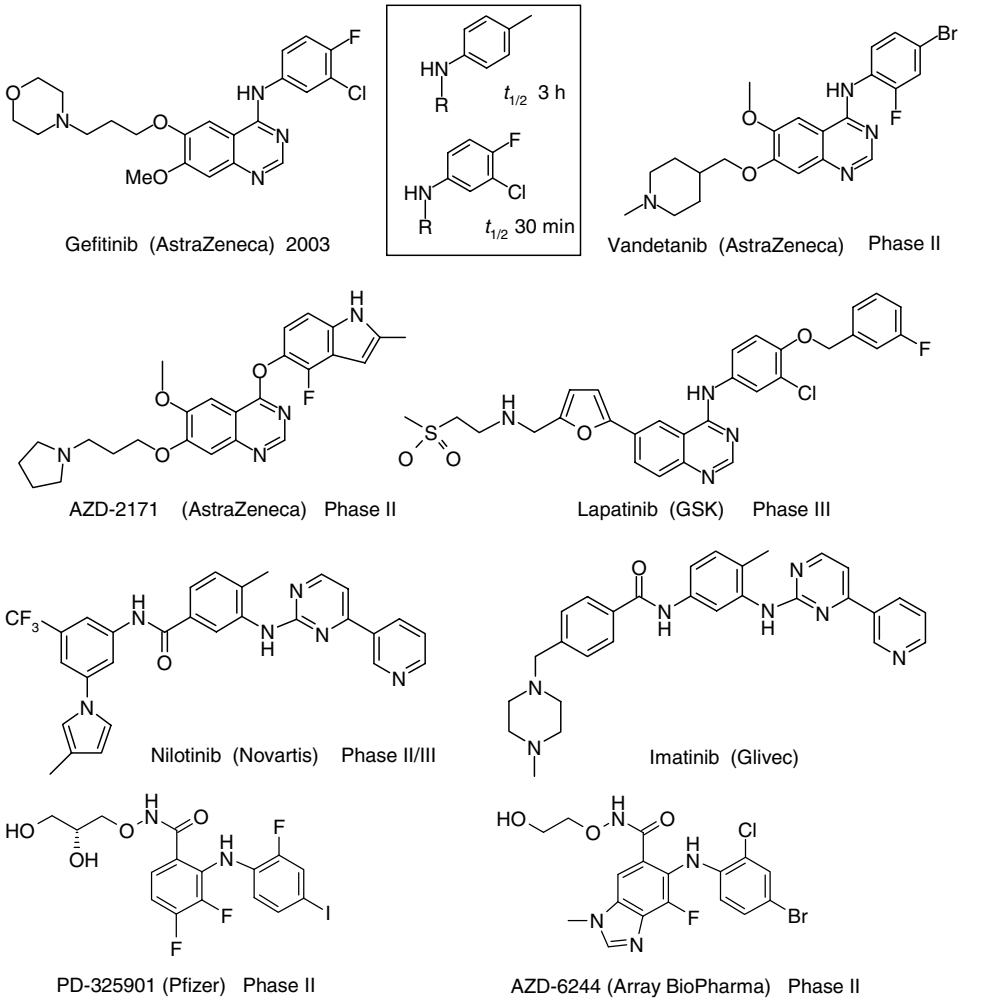


Figure 8.8 Fluorinated inhibitors of kinases for treatment of cancer.

Nevertheless, clinical development continues for other cancer treatments.[14a, 15] Fluorine and chlorine atoms on the aromatic ring increase plasma half-life of the lead from 30 min to 3 h.[14b] *Vandetanib* and *AZD-2171* are other aminoquinazoline inhibitors of VEGF receptor tyrosine kinase. Vandetanib displays inhibitory activity toward epidermal growth factor receptor (EGFR). This angiogenesis inhibitor is currently in Phase II clinical development for a range of solid tumors.[16]

Lapatinib, another 4-aminoquinazoline, is a dual ebB1/erbB2 kinase inhibitor. It is currently undergoing Phase III clinical trials for several cancers.[15]

Sorafenib is a diphenylurea multitargeted inhibitor of kinases (VEGFRs, *C*-Raf kinase, etc.). It has been registered for treatment of renal cell carcinoma. It is still undergoing Phase II evaluation for other indications.[15]

PD-325901 and *AZT-6244* are mitogen-activated protein kinase (MAPK) pathway inhibitors. These structurally close compounds are in Phase II clinical trials for the oral treatment of NSCLC (PD-325901)[15] and of melanoma and NSCLC (AZT-6244).[17]

Sunitinib maleate is the first in a new class of orally active multitargeted tyrosine kinases launched for the treatment of metastastic cancers.

Ro-4584820, a cyclin-dependent kinase (CDK) inhibitor, is in Phase I of clinical evaluation. CDKs are a family of serine/threonine protein kinases that play key roles in the normal growth and life cycle of eukaryotic cells.

Nilotinib is a phenylaminopyrimidine structurally related to *imatinib* (Glivec)®. It is a signal transduction inhibitor that potently and selectively inhibits tyrosine kinases. It was developed (Phase II/III) for treatment of leukemias.[18]

(b) Other Fluorinated Antitumor Drugs (Figure 8.9) *Exulind* (Aptosyn®) and *OSI-461* are inhibitors of cGMP phosphodiesterases (PDE) II and V; they are apoptosis inductors.[19] They are respectively in Phase III and Phase II clinical trials for cancer therapies. *Exulind* is the sulfone corresponding to the NSAID sulfoxide *sulindac*, which is also being evaluated for breast cancer treatment (Phase I) (*vide infra*).

Flurizan is the (*R*)-enantiomer of the well-known NSAID *flurbiprofen* (*vide infra*) and is currently undergoing Phase IIb clinical trials for prostatic cancer treatment.

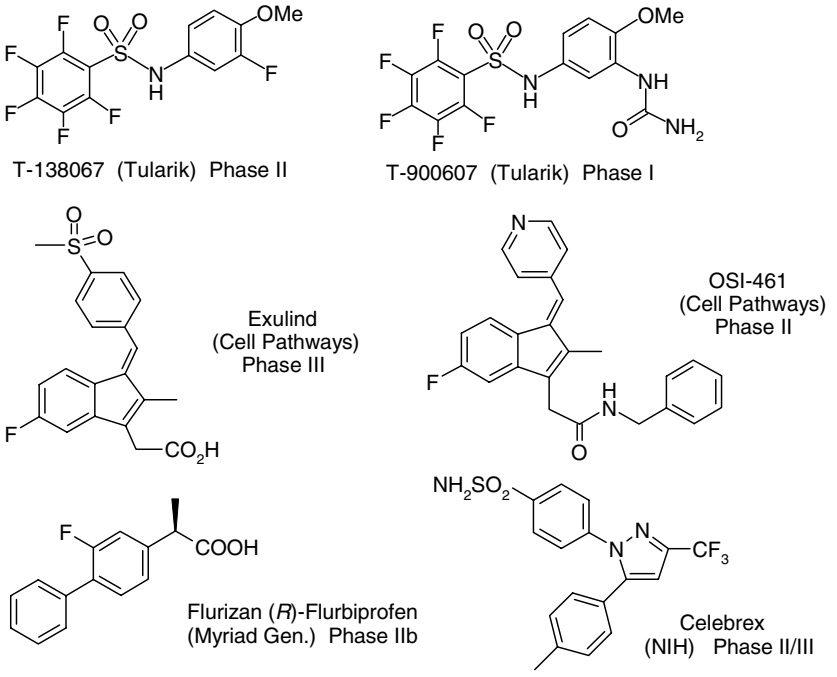


Figure 8.9 Other fluorinated antitumor drugs.

Conversely, to the (*S*)-enantiomer, it does not inhibit COX enzymes, but it is an apoptosis inductor. It is also in phase III evaluation for treatment of Alzheimer dementia (*vide infra*).[20] *Celebrex*, another NSAID drug, is also being evaluated for the treatment of several cancers.

T-138067 is a sulfamide apoptosis inductor developed as an antitumor (Phase II). It binds irreversibly to β-tubulin.

ZD-9331 is a non-nucleosidic inhibitor of thymidylate synthase. It is also an antifolate, in which the quinazoline moiety replaces the pteridine entity, structurally close to methylene tetrahydrofolate (i.e., the second substrate of thymidylate synthase). Moreover, replacement of the acid function of glutamic acid by a tetrazole renders polyglutamination impossible. Consequently, ZD-9331 is active on tumors that are resistant to the usual antifolates.[21]

Zosuquidar is a potent inhibitor of P-glycoprotein (Pgp), the major cause of clinical resistance to many oncolytics. Pgp is overexpressed in multidrug resistant (MDR) cells. Since Zosuquidar's affinity for Pgp is greater than that of current antitumor drugs, it is supposed that it could reverse resistance to these drugs. Diaminohydroxypropane, typical of β-blockers, is present in zosuquidar. This compound is undergoing Phase III trials with patients having acute myeloid leukemia and cancer. A key step in the synthesis of *zosuquidar* involves the addition of a difluorocarben (generated from chlorodifluoroacetic acid) onto dibenzosuberon (Figure 8.10).[22]

8.1.2.3 Nonnucleosidic Antiviral Drugs

Efavirenz is a nonnucleosidic inhibitor of HIV-RT with a rather uncommon structure. This drug is used in polytherapies with antiproteases for patients infected by HIV. It is prepared as a pure (*S*)-enantiomer on a very large scale (24 tons in 2001), including an asymmetric catalyzed addition of a lithium reagent onto trifluoromethyl ketone (Figure 8.11).[23] *DPC-963* is a new generation analogue of efavirenz currently in development.[24]

Tipranavir, a VIH-PR inhibitor, was launched for AIDS therapy (Figure 8.12).[25]

Pleconaril inhibits adhesion by binding the viral capsid. It is currently being evaluated for viral infections of the respiratory tract, in particular, for picornavirus (meningitis) and rhinovirus (colds) (Figure 8.12).

HIV-1 integrase inhibitors, such as *L-870812*, *L-870810, S-1360*, and *GS-9137*,[26] are undergoing clinical trials for use as HIV therapies (Figure 8.11).

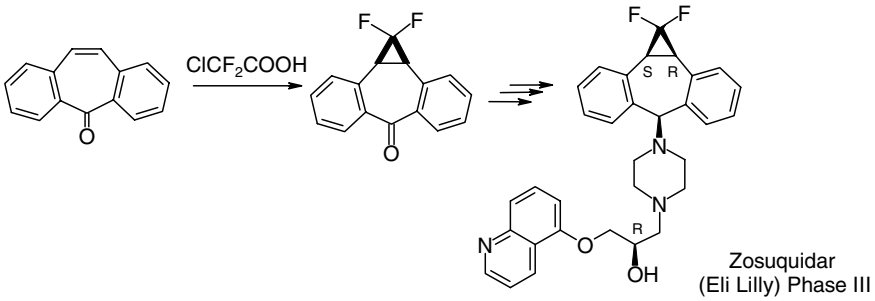
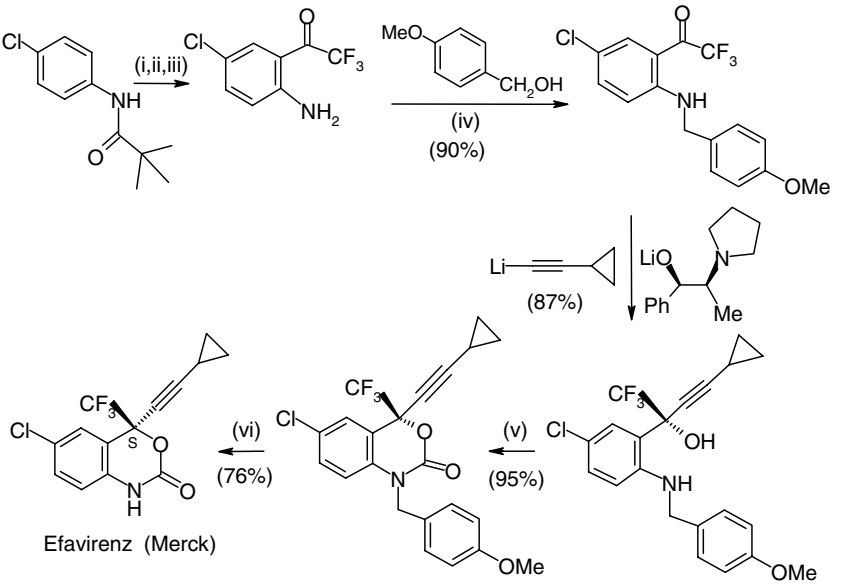
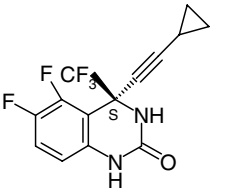


Figure 8.10 Zosuquidar.[22]



(i) BuLi/TMEDA; (ii) CF_3COOEt; (iii) NaOAc; (iv) APTS, MeCN; (v) $COCl_2$, Et_3N; (vi) CAN



DPC-963 (BMS)

Figure 8.11 Synthesis of efavirenz, a nonnucleosidic inhibitor of HIV-RT.[23, 24]

Chemokine CCR5 receptor antagonists *vicriviroc* and *maraviroc* prevent viral entry into white blood cells. They are, respectively, undergoing Phase II and Phase III clinical trials for the treatment of HIV infection as part of polytherapies.[27]

8.2 ANTI-INFECTIOUS DRUGS

8.2.1 Fluorinated Antibiotic Drugs

The field of fluorinated antibiotics is largely dominated by fluoroquinolones. However, some fluorinated macrolides, cephalosporine, and oxazolidones are marketed or in clinical development.

8.2.1.1 Fluoroquinolones The story of fluoroquinolones began in the 1950s with the discovery of the antibacterial properties of 7-chloroquinolone, a side product of the preparation of chloroquin and glafenin. Further research led to the

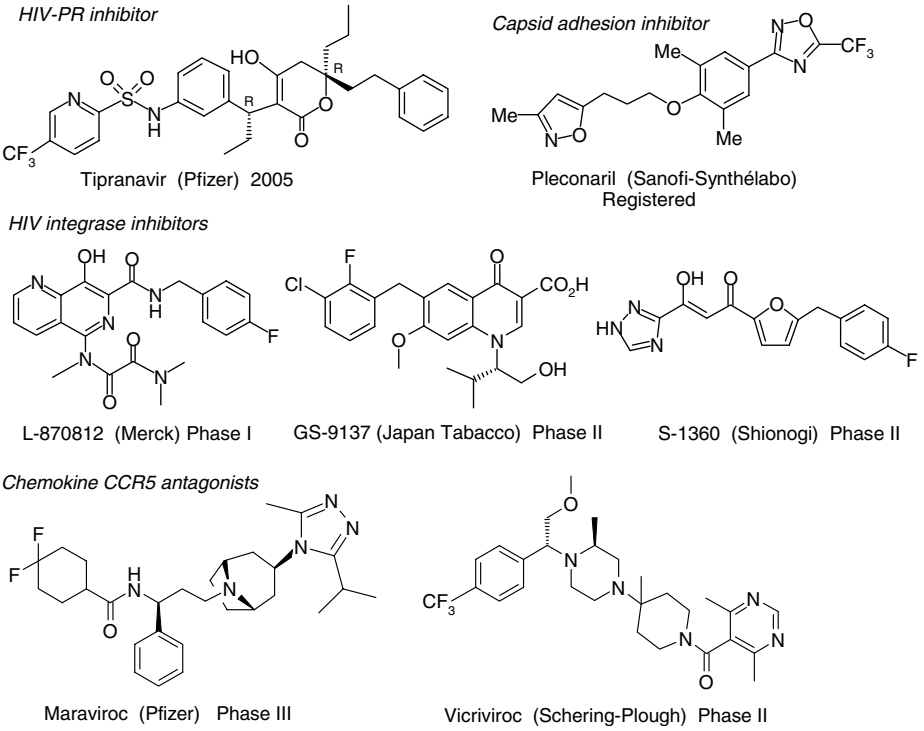


Figure 8.12 Other fluorinated antivirals.

first antibacterial quinolone, *nalidixic acid* (1962). This latter compound, active on gram-negative strains, fostered intense investigations with the production of *flumequin* as an outcome (1973). The structure and activity of flumequin highlights the importance of the presence of fluorine substitution at position 6 for antibiotic properties (Figure 8.13). Following this, introduction of aminosubstitution at position 7 was performed, leading to *pefloxacin* (1978). This latter is the first fluoroquinolone with systemic activity (Figure 8.14).[28]

The third generation of fluoroquinolones (Figure 8.15) combines a large spectra of activity on both gram-negative and gram-positive strains with strong systemic activities. Fluoroquinolones act on infections with various localizations (e.g., osteoarticular, urogenital, meningeal, pulmonary), thanks to good tissue diffusion.

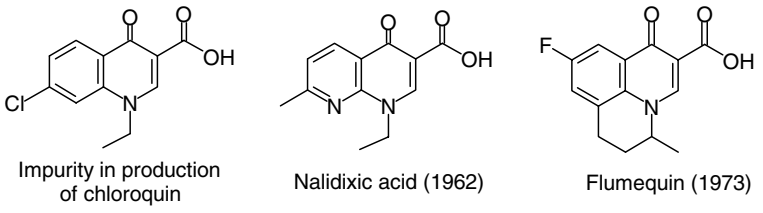


Figure 8.13 First antibacterial quinolones.

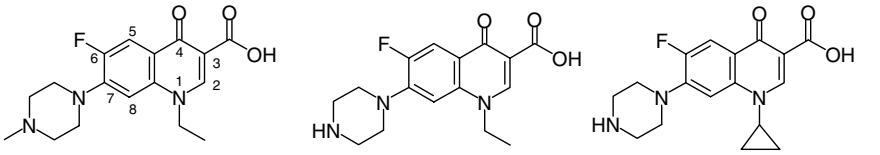


Figure 8.14 7-Amino-6-fluoroquinolones.

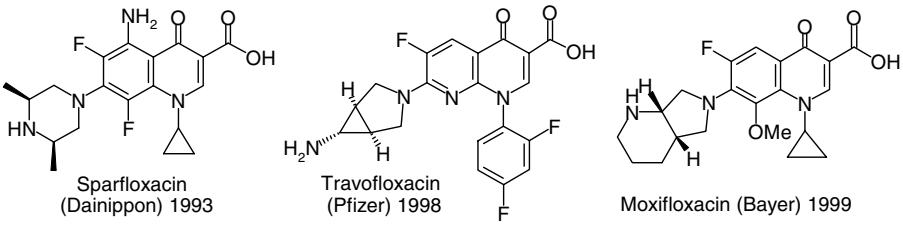


Figure 8.15 Some examples of third generation fluoroquinolones.

More than 10,000 quinolones have been prepared over a thirty year period. Almost all the quinolones used in therapies bear a fluorine atom at position 6.[28, 29] During these years, fluoroquinones have passed from a topical activity on gram-negative strains to systemic activities with large spectra. Antibiotic activities on gram-negative strains (*Salmonella* spp., *Escherichia coli*, *Shigella* spp., etc.) and on gram-positive strains (*Staphylococcus* spp., *Streptococcus* spp., etc.) have been increased by a factor of 1000 (Table 8.1).[28]

Fluoroquinolones are a widely used family of antibiotics with a large number of indications and few side effects. More than 20 fluoroquinolones are on the market and

Table 8.1 Miminal inhibitory concentrations (CMI in mg/L) of different generations of quinolones.[28]

	Gram-Negative (CMI in mg/L)		Gram-Positive (CMI in mg/L)	
	E. coli	*P. aeruginosa*	*S. aureus*	*Streptococcus* spp.
Nalidixic acid	8	>128	32	128
Pipemidic acid	8	32	64	>128
Flumequin	0.12	64	2	64
Pefloxacin	0.12	0.25	0.06	4
Ciprofloxacin	0.03	0.12	0.25	1
Sparfloxacin	0.015	0.25	0.03	0.25

about ten of them are undergoing clinical trials. Production of these drugs is large (in 2001, *ciprofloxacin*—954 tons; *levofloxacin*—130 tons), with a turnover of several thousand million of dollars.

Fluoroquinolones are inhibitors of bacterial topoisomerase II (DNA gyrase). This enzyme reduces the supercoiling of DNA in order to allow separation of the two strands of DNA that are required for replication and transcription. In the first stage, topoisomerase II cleaves the two strands of DNA, after repairing it, and restores the supercoiling of DNA.[28]

Although it has become obvious that a fluorine atom in position 6 is the best substituent for antimicrobial activity,[30] the reasons for this effect remain unclear. A comparative study of numerous quinolones seems to indicate that this F-substitution in position 6 affords both a better affinity with gyrase (2–17 times) and the best cell penetration (1–70 times).[31] The presence of this fluorine lowers the basicity of the nitrogen-containing substituent in position 7, and this fact could play a role. However, there are multiple factors to take into account and interpretations must be carefully considered. Thus, replacing the fluorine atom by a chlorine in pefloxacin does not affect the activity on the enzyme, but a decrease of the bacterial activity is observed. This shows the importance of the pharmacokinetic factors.[28]

The acid group in position 3 is essential for activity, and a basic and bulky amino substituent (piperazine derivative) in position 7 generally favors this activity. Among other modulations, the presence of a second fluorine atom in position 8 (*lomefloxacin*, *sparfloxacin*) and the replacement of carbon 8 by a nitrogen (*enoxacin*) have been reported. While an ethyl group is often present on the nitrogen-1, it can be replaced by various other groups: difluorophenyl (*travofloxacin*, *tosufloxacin*), heteroaromatic moiety (*fandofloxacin*), or cyclopropyl (*ciproxacin*).[29] Some tricyclic molecules have also been described. They are obtained by ring closure from the substituents in positions 1 and 8. Some fluoroquinolones that are produced commercially or are in development are reported in Figures 8.15 and 8.16.

Researc for new fluoroquinolones is still active: ten compounds are currently in clinical trials. The current trend for new fluoroquinolones focuses on substitution at position 8 by an electron-donating group (alkoxy or amino), and the presence at position 7 of more and more sophisticated amino groups (Figures 8.16 and 8.18).

The synthesis of fluoroquinolones generally involves heterocyclization reactions starting from halogenofluoroaromatics. The halogen atom is then used as a leaving group in order to introduce the amino group into position 7. Tetrafluorophthalimide is often used as a precursor (it is prepared form tetrachlorophthalimide through halogen exchange with KF) (Figure 8.17).[28]

Introducing fluorine atoms on position 1, 7, or 8 is one current trend. The substituent of the nitrogen in position 1 is often a fluorinated fragment: fluoroethyl (*fleroxacin*) (Figure 8.18), fluoroaromatic (*travofloxacin*) (Figure 8.15), heteroaromatic (*fandofloxacin*) (Figure 8.16), (*S*)-fluorocyclopropane (*sitafloxacin*, *DQ-113*, *DK-507k*), and fluorovinyl (Figure 8.18).[32] 1-*N*-CF_3 compounds have also been synthesized by oxidative desulfurization fluorination reactions (cf. Chapter 2).[33] Surprisingly, they are very stable (Figure 8.18).[34]

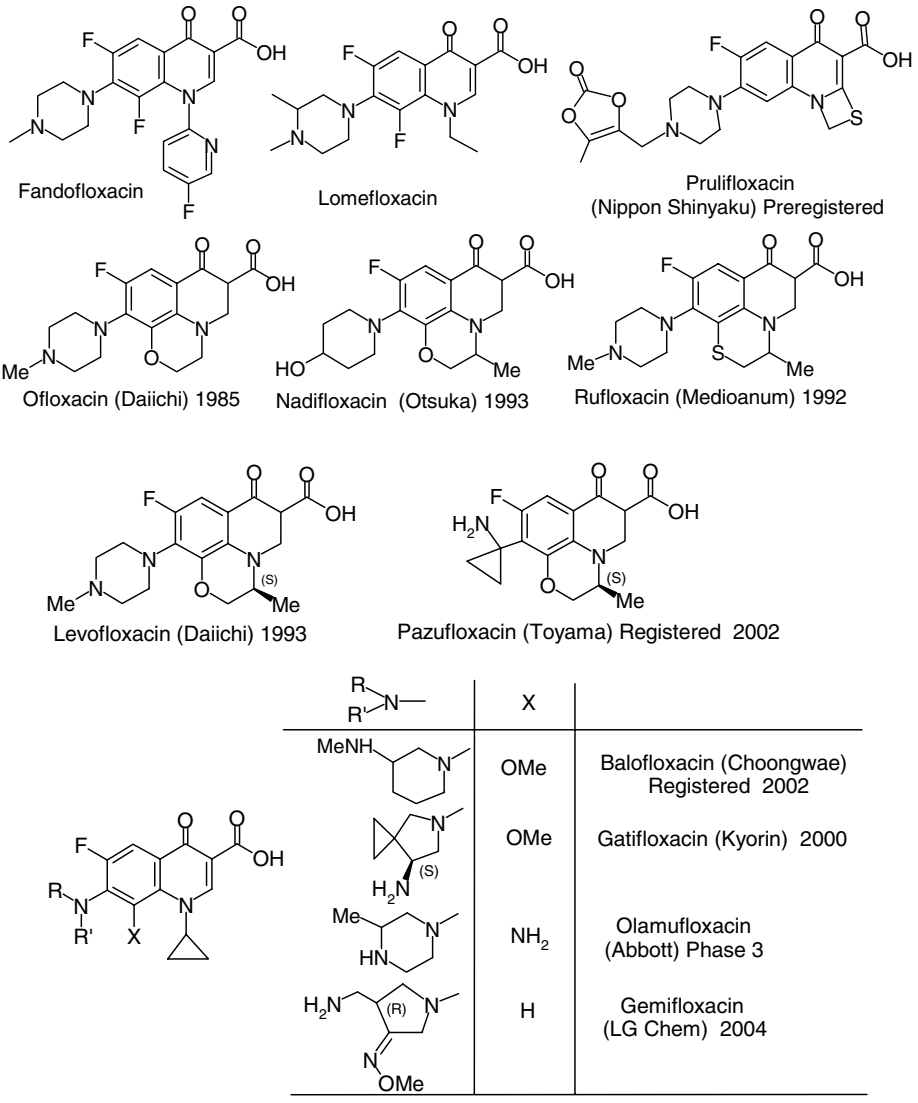


Figure 8.16 Recent fluoroquinolones.

The electron-donating group required in position 8 can bear fluorine atoms (difluoromethoxy), such as in *caderofloxacin*, *garefloxacin*, and *BMS-284756* (Figure 8.18).

In position 7, the nitrogen-containing substituent could be a structurally complex chiral 3-fluoropyrrolidine (*DQ-113*). Monofluorocyclopropyl amine is one fragment of DQ-113. Its synthesis involves a Curtius reaction, followed further by a resolution to afford the desired (*S*)-enantiomer (Figure 8.19).[35, 36] Synthesis of the fluropyrrolidine fragment and the total synthesis of DQ-113 are shown in Figure 8.20.

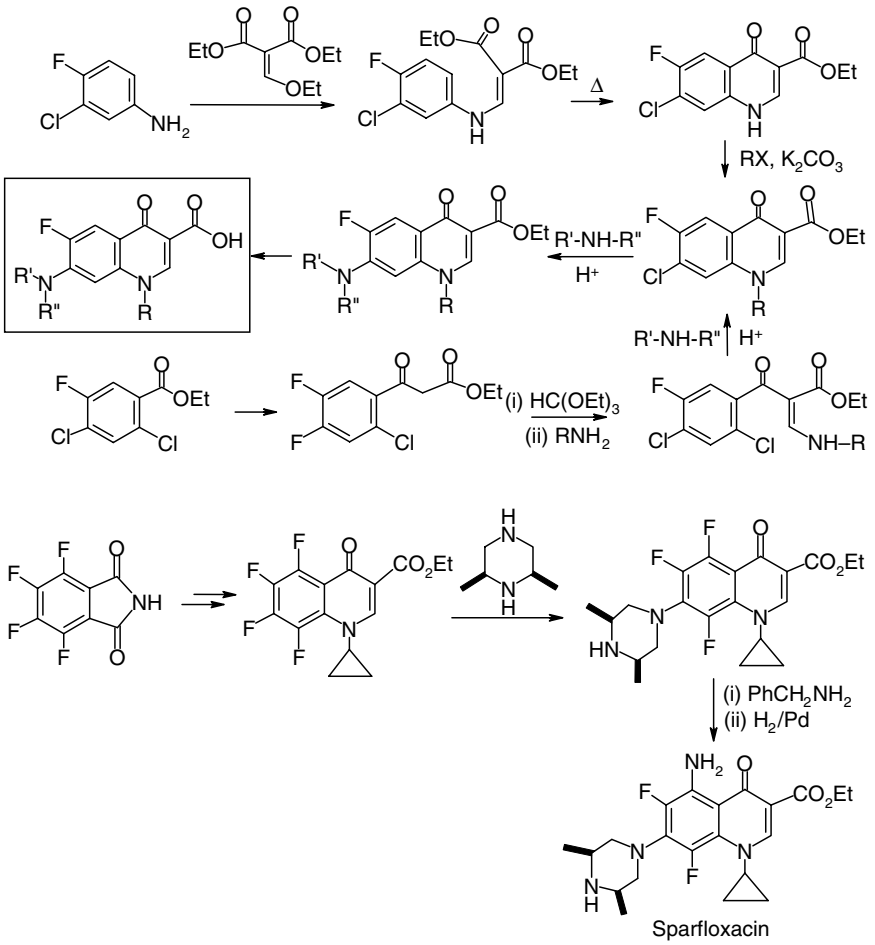


Figure 8.17 Examples of the synthesis of fluoroquinolones.

8.2.1.2 Other Fluorinated Antibiotic Drugs *Flurithromycin* is an erythromycin fluorinated at C-9. It was launched some years ago (Figure 8.21). Its preparation involves electrophilic fluorination of 8,9-anhydroerythromycin-6,9-hemiacetal or of erythronolide A with CF_3OF,[37] or with a N—F reagent (NFSI) (cf. Chapter 4).[38] The advantage of the fluorine substitution is a better stability in acidic medium and an increased bioavailability. Two erythromycins fluorinated at C-14 are in clinical development (*HMR-3562* and *HMR-3787*).

Flomorex is a fluorocarbacepem. It is a structural analogue of cephalosporin, in which the 7β-amine is acylated by *S*-difluoromethyl thioacetic acid. This latter is prepared by reaction of CHF_2Cl with methyl thioacetate (Figure 8.22).[39]

Linezolid is an oxazolidinone. It binds to the 50S bacterial ribosomal subunit and prevents it from forming a complex with the 30S subunit, resulting in blockade of the

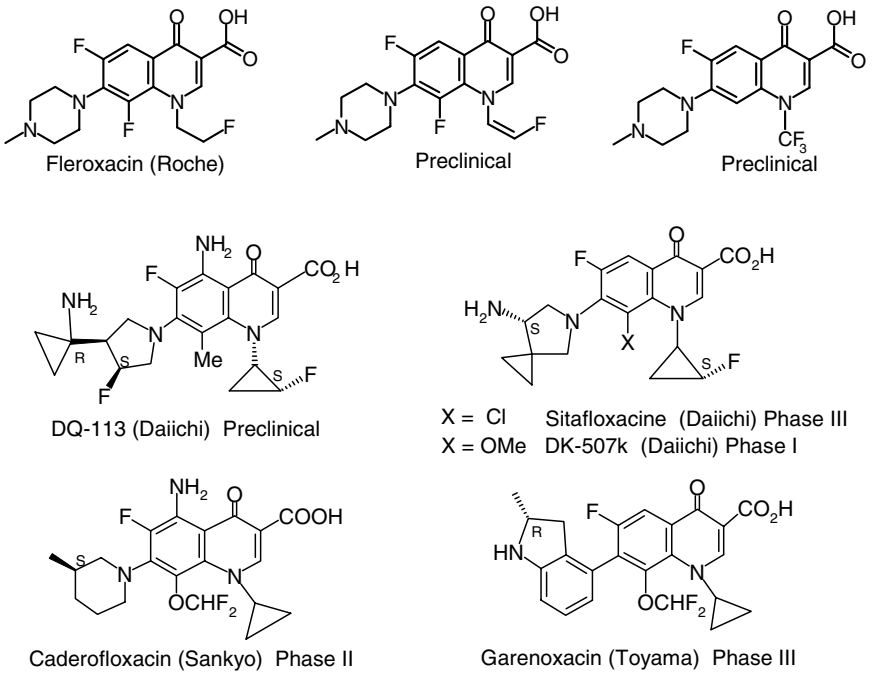
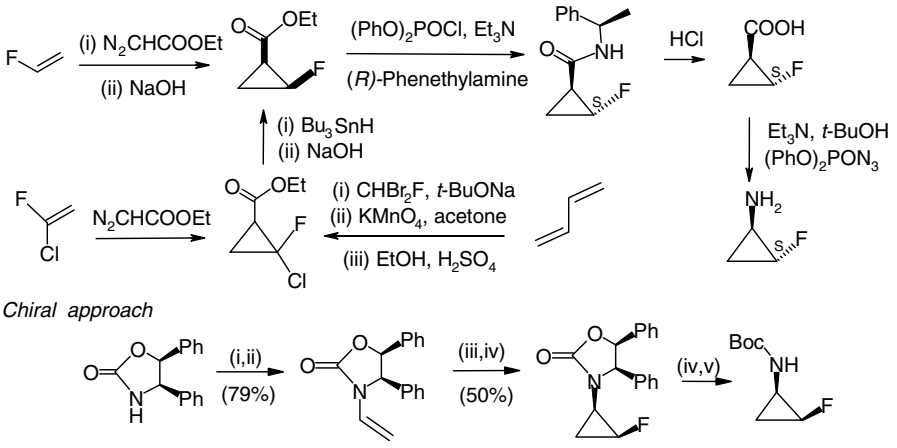


Figure 8.18 6-Fluoroquinolones fluorinated at position 1, 7, or 8.



(i) $MeCH(OMe)_2$, APTS; (ii) 150 °C, 15 mm Hg; (iii) $CHFI_2$, Et_2Zn, *trans*-1,2-dimethoxycyclohexane; (iv) diastereomer mixture separation; (iv) Pd/C, H_2, H^+; (v) Boc_2O

Figure 8.19 Synthesis of the fluorocyclopropylamino moiety of fluoroquinolones.[35, 36]

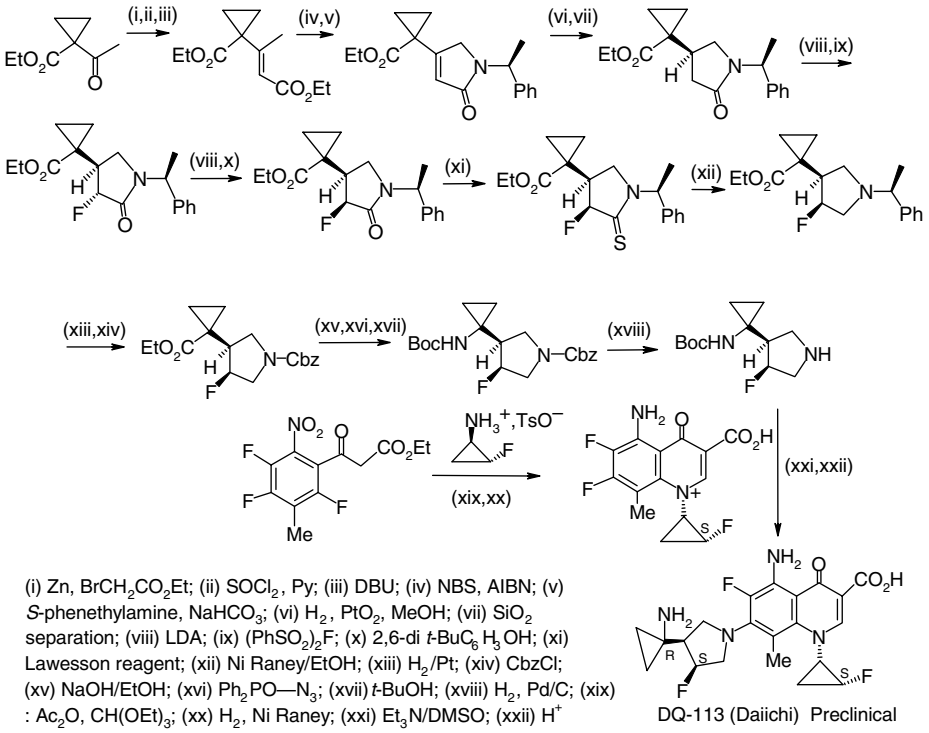


Figure 8.20 Synthesis of DQ-113.[36]

initiation of protein synthesis in prokaryotes. It is active on gram-positive strains.[40–42] Due to its novel mode of action, it is active against pathogens that have acquired resistance to existing drugs. *Ranbezolid* and *eperezolid* are structurally similar to linezolid; only substitutions of the aromatic ring are different (Figure 8.22).

LBM-415 is a selective inhibitor of peptide deformylase ($IC_{50} < 10$ nM), a new family of antibiotic. It is currently undergoing Phase III clinical trials (Figure 8.22).

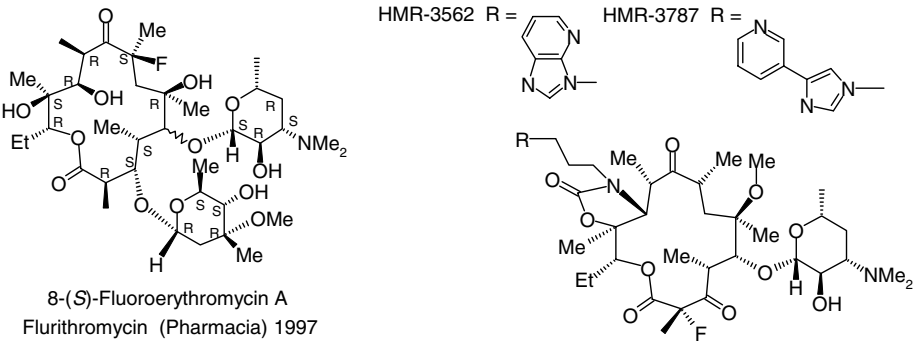


Figure 8.21 Fluorinated macrolide antibiotic drugs.

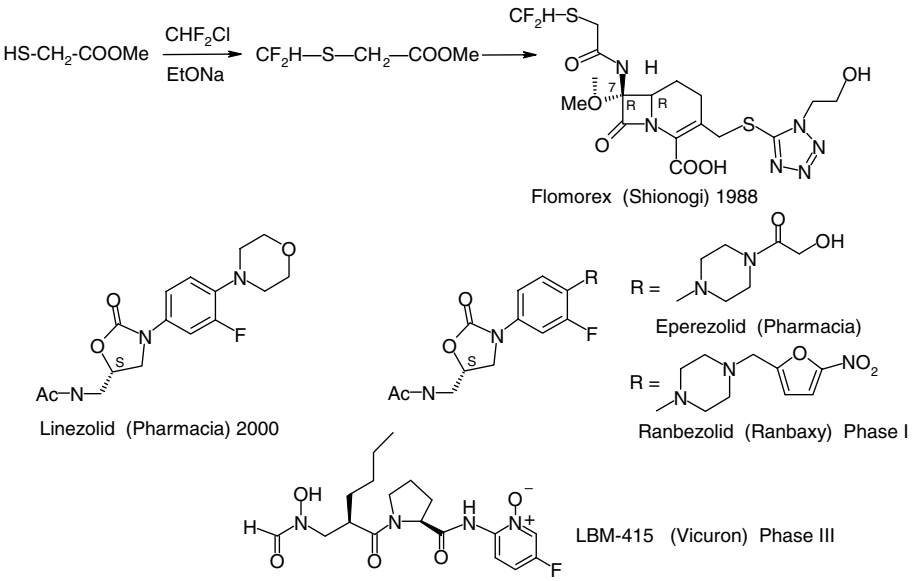


Figure 8.22 Other fluorinated antibiotic drugs.

8.2.2 Antifungal Drugs

Due to the increase in the incidence of opportunistic nosocomial infections over the past years and the risk they pose to immunocompromised individuals, the search for potent large spectrum antimycotics is active. Fluorinated triazole agents have emerged as a standard therapy for fungal infections with agents as *fluconazole*. They inhibit the biosynthesis of ergosterol, required for the building of fungal cell walls through inhibition of the lanosterol *C*-14 demethylase. These fluorinated triazoles exhibit broad spectrum activity and improved safety profiles over other antifungal compounds.

Fluconazole is the drug leader on the market for systemic fungal infections in terms of production and turnover (23 tons in 2001). Interestingly, it results from optimization of a lead that was hepatotoxic. Replacement of two chlorine atoms by fluorine atoms decreases the lipophilicity (log *D* at pH 7, being respectively, 1.5 and 0.4), allowing faster clearance of the drug by the kidney. The resulting lack of accumulation of the drug is accompanied by a lower toxicity (Figure 8.23).[43]

Other fluoroazoles are emerging: *flutrimazole* (for topical treatment) and *voriconazole*, which has a good diffusion in cephalorachidian liquid. *Posoconazole* (Phase III) is the fluoro analogue of itraconazole. The structural complexity (four chiral centers) of posoconazole is remarkable (Figure 8.23).[44] *Albaconazole*, *CS-758*, *Syn-2869*, and *Azoline*[45] have the same structural core as voriconazole; they are in the early stage of clinical development.[46]

Interestingly, a rarely found moiety in medicinal chemistry, the difluorosulfonyl group, is present in *SS-750* (Figure 8.23).

Flucytosine (5-fluorocytosine) is also an inhibitor of lanosterol *C*-14 demethylase (Figure 8.3) with the same indications as fluoroazoles.

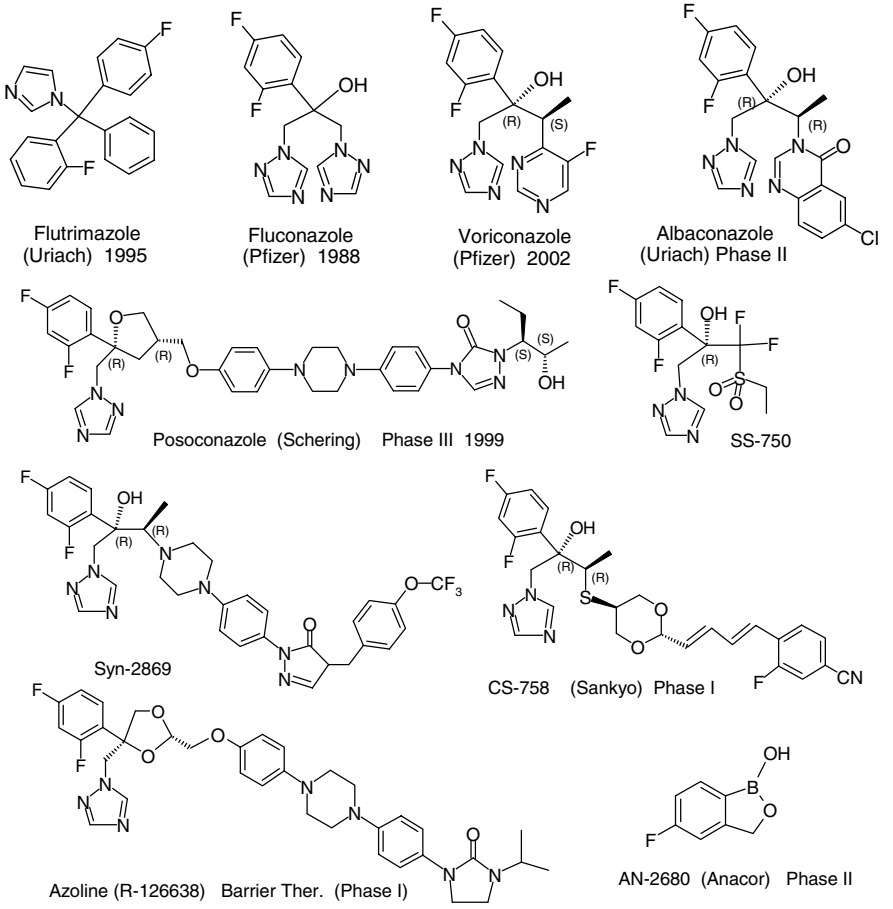


Figure 8.23 Fluorinated antifungals.

An atypical fluorinated benzoxaborol, *AN-2680*, is currently in Phase II clinical trials as a typical antifungal agent, in particular, for the treatment of onychomycosis.[47]

The synthesis of fluoroazoles usually involves a chiral epoxide ring opening by the azole, as exemplified by the synthesis of albaconazole (Figure 8.24).[46a]

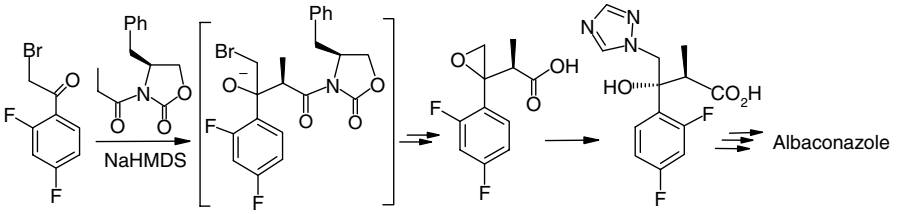


Figure 8.24 Synthesis of albaconazole.[46a]

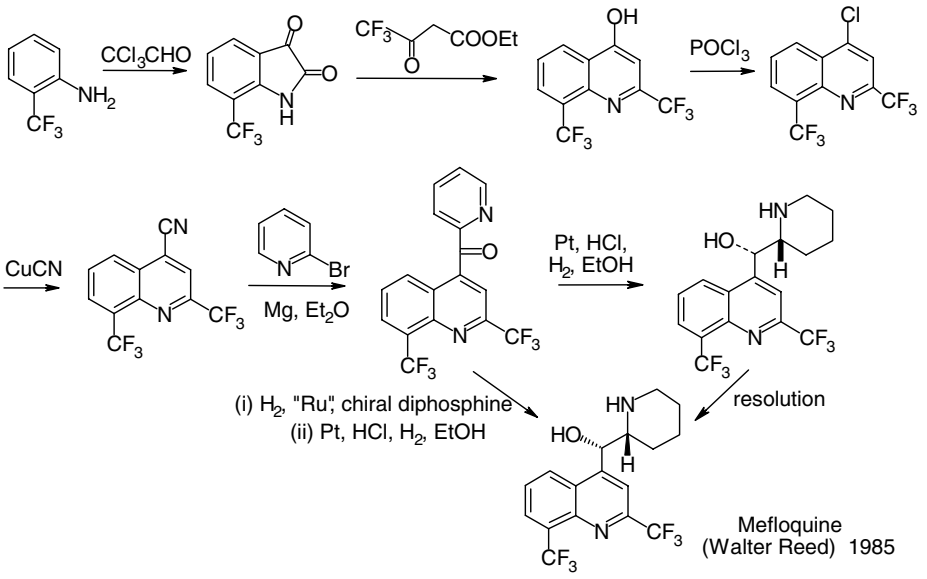


Figure 8.25 Synthesis of mefloquine.[50]

8.2.3 Fluorinated Drugs for Parasitic Diseases

8.2.3.1 Antimalarials *Mefloquine* is a major drug for malaria, in particular, for chloroquine-resistant malaria.[48] However, some cases of neuropsychiatric adverse events and the apparition of resistance tend to limit its use. Metabolism into inactive and phototoxic 1-*H*-2-oxoquinoline is blocked by the presence of the CF_3 group.[48] Instead of performing the resolution of enantiomers at the end of the synthesis,[49] the asymmetric reduction of the carbonyl group in the presence of ruthenium catalyst and a chiral diphosphine provided *mefloquine* with an excellent enantiomeric excess (Figure 8.25).[50]

Halofantrine was an important antimalarial drug. It is now infrequently used because of worldwide strain resistance phenomena. *Tafenoquine* is a new 8-aminoquinoline currently in clinical trials (Phase III) (Figure 8.26).[51]

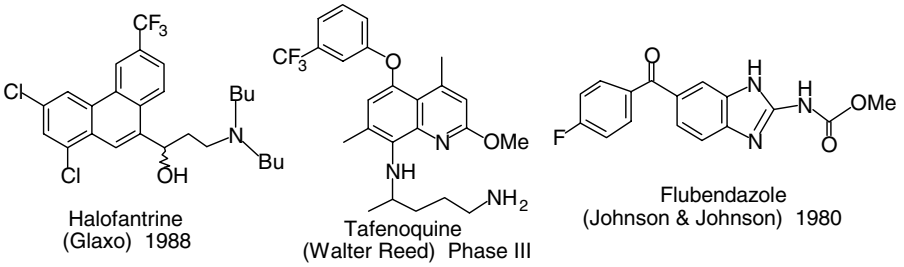


Figure 8.26 Other fluorinated antiparasitic drugs.

8.2.3.2 Antihelmintics *Flubendazole* was launched as an antihelmintic. It seems to have a mode of action close to that of benzimidazole derivatives used as antihelmintics (*mebendazole*, *albendazole*), which are reported to block the capture of glucose by the parasite (Figure 8.23).

8.2.3.3 Treatment of Trypanosomiasis The difluoromethylornithine (DFMO), *eflornithine* is a mechanism-based inhibitor of ornithine decarboxylase—a pyridoxal-dependent key enzyme of the polyamine's biosynthesis from ornithine. Fluorine atoms are essential for the inhibition process (cf. Chapter 7). Eflornithine was first clinically developed for cancer, but its development has been abandoned for this indication. The activity of eflornithine on trypanosomes was then discovered.[52] Now, despite its very low bioavailability, eflornithine is the best therapy for sleeeping sickness (trypanosomiasis)—in particular, at the cerebral stage—due to *Trypanosoma brucei gambiense* parasite. Eflornithine is registered with orphan drug status and is distributed by the WHO.

Currently, production of eflornithine has been stopped because of industrial policy and environmental problems: it involves the use of Freon (CHF_2Cl) as a reagent in its synthesis (Figure 8.27).[53a] However, production of eflornithine may start again in order to supply the WHO. Another reason is that a topical formulation for the treatment of female hirsutism has recently been launched (*Vaniqa*). Its synthesis has recently been improved by using the selective catalytic reduction of the cyano group without any cyclization into lactam.[53b]

8.3 DRUGS FOR CNS DISORDERS

8.3.1 Neuroleptics

Neuroleptic drugs are used in the treatment of psychosis, such as schizophrenia: they are generally antagonist ligands of dopamine at the central nervous system level.[54] Indications and therapeutic effects of the various families of neuroleptics result from two factors. The first one is the specifity of the ligand toward the different types of dopaminergic receptors, which are unequally distributed in the

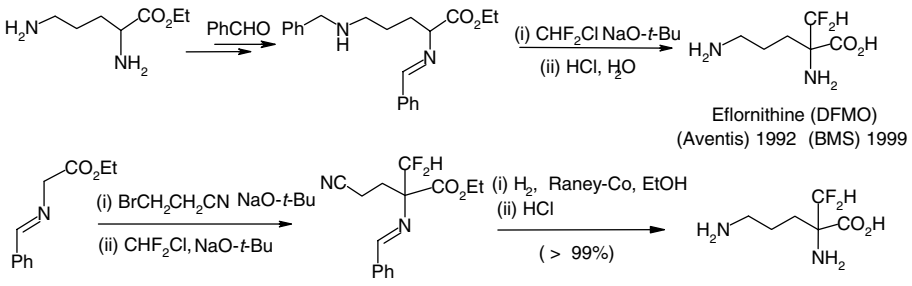


Figure 8.27 Synthesis of difluoromethylornithine.[53]

brain structures. The second factor can be either the selectivity or the lack of selectivity of the ligand toward other neuroamine receptors. Fluorinated butyrophenone and phenothiazine neuroleptics are numerous and they are generally used for a long period of time. 5-HT_2 antagonists are atypical neuroleptics that are more recently being used in psychotic disorders. The main fluorinated neuroleptics currently being used are described next.

Butyrophenones are a very old family of nonspecific antagonists of dopamine. Nevertheless, *haloperidol* and its close analogues (*melperone*, *bromperidol, trifluperidol)* are still marketed. *Timiperone*, *biriperone*, *benperidol, droperidol, fluanisone*, and *pipamperone* have more structural changes in the piperidine moiety (Figure 8.28).

Phenothiazines are also nonspecific dopaminergic antagonists and are an old family of neuroleptics. However, they are less and less used (*fluphenazine*, *oxaflumazine*, *trifluoperazine, triflupromazine*). *Flupenthixol* and *isofloxythepine* are recent neuroleptics that can be grouped with phenothiazines (Figure 8.29).

Selective dopaminergic D_2 antagonists are ***pimozide*** and ***penfluridol*** (Figure 8.30).

Risperidone is a selective antagonist of both D_2 and 5-HT_2 receptors. It is currently the neuroleptic leader in the treatment of schizophrenia and of dementia,

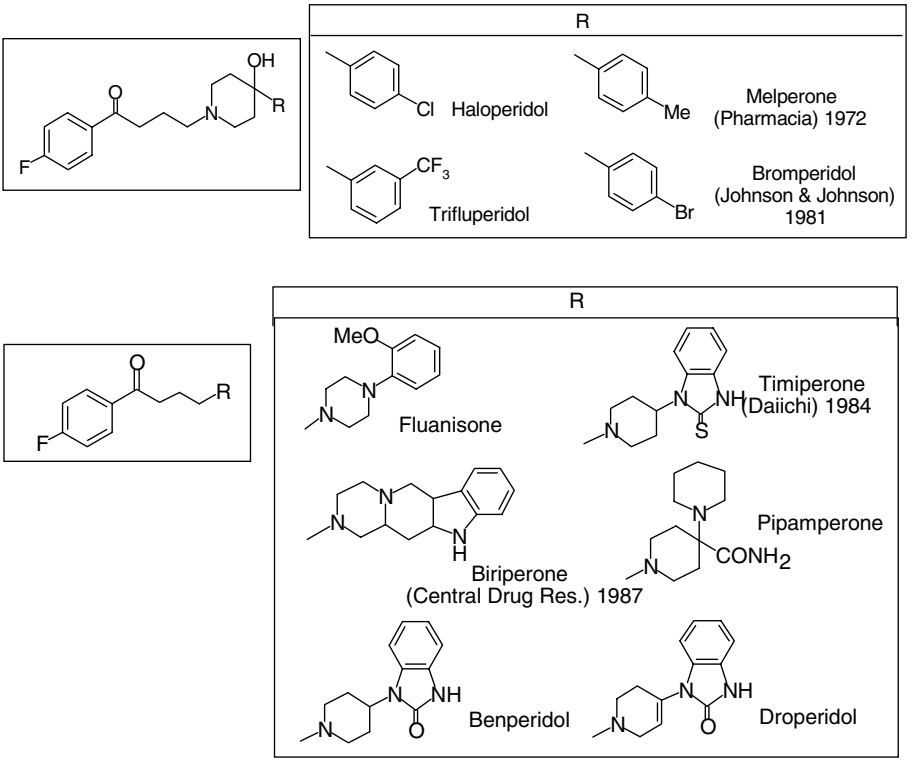


Figure 8.28 Fluorobutyrophenone neuroleptics.

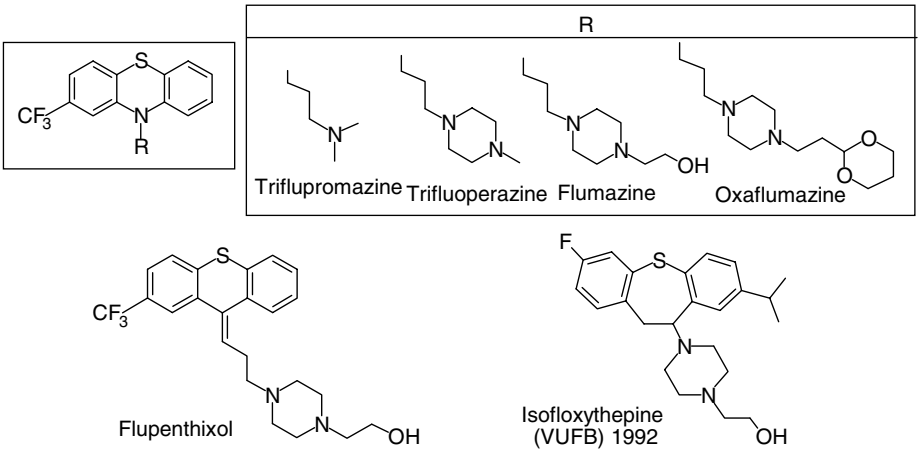


Figure 8.29 Fluorinated phenothiazine neuroleptic drugs.

with few extrapyramidal side effects. Its active metabolite, ***paliperidone***, has now been developed (Phase III). 5-HT_2/D_2 receptor antagonists ***blonanserine*** (Lonasen®) and ***iloperidone*** are being evaluated in Phase III clinical trials as potential antipsychotic agents (Figure 8.31). ***Sertindole*** is an antipsychotic non-specific antagonist of D_2, α_1, and 5-HT_2 receptors. ***ACP-103*** is a potent and selective 5-HT_{2A} inverse agonist shown to possess excellent antipsychotic-like effects; it is currently in (Phase II) clinical trials.[55]

8.3.2 Drugs for Depressive Disorders

Currently, the drugs used in the treatment of depression are mainly inhibitors of serotonin reuptake. Inhibition of reuptake of serotonin by transport protein increases the synaptic concentration of 5-HT and, consequently, also the stimulation of post synaptic receptors. This family of drugs has a very large market, with *fluoxetine* (Prozac®) and *paroxetine* as leaders (>50 tons/year, >$3 billion (U.S.) each). *Citalopram* and *fluvoxamine* are other 5-HT recapture inhibitors (Figure 8.32). As the industrial patent protection of some of these racemic drugs is expiring, companies are doing chiral switches and the pure enantiomers are now being developed and

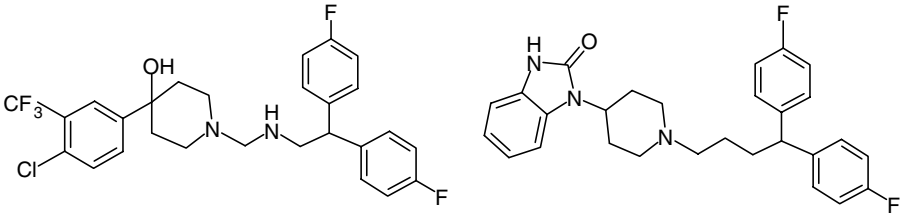


Figure 8.30 D_2 antagonist neuroleptics.

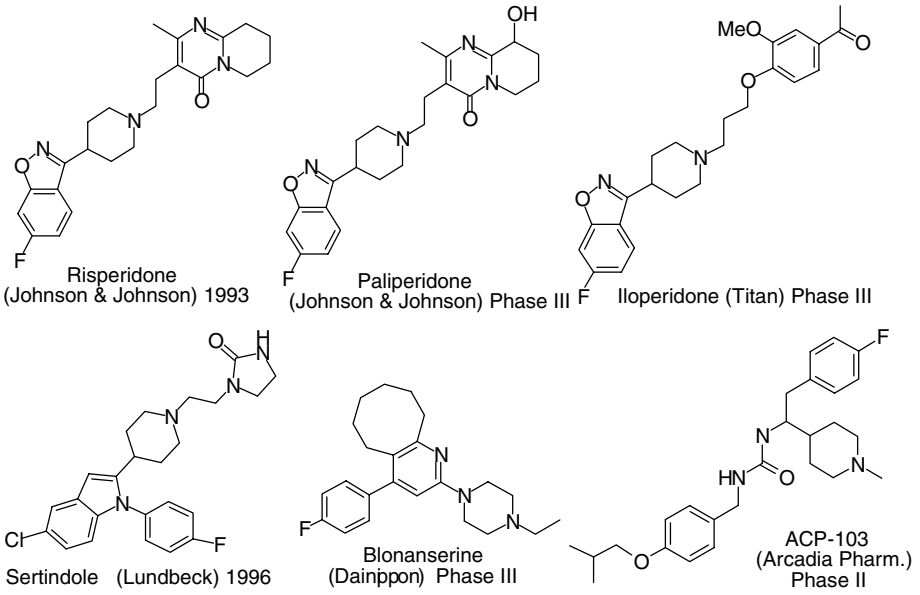


Figure 8.31 D_2 and 5-HT_2 antagonist neuroleptics.

marketed: (*S*)-*fluoxetine* is now in Phase II clinical trials with migraine treatment as the indication, while (*S*)-*citalopram* (*escitalopram*) is marketed for initial and maintenance treatment of major depressive disorders and for the treatment of panic disorder.

A 5-HT_1 agonist, *oxaflozane*, originally marketed for depressive disorders, has been abandoned.

Casipitant, a tachykinin NK1 receptor antagonist, is in Phase II clinical evaluation for the treatment of depression and anxiety (Figure 8.33).[56]

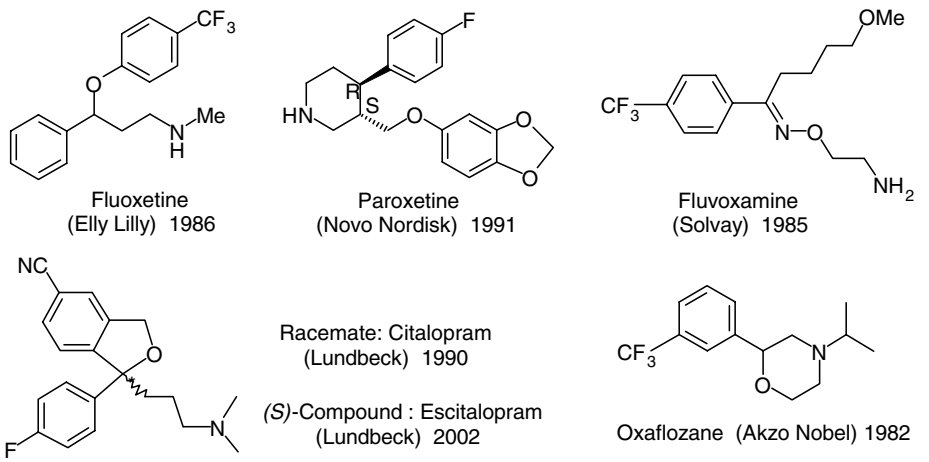


Figure 8.32 Fluorinated inhibitors of 5-HT reuptake and 5-HT_1 agonist used for depression.

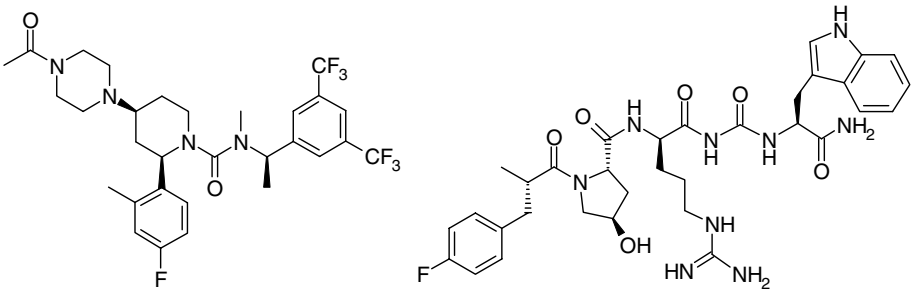


Figure 8.33 NK1 receptor antagonists casipitant and nemifitide.

Nemifitide, a pentapeptide, is in Phase II/III clinical trials for the treatment of major depression.

8.3.3 Anxiolytics and Sedatives

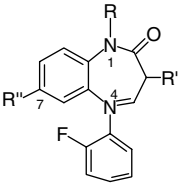
$GABA_A$ is a membrane receptor. It is an ionic channel permeable to Cl^- anions. Binding of the natural ligand—GABA (γ-aminobutyric acid)—brings about channel opening, entrance of chloride anions into the cell, and hyperpolarization of the cell. Benzodiazepines are allosteric modulators of $GABA_A$ receptor, facilitating the binding of GABA on the receptor. This effect is in part responsible for the pharmacological effects (anxiolytic, sedative, myorelaxing) of benzodiazepines.

Benzodiazepines are very important drugs from a turnover point of view. A large number of these compounds has been synthesized, developed and marketed (about thirty have been launched), a dozen of which contain fluorine atoms. Specific clinical indications for each compound do not result from a difference in the mechanism but from the pharmacokinetic and pharmacodynamic behavior of each one.

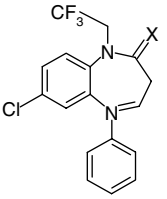
Fluorobenzodiazepines respond to the classical pharmacophore of benzodiazepines with an electron-withdrawing substituent (Cl or NO_2) at position 7 and with the 4-*N* substituted by an aromatic ring. Fluorine could be present either in the ortho position of this ring (*flunitrazepam*, *cinelazepam*, *ethyl loflazepate*) or on the *N*-1 substituent ethyl, as a trifluoroethyl (*halazepam, quazazepam*). *Midalozepam*, which is used in general anesthesia, and *flutazolam* have atypical structures (Figure 8.34). *Flumazenil* is an antagonist of the $GABA_A$ receptor, although it is structurally very close to the other diazepines, which are agonists of this receptor. *Flumazenil* is an antidote in the case of overdose with benzodiazepines.

8.3.4 Other Drugs for CNS Disorders

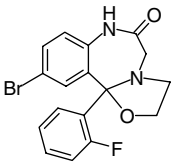
Several fluorine-containing compounds are being marketed or investigated as antiepileptics, as antidegeneratives in Azheimer and Parkinson diseases, and as sleep inductors. Several of these compounds are also being developed for other indications at the same time.



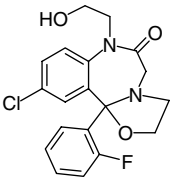
R	R'	R"	
CH_3	H	NO_2	Flunitrazepam (Hypnotic)(Hoffman-LaRoche) 1975
CH_2CH_2CN	OH	Cl	Cinolazepam (Hypnotic) Gerot (1993)
CH_2CH_2OH	OH	Cl	Doxefazepam (Hypnotic) (Alfa Wasserman) 1984
H	CO_2Et	Cl	Loflazepate (Anxiolytic) (Sanofi-Synthélabo) 1982
	H	Cl	Flutoprazepam (Anxiolytic) (Akzo Nobel) 1985
CONHMe	CO_2Et	Cl	Haloxazolam (Hypnotic) (Sankyo) 1980



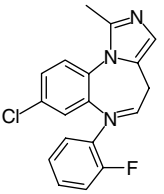
X = O Halazepam Anxiolytic Schering-Plough (1981)
X = S Quazepam Hypnotic Schering-Plough (1987)



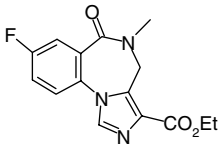
Haloxazolam Hypnotic
Sankyo 1980



Flutazolam Anxiolytic
Hoffmann-LaRoche (1984)



Midazolam Hypnotic
Hoffmann-LaRoche (1992)



Flumazenil (Roche) 1992
Antagonist GABA

Figure 8.34 Fluorobenzodiazepines.

(a) Anticonvulsant (Figure 8.35) *Progabide* is an agonist of $GABA_A$ and $GABA_B$ type receptors. It is marketed as an anticonvulsant for the treatment of epilepsy.

Rufinamide is a structurally novel antiepileptic agent that acts by reducing the frequency of firing of sodium-dependent neuronal action potentials. This drug is in Phase III clinical trials as a broad-spectrum anticonvulsant.

Retigabine is a novel anticonvulsant drug in development (Phase II). It activates voltage-gated potassium channels and also affects GABA neurotransmission in the $GABA_A$ receptor.[57]

Seletracetam is currently in Phase II clinical trials as an antiepileptic agent. This structural analogue of *levetiravetam* possesses a difluoromethylene moiety that is unusual in medicinal chemistry.

(b) Neuroprotectors (Figure 8.36) *Riluzole* is a glutamate receptor antagonist, marketed as a neuroprotector, in this treatment of amyotrophic lateral sclerosis (ALS).

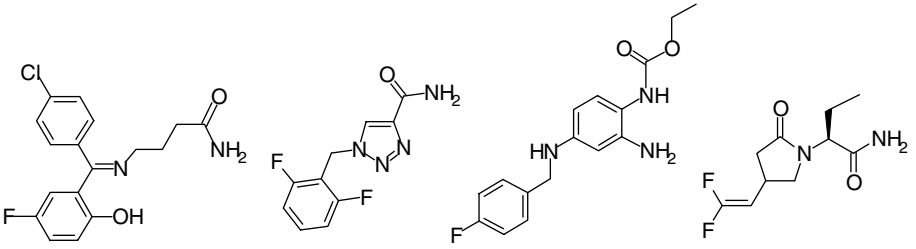


Figure 8.35 Fluorinated anticonvulsant.

Its activity seems related to the decrease in the release of glutamate, and to the probable inhibition of Na^+ ionic channels.

Xaliproden is a selective nonpeptidic neurotropic-like compound that increases neuronal survival. This 5-HT_{1A} agonist is also an NGF agonist and reduces apoptosis and improves neurogenesis. Phase III clinical trials are being conducted in patients with Alzheimer disease.

Flupirtine is both a nonspecific antagonist NMDA and an agonist of opioid receptors. This analgesic is prescribed for migraine. Neuroprotector effects in neurodegenerative diseases (Alzheimer and prion diseases) are being investigatived.[58]

FK-960 was initially developed for treatment of Alzheimer disease, but it has been abandoned for this indication. However, it is still under clinical trials for therapy of cognition disorders related to schizophrenia.

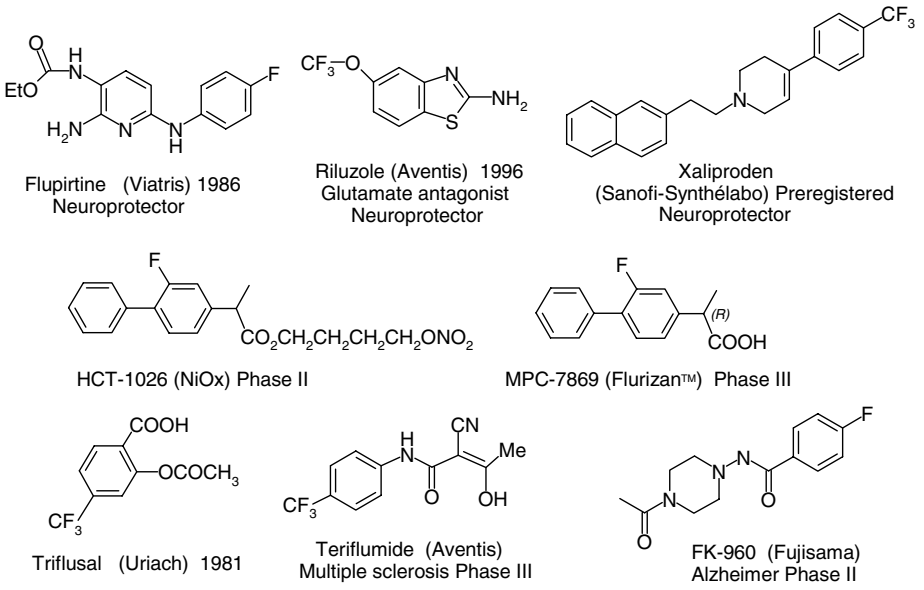


Figure 8.36 Neuroprotectors and treatments for Alzheimer disease.

Triflusal, a known antiplatelet agent used in the treatment of thromboembolic disorders, is currently being evaluated for use in Alzheimer disease. It has been shown to inhibit the activation of the mediators of neuroinflammation.

HCT-1026 (*nitroflurbiprofen*) is a nitric oxide–donating derivative of the NSAID *flurbiprofen*. It is undergoing Phase I clinical evaluation for the treatment of Alzheimer disease, but it is more advanced (Phase II) for overactive bladder and osteoporosis.

These NSAID *MPC-7869* (*R*)-*flurbiprofen*) is a drug candidate (Phase III) for Alzheimer disease. It affects β-amyloid deposition and metabolism and prevents cognitive deficits in transgenic animals. It is also being evaluated in hormone-naive prostate cancer (cf. *infra*).[20]

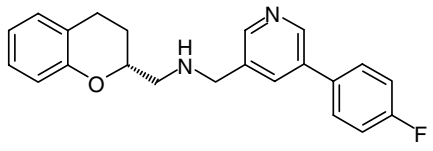
Teriflunomide is the active metabolite of *leflunomide* (*vide infra*). It is in late-stage clinical development as potentially the first oral agent for multiple sclerosis.

(c) Treatment of Parkinson Disease *E-2007* is an AMPA receptor antagonist currently being evaluated in phase II clinical trials as a potential therapy for Parkinson disease, epilepsy, and multiple sclerosis (Figure 8.37).

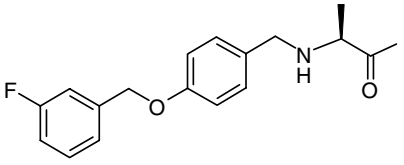
Safinamide is in Phase III clinical trials for Parkinson disease. The molecule possesses multiple mechanisms of action: it combines inhibition of dopamine uptake and potent, selective, and reversible inhibition of MAO-B, sodium (Na^+) channel blockage, and calcium channel modulation, while being devoid of a MAO-A inhibitory effect (Figure 8.37).

Fipamezole exhibits potent antagonism against all α_2-adrenoceptor human subtypes and is currently undergoing Phase II development for the treatment of dyskinesia associated with Parkinson disease (Figure 8.37).

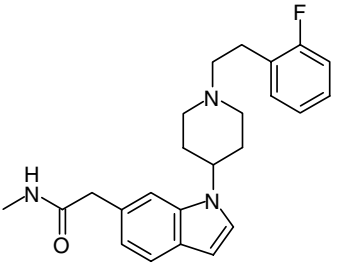
Sarizotan is a mixed D_2 antagonist/5-HT_{1A} agonist currently in Phase II clinical trials for treatment of dyskinesia in Parkinson disease (Figure 8.37).[59]



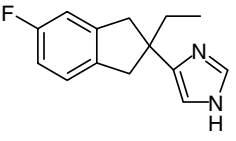
Sarizotan (Merck) Parkinson Phase II



Safinamide (Newron)
Parkinson Phase III , Epilepsy Phase II



E-2007 (Eisai) Phase II



Fipamezole (Orion)
Parkinson Phase II

Figure 8.37 Treatments for Parkinson disease.

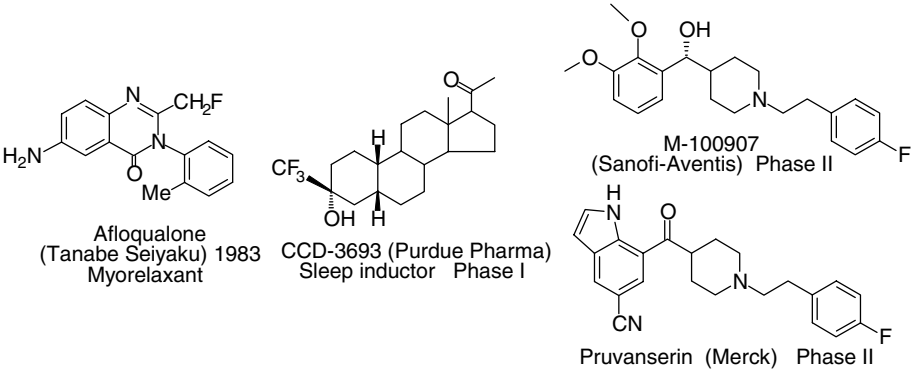


Figure 8.38 Other fluorinated drugs for CNS disorders.

(d) Other Indications *CCD-3693* is the trifluorinated analogue of *ganaloxone* (3β-methyl allopregnanolone). Like its nonfluorinated parent compound, CCD-3693 is a specific ligand of $GABA_A$ receptor. However, conversely to ganaloxone, which is an anticonvulsant, CCD-3693 is being developed as a sleep inductor.[60] It is prepared by addition of Ruppert reagent on the corresponding ketone (Figure 8.38).

Afloqualone is a nicotinic antagonist marketed as a myorelaxant. A CH_2F group, very uncommon in medicinal chemistry, is present in afloqualone.

Two 5-HT_{2A} antagonists, *M-100907* and *pruvanserin*, are currently in Phase II clinical trials for the treatment of insomnia.

8.4 DRUGS OF INFLAMMATORY AND IMMUNITY DISORDERS

Drugs for inflammatory and immunity disorders have various clinical indications (inflammation, allergy, asthma, dermatology diseases, arthritis, analgesia, etc.). The mechanisms of action are multiple and various. We successively focus on ligands of nuclear receptors with the fluorocorticoids, which are both anti-inflammatory and immunosuppressant, and antagonists of histamine receptor, which are purely anti-allergic compounds, and on inhibitors of different enzymes (e.g., HLE, arachidonic cascade enzymes, phosphodiesterase 4) with prostaglandin derivatives and NSAID.

8.4.1 Fluorocorticosteroids

Glucocorticoids are important metabolic hormones with a central role and many implications. They interact with nuclear receptors. The latter act on transcription factors of the genes coding proteins that are involved in the control of inflammation.

Inhibition of transcription of genes coding for phospholipase A_2 (PLA_2) and the activation of gene coding for lipocortine (endogen inhibitor of PLA_2) reduces the release of arachidonic acid (AA) from membrane phospholipids. This is the reason why glucocorticoids have—at least partially—anti-inflammatory properties.

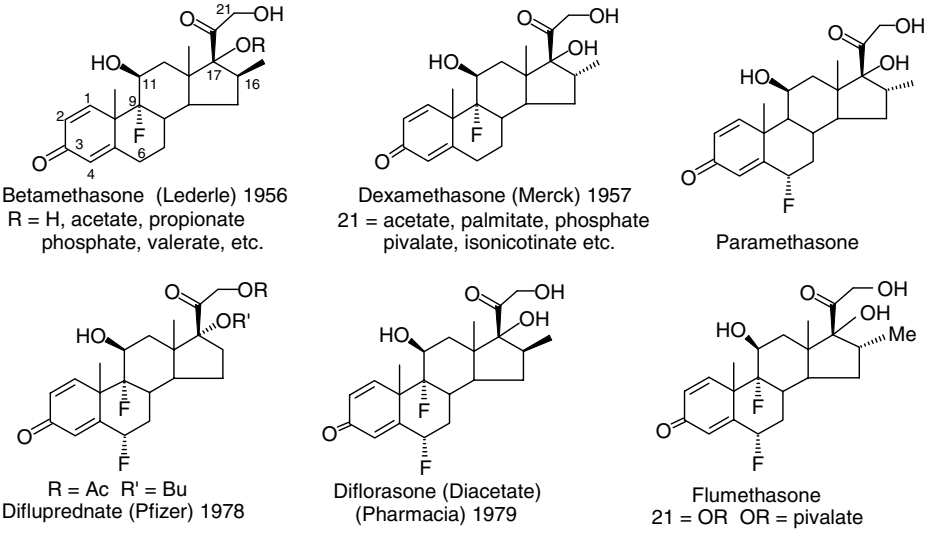


Figure 8.39 Examples of 6-, 9-, and 6,9-fluorocorticosteroids.

On the other hand, glucocorticoids repress the synthesis of NF-κB (nuclear factor κB), which is an activator of gene transcription coding for proinflammatory molecules (TNF, interleukin 1 and 2, cyclooxygenase 2, etc.). Glucocorticoids also partially neutralize the heterodimeric protein AP-1, formed of proteins Fos and Jun, which activate the transcription of several genes involved in the synthesis of proinflammatory proteins: NO synthase (NOS), cyclooxygenase 2 (COX-2), and PLA_2.

Fluorination of corticosteroids at C-9 or/and C-6 increases glucocorticoid activity, while mineralocorticoid activity, responsible for sodium retention (the main adverse effect of corticoids), is decreased (cf. Chapter 4). Fluorocorticosteroids were the first fluorinated compounds to be used clinically. They are still major drugs against many inflammatory disorders: rheumatoid polyarthritis, ORL (asthma, rhinitis), brain edema, dermatological, allergies, anaphylactic shock, Quincke's edema).

Fluorine substitution can take place in positions 9α, 6α, or both of these two positions (Figure 8.39). A very large number of compounds have been designed from the corticoid core with these common structural elements: for example, 1,4-diene, 17-hydroxymethylacetyl, and 11β-hydroxy.

Generally, a substitution at C-16 (Me or OH) is introduced (*difluprednate* excepted); this usually contributes to a decrease in mineralocorticoid activity. The substituent could be α (*dexamethasone, paramethasone, flumetasone*) (16α-Me) or β (*betamethasone*, *diflorasone*) (16β-Me) (Figure 8.39). When a hydroxyl is present at C-16α (*triamcinolone)*, it is frequently engaged with the 21-hydroxy in an acetonide (*flunisolide, rofleponide*, etc.) (Figure 8.40).

A substitution can be made with another halogen at C-2 (*halomethasone*, *halopredone*) or at 21 (21-OH $\rightarrow$ 21-Cl) (*clobetasol, halobetasol*). *Fluclorolone* is an

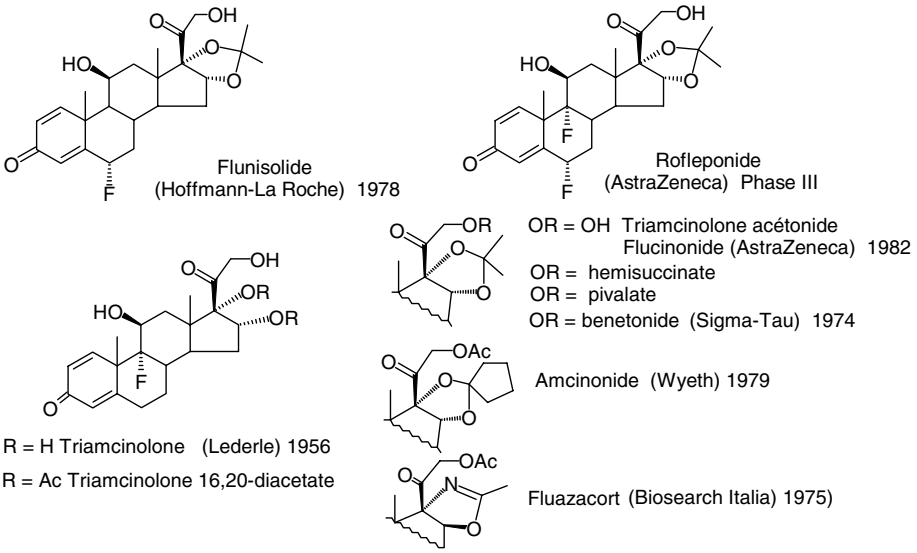


Figure 8.40 16-Hydroxy fluorocorticoids.

atypical fluorocorticosteroid, in which the 11β-OH and 9α-F are replaced by chlorine atoms (Figure 8.41).

Deletion of 17-hydroxyl (*desoximethasone*, *fluocortolone*, *diflucortolone*, *fluocortine*) (Figure 8.42) can also be done.

There are also several compounds with more atypical substitution; for instance, *fluocortine* in which the 20-CH_2OH is replaced by a butyl ester group (Figure 8.39), *fluticasone* in which the 17-CO—CH_2OH is replaced by a α-fluoromethylthioester

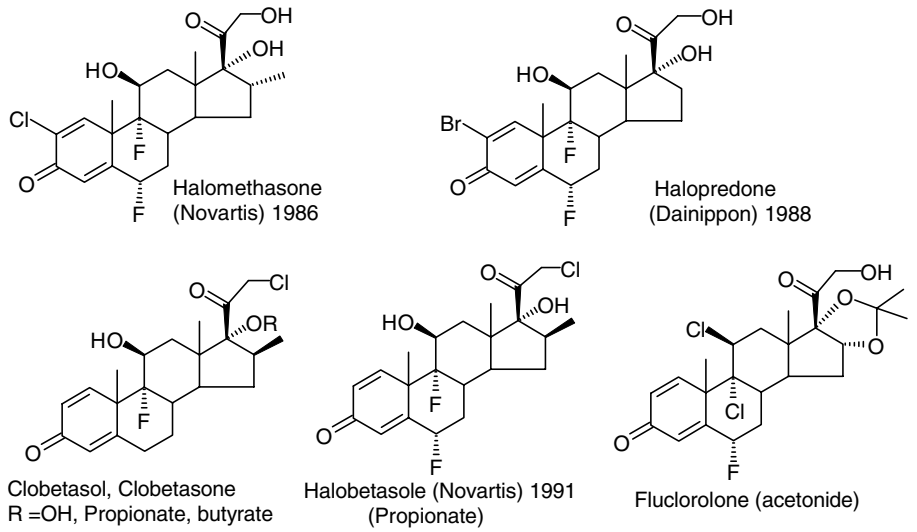


Figure 8.41 Halogenofluorocorticosteroids.

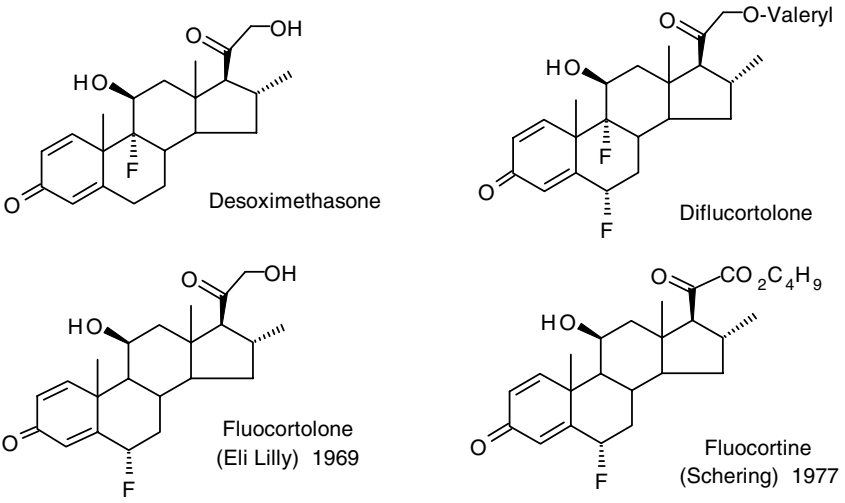


Figure 8.42 Fluorocorticosteroids without 17-OH.

(Figure 8.40),[61] *fluorometholone*, which is 6α-Me-substituted, and *fluprednidene*, substituted in C-16 with an *exo*-methylene (Figure 8.43).

Fludrocortisone and *fludroxycortide* are mineralocorticoids. They are more potent than cortisol. Reduction of the Δ-1 unsaturation contributes to the decrease of the glycocorticoid and anti-inflammatory activities (Figure 8.44).

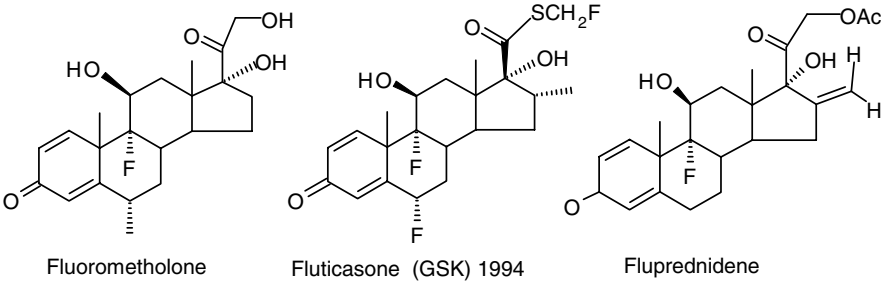


Figure 8.43 Examples of fluorocorticosteroids with atypical substitution.

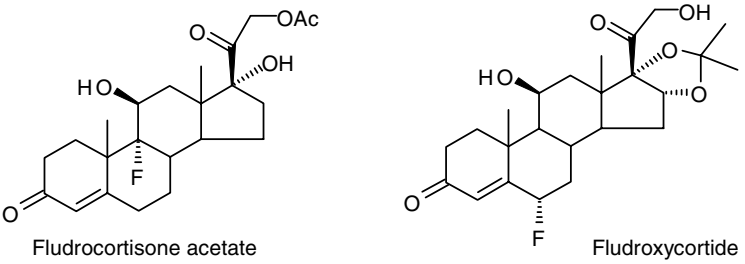


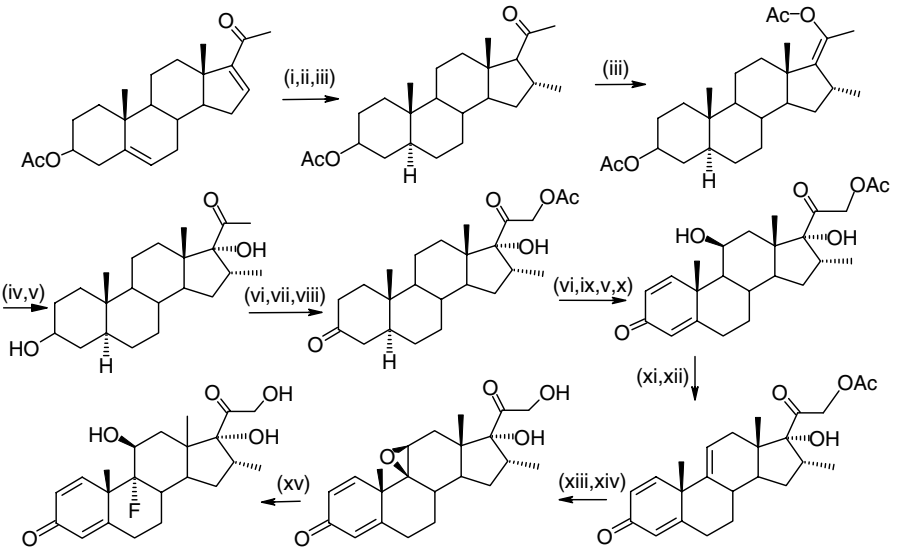
Figure 8.44 Fluoro mineralocorticoids.

All these structural modulations are accompanied by the esterification of 17- and 21-hydroxyl. This has been done in order to prepare oral, topical, spray, and delayed-delivery formulations. A huge number of patent medicines have been marketed from more than twenty basic molecules (Figures 8.39–8.44). Despite the fact that fluorocorticosteroids are considered "old" compounds, they are still major drugs in therapies of inflammation, allergy, and asthma, as well in dermatology and ophthamology, as shown by the new galenic formulations that are regularly being launched.

Fluorocorticoids are produced on the ton-scale (e.g., 1.1 tons of fluticasone in 2001). The industrial production of fluorocorticosteroids has been a triple chemical challenge: availability of the starting material, use of hazardous and toxic fluorination reagents, and a large number of chemical or biotechnological steps involved in the synthesis, as highlighted by the synthesis of *dexamethasone* (Figure 8.45).

Access to corticosteroids from animal or vegetal steroids has been the focus of important studies. Steroids that are accessible in high tonnage (e.g., diosgenin, hecogenin, stigmasterol, β-sitosterol, and biliary acids) were the industrial precursors of hydrocortisones.[62–64] Current industrial processes utilize biliary acids, which afford acetoxydehydropregnenolone as precursor (Figure 8.46).[63c] They can also involve a crude mixture of β-sitosterol, coming from soya oil, and whose fermentation leads to 9α-hydroxy-androstenolone.[64] Dehydration can be performed selectively to yield the Δ-9–11 compound. The pregnane side chain is then further rebuilt.

In all cases, introduction of the fluorine on 9α is conducted by means of the Fried method. To date, there is no alternative method for this purpose.[65]



(i) MeMgBr; (ii) H_2; (iii) Ac_2O; (iv) MCPBA; (v) OH^-; (vi) Br_2; (vii) NaOAc/KI; (viii) CrO_3,Py; (ix) DMF; (x) biotransformation; (xi) TsCl; (xii) NaOAc; (xiii) AcNHBr/H_3O^+; (xiv) OH^-; (xv) HF

Figure 8.45 Synthesis of dexamethasone.[63]

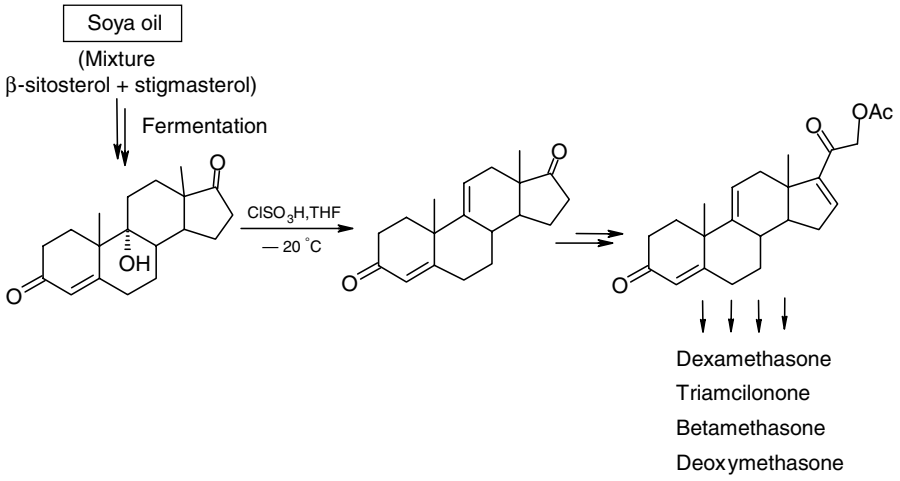
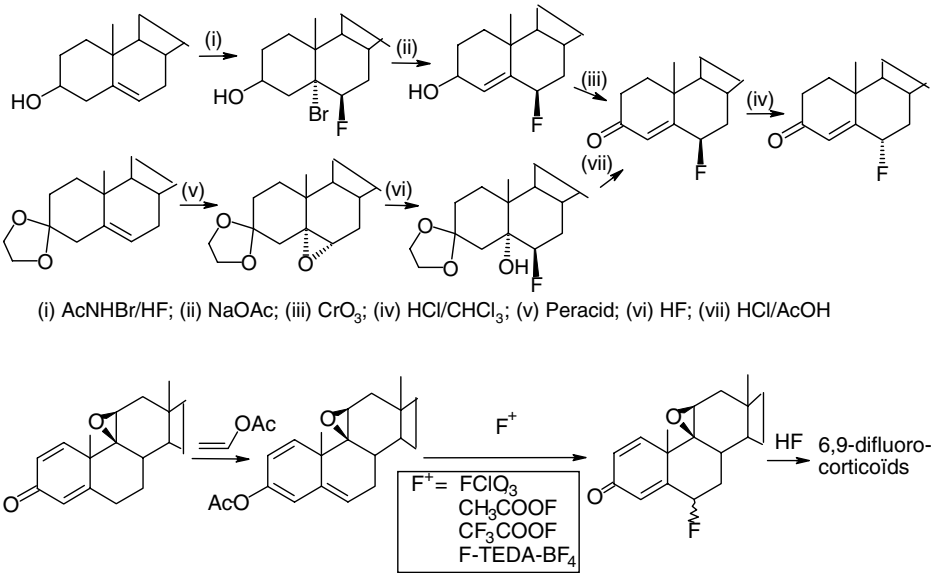


Figure 8.46 Upjohn process for production of the precursor of 9α-fluorocorticosteroids.[64]

The introduction of fluorine on position 6 can be performed according to various pathways: fluorohalogenation,[66] via the oxirane 5α-6α,[67] or electrophilic fluorination ($FClO_3$,CF_3COONa/F_2, and now F-TEDA-BF_4) (Figure 8.47).[62, 68, 69] The stereochemistry of the electrophilic fluorination product is dependent on the reagent used. However, the 6α compound is generally the major one. In acidic medium, it is possible to isomerize the 6β-F compounds into 6α-F compounds.[70] Methods to introduce



(i) AcNHBr/HF; (ii) NaOAc; (iii) CrO_3; (iv) HCl/$CHCl_3$; (v) Peracid; (vi) HF; (vii) HCl/AcOH

Figure 8.47 Synthesis of 6α- and 6β-fluorocorticosteroids.

fluorine on position 6 are based on electrophilic fluorination. They are generally adapted to the further introduction of a fluorine on position 9.

8.4.2 H_1 Antagonist Antiallergics

Conversely to the ubiquitous effects of fluorocorticosteroids, antagonists of H_1 histamine receptors are purely antiallergics.

Astemizole, *mizolastine*, *tecastemizole*, and *levocastatine* are selective H_1 histamine inhibitors indicated particularly for allergic rhinitis (Figure 8.48). They have few or even no sedative effects. Indeed, the effects are mainly peripheral since these compounds do not easily cross through the blood–brain barrier. *Astemizole*, *mizolastine,* and *tecastemizole* contain the same *N-p*-fluorobenzyl benzimidazole moiety.

The H_1 histamine antagonist *efletirizine* is in Phase III clinical evaluation for the treament of allergic rhinitis. It is structurally very close to the marketed *cetirizine*.

8.4.3 Drugs for Asthma and Respiratory Disorders

Besides corticosteroids, other drugs with various modes of action are being marketed or developed for asthma and other respiratory disorders.

8.4.3.1 Bronchodilators *Mabuterol* is an adrenergic β-2 agonist. It is more selective and potent than *salbutamol*, the reference bronchodilator used in asthma therapy (Figure 8.49).

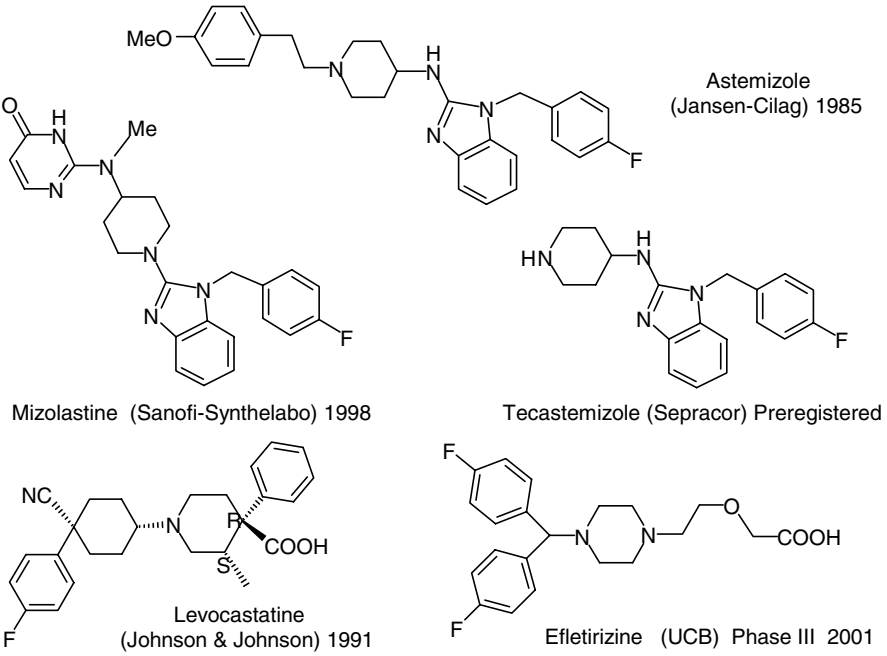


Figure 8.48 Fluorinated H_1 antagonists.

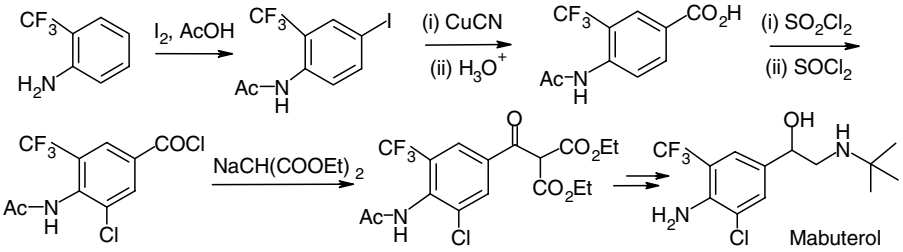


Figure 8.49 Synthesis of mabuterol.[71]

Almitrine is a respiratory stimulant used in the treatment of respiratory insufficiency. It is an agonist of neurotransmitter, but its mode of action is not well known (Figure 8.50).

Frutropium bromide is a derivative of atropine, indicated in the treatment of asthma and bronchitis. It has a cholinergic central effect; it is also a muscarinic and histaminic antagonist (Figure 8.50).

8.4.3.2 PEE-IV Inhibitors Selective inhibitors of phosphodiesterase IV (PDE4) are in development for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Two of them contain fluorine atoms: *roflumilast* (preregistered) bears a difluoromethyl ether and *AWD-12-281* (Phase II) has a single fluorine atom (Figure 8.51).

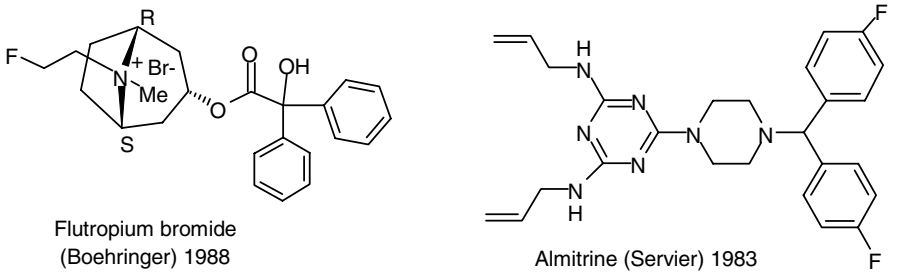


Figure 8.50 Drugs for asthma.

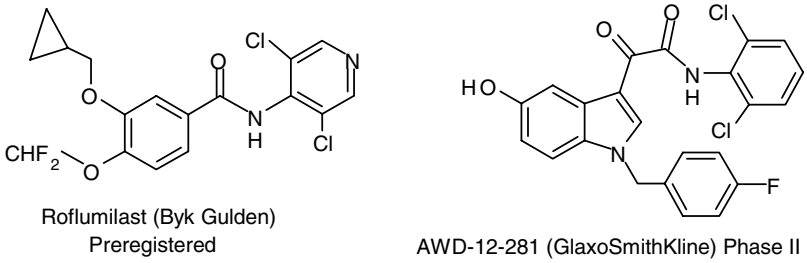


Figure 8.51 PDE-IV inhibitors for the treatment of asthma and COPD.

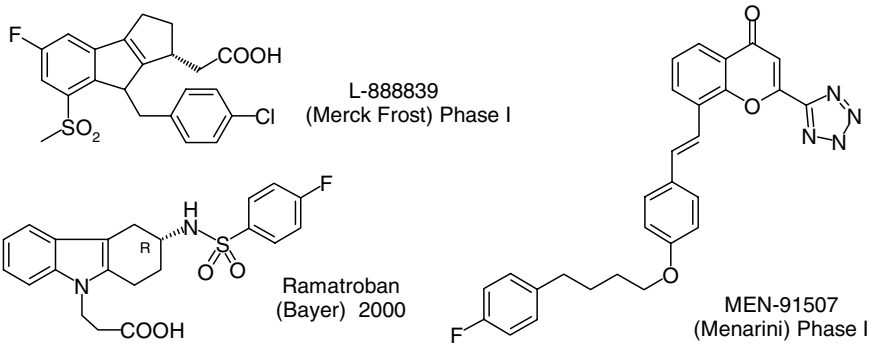


Figure 8.52 Prostanoid antagonists developed for asthma treatment.

8.4.3.3 Prostaglandin Inhibitors *Ramatroban* is an antagonist of prostaglandin H_2 and of thromboxane A_2 receptors. It is marketed as an antiallergic in the treatment of asthma. *L-888839* and *MEN-91507* are also antagonists of prostaglandin receptor with the same indications (Figure 8.52).

8.4.3.4 HLE Inhibitor Inhibition of HLE (human leukocyte elastase) by peptidyl fluoroketones has been well studied (cf. Chapter 7). However, only one compound, ***AE-3763***, a potent and selective HLE inhibitor, is still under clinical development (Phase I) for the treatment of lung injury associated with systemic inflammatory response syndrome. It is the only example of α-peptidyl-β-CF_3-ketone currently being developed, despite the high inhibition potency of this family for protease inhibition (HLE, VIH-PR, renin, etc.) (cf. Chapter 7) (Figure 8.53).

8.4.4 Analgesic and Antiarthritic Drugs

8.4.4.1 Fluorinated NSAIDs NSAIDs (nonsteroidal anti-inflammatory drugs) have become the standard therapy for the management of inflammation and pain. They have proved to be very useful in the symptomatic treatment of arthritis because of their potent analgesic, anti-inflammatory, and antipyretic properties. NSAIDs inhibit cyclooxygenases (COXs), thus preventing the synthesis and secretion of protaglandins, which are endogenous mediators of pain and inflammation. However, protaglandins also play beneficial roles, in particular, in protecting gastric mucosa. Thus, NSAIDs can induce serious adverse events such as gastric mucosal erosion and ulcer.

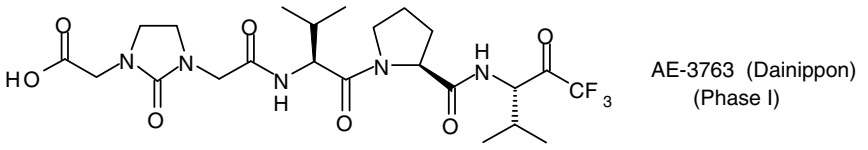


Figure 8.53 AE-3763 Inhibitor of HLE.

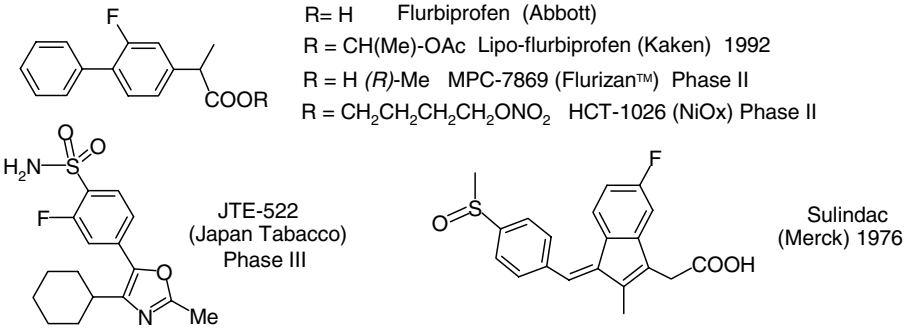


Figure 8.54 Arylacetic NSAIDs.

Fluorinated NSAIDs are present in all the main families of nonspecific COX inhibitors: arylacetic acid derivatives, anthranilic acid derivatives, and salicylic acid derivatives.

(a) Arylacetic Derivatives (Figure 8.54) *Flurbiprofen* and its (*R*)-enantiomer *(MCP-7869)* are currently in clinical trials for other indications (Phase II for treatment of Alzheimer disease *vide supra*, and also Phase II for nonhormonedependent prostatic cancer) (*vide supra*). The reason is that (*R*)-*flurbiprofen* does not inhibit COXs, but is an inhibitor of γ-secretase and of NF-κB, a factor of transcription. *NiOx* is also in Phase II clinical trials for treatment of Alzheimer disease.

Sulindac is a racemic sulfoxide. Its deoxygenated metabolite (i.e., a sulfide) induces apoptosis, probably through inhibition of PPAR (Peroxisome Proliferator-Activated Receptor).[72] It is probably the reason why sulindac seems to protect against colorectal cancers. Indeed, sulindac inhibits colorectal tumor cell growth. One other metabolite of sulindac, the sulfone *exulind*, is an inductor of apoptosis, and is currently in Phase III clinical trials for treatment of tumors (Figure 8.3).

(b) Anthranilic Acid Derivatives (Figure 8.55) *Niflumic acid, morniflumate, flufenamic acid, etofenamate, ufenamate*, and *talniflumate* are currently being marketed. *Talniflumate* is also a Cl^- channel Ca-dependent antagonist. It is now being studied for the treatment of pulmonary cystic fibrosis (Phase II).

Floctafenine and *glifanine* are also anthranilic acid derivatives. However, while they are analgesics, they are not NSAIDs.

(c) Salicylic Derivatives *Flufenisal*, *diflunisal*, and *trifusal* are three fluorinated NSAIDs derived from salicylic acid. Trifusal, being also an inhibitor of cyclic AMP phosphodiesterase, is an antiplatelet agent currently being developed as an antithrombotic agent (*vide infra*) and also as a neuroprotector in the treatment of Alzheimer disease.

(d) Atypical NSAID An atypical molecule, *JTE-522* is, in Phase III clinical development (Figure 8.54).

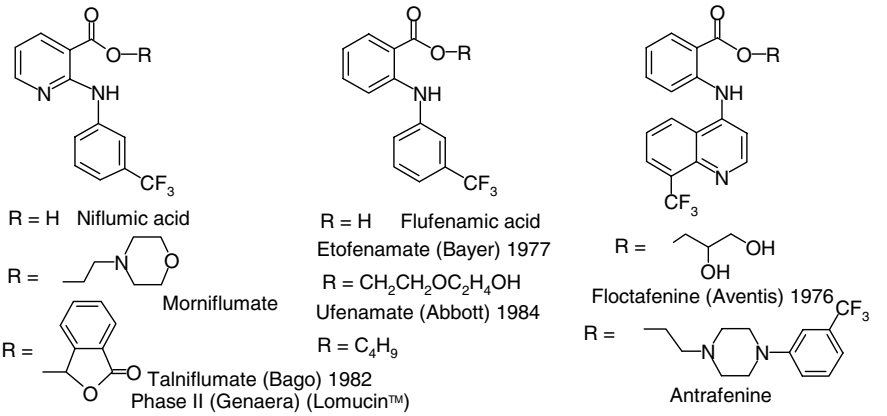


Figure 8.55 Anthranilic acid derivative NSAIDs.

More recently, it was discovered that there are two COX isoforms—COX-1 and COX-2. COX-1 is constitutive, but the COX-2 isoform is inducible by inflammatory phenomena. This explains the intense search for selective inhibitors of COX-2, which could provide beneficial anti-inflammatory and analgesic effects without the gastrointestinal toxicity associated with conventional NSAIDs. Selective COX-2 inhibitors have recently been launched. *Celecoxib* is a major one: it has a production of 450 tons/year. *Lumaracoxib* (Phase III) and *cimicoxib* (Phase II) are currently being clinically evaluated (Figure 8.56). However, it must still be proved that these COX-2 inhibitors are effectively lacking in the same adverse effects of conventional NSAIDs. Moreover, an increased risk of thrombosis seems to exist. Some COX-2 inhibitors have been withdrawn from the market, and the future of this family may be compromised, despite the huge commercial stake.

SMP-114 (licofelone) is a drug candidate for rheumatoid arthritis, currently in Phase II clinical trials (Figure 8.57). It inhibits all three of the major enzymes involved in the arachidonic acid pathway (5-LOX, COX-1, and COX-2), thereby preventing production of both leukotrienes and prostaglandins. This mode of action could therefore lead to a better tolerability than that of conventional cyclooxygenase (COX-1 and COX-2) inhibitors because of the shunt of arachidonic acid metabolism toward the production of proinflammatory leukotrienes, via 5-lipoxygenase (LOX).

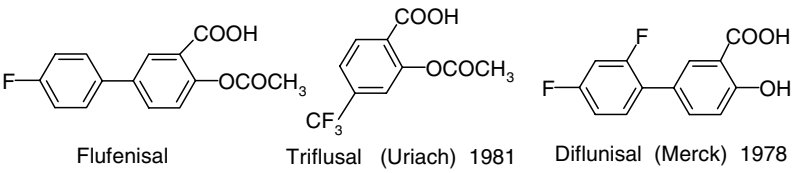


Figure 8.56 Fluorinated salicylic NSAIDs.

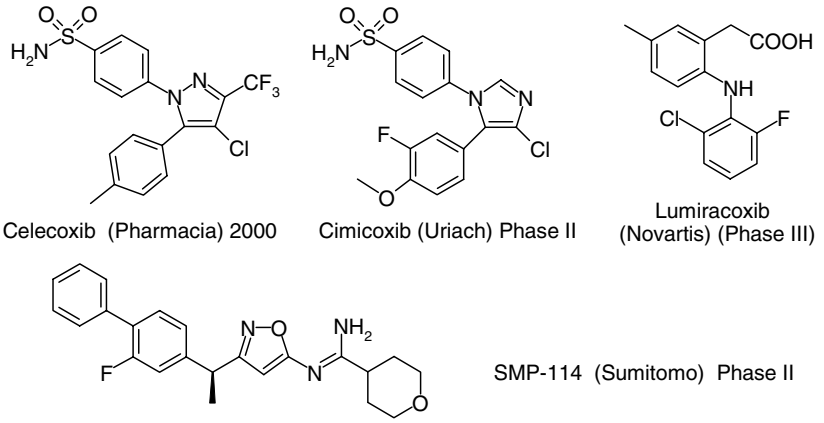


Figure 8.57 COX-2 selective inhibitors and SMP-114.

8.4.4.2 Other Drugs for Arthritis *Leflunomide* is an inhibitor of hydrorotate deshydrogenase, an enzyme involved in pyrimidinic nucleotide biosynthesis. This immunosuppressant agent was launched for the treatment of psoriatic arthritis and rheumatoid arthritis. Its active metabolite, *teriflunomide,* is currently being evaluated in Phase III clinical trials in the treatment of multiple sclerosis. *FK-778*, a short-acting leflunomide analogue, is also an immunosuppressant agent. It is currently in Phase II clinical trials for transplant rejection (Figure 8.58).

ERB-041 and *ERB-196* are estrogen receptor agonists in early clinical development for treatment of rheumatoid arthritis.

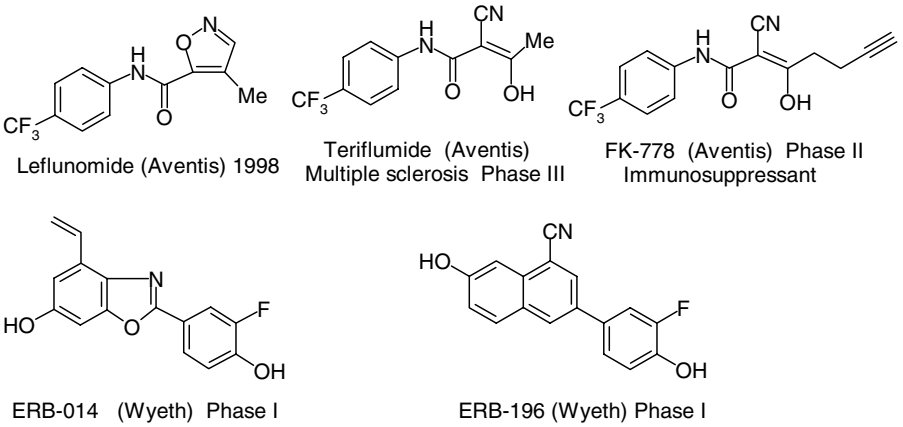


Figure 8.58 Arthritis drugs and immunosuppressant drugs.

8.5 DRUGS FOR CARDIOVASCULAR DISORDERS

8.5.1 Cholesterol Lowering Drugs

Cholesterol lowering drugs are indicated for the prevention and treatment of atherosclerosis. There are three families of these drugs: inhibitors of HMG-CoA reductase (statins), inhibitors of cholesterol transport protein, and inhibitors of cholesteryl ester transfer protein (CETP). They are important drugs from an economical point of view. Among them, several are fluorinated.

8.5.1.1 HMG-CoA Reductase Inhibitors Statins inhibit HMG-CoA reductase, the enzyme synthesizing mevalonic acid (a key step in cholesterol biosynthesis). These drugs are indicated to treat hypercholesterolemia and to reduce LDL cholesterol.

The fluorinated statins *atorvastatin*, *rosuvastatin, pitastatin*, and *fluvastatin* come from pharmacomodulation of *simvastatin* (Figure 8.59). Production and turnover of fluoro statins are very important (e.g., atorvastatin 81 tons, $7 billion (U.S.)).

Another HMG-CoA reductase inhibitor, *benfluorex* (structurally an amphetamine), and its *D* enantiomer, *dexfenfluramine*, have been withdrawn after several serious pulmonary arterial hypertension cases (Figure 8.59).

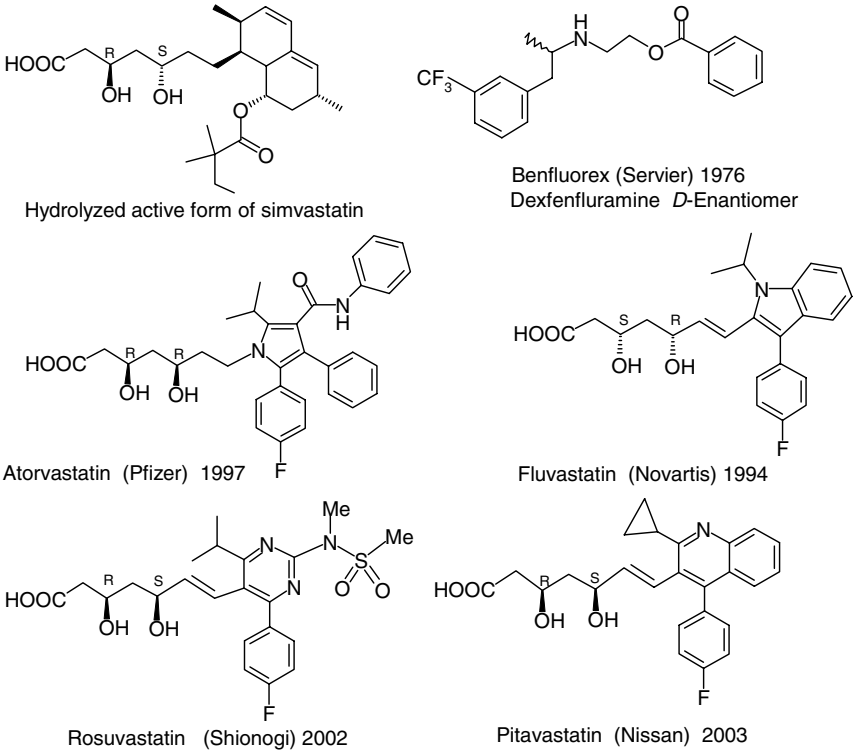
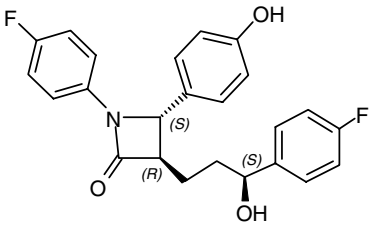


Figure 8.59 HMG-CoA reductase inhibitors.



Ezetimibe (Schering)
2002

Figure 8.60 Cholesterol transport protein inhibitor.

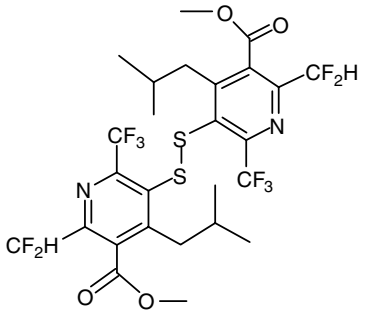
8.5.1.2 Cholesterol Transport Protein Inhibitor *Ezetimibe* is the first hypolipidemic agent to act by blocking the absorption of dietary cholesterol at the intestinal level. It represents a novel treatment option for patients with hypercholesterolemia, alone or in combination with statins (Figure 8.60).

8.5.1.3 Cholesteryl Ester Transfer Protein Inhibitors Cholesterol ester transfer protein (CETP) is a glycoprotein that transfers cholesteryl ester from HDL (high density lipoprotein) to proatherogenic apolipoproteins (LDL—(low density lipoprotein). Its inhibition has beneficial effects at the level of HDL cholesterol. *SC-71952* and *torcetrapib* are highly fluorinated CETP inhibitors. *SC-71952* is a disymmetrical sulfide with 10 fluorine atoms. *Torcetrapib* contains three CF_3 groups (Figure 8.61).[73]

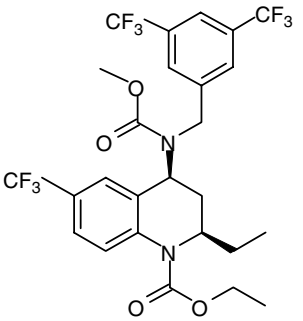
8.5.2 Drugs for Hypertension

8.5.2.1 Propanolol Derivatives *Butofilol* and *nebivolol* are β-blockers, derivatives of propanolol, a typical β-adrenergic antagonist. Nebivolol is a β_1 selective antagonist (Figure 8.62).

SUN-8075 is also a propanolol derivative, but it does not act as a β-blocker: it is a dual Na^+/Ca^{2+} channel blocker and channel inhibitor. It is being studied in Phase I clinical trials as a therapeutic agent for acute stroke.

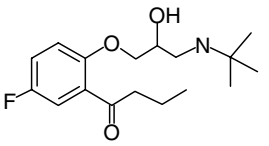


SC-71952 (Pharmacia) Preclinical

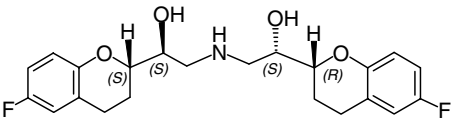


Torcetrapib (Pfizer) Phase III

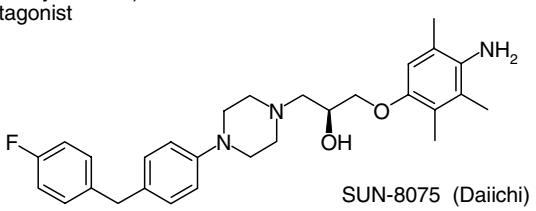
Figure 8.61 Cholesteryl ester transfer protein (CETP) inhibitors.



Butofilol (Sanofi-Synthélabo) 1982
β antagonist



Nebivolol (Johnson & Johnson) 1997 β_1 antagonist



SUN-8075 (Daiichi) Phase I

Figure 8.62 Fluorinated derivatives of propanolol.

8.5.2.2 Other Drugs for Hypertension *Flutonidine*, a close *clonidin*e analogue, is an agonist of α_2-adrenergic presynaptic central as well peripheral receptors. Clinical development for hypertension seems to be recently stopped (Figure 8.63).

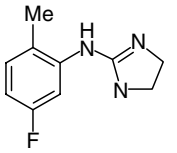
Ketanserine, a 5-HT_2 serotonin peripheral receptor antagonist, is being marketed for the treatment of hypertension.

8.5.2.3 Diuretic Agents *Bendroflumethiazide*, *hydroflumethiazide,* and *paraflutizide* are thiazidic fluorine-containing derivatives. These diuretic agents are indicated for hypertension treatment (Figure 8.64).

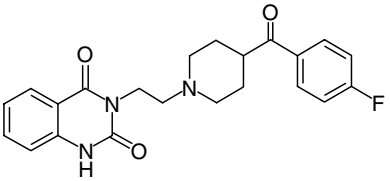
A vasopressin V_2 receptor antagonist, *lixivaptan*, is currently being developed (Phase II) for the treatment of hyponatremia. This agent blocks the effect of the antidiuretic hormone arginine-vasopressin.

8.5.2.4 Ionic Channel Ligands The vasodilators *lidoflazine, flunarizine,* and *lomerizine* are calcium channel antagonists with very similar structures (Figure 8.65). Lidoflazine is indicated as a coronary vasodilator. Flunazirine and lomerizine are mainly cerebral active; they are indicated for migraine treatment and dizziness prevention.

KC-515 is a K^+ channel ATP-dependent agonist. It is a close analogue of *cromakalim,* investigated for the treatment of hypertension. Its close, more fluorinated

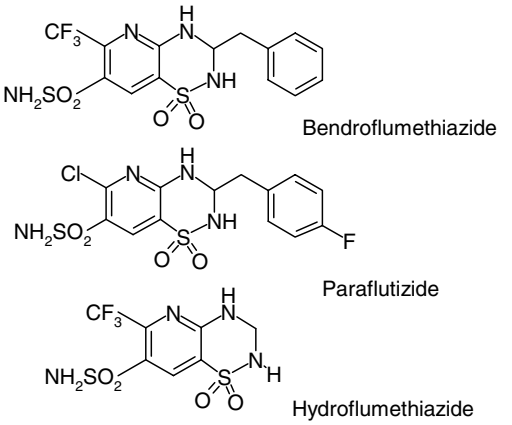


Flutonidine (Boeringher)
α_2 agonist



Ketanserine (Johnson & Johnson) 1985
Peripheral 5-HT_2 antagonist

Figure 8.63 Other fluorinated drugs for hypertension.



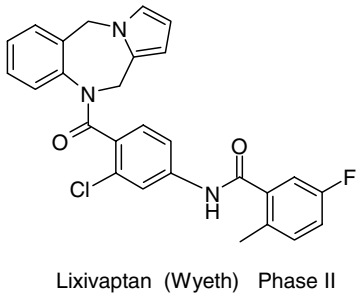
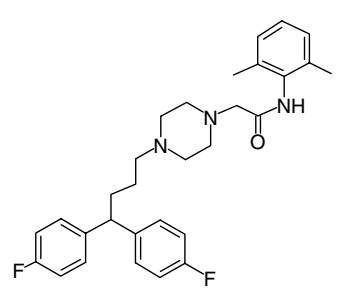
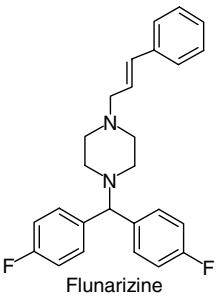


Figure 8.64 Fluorinated diuretic agents.

analogue, *K-399*, is being developed for the treatment of alopecia (Figure 8.66). The *gem*-di(fluoromethyl) moiety is introduced from 1,3-difluoroacetone (Figure 8.67). *gem*-Di(difluoromethyl) and *gem*-di(trifluoromethyl) compounds have also been prepared by the same reaction from tetrafluoroacetone and hexafluoroacetone respectively.[73]





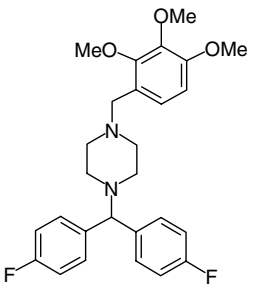
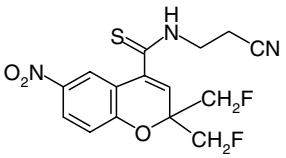


Figure 8.65 Calcium channel antagonists.



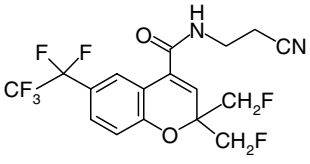
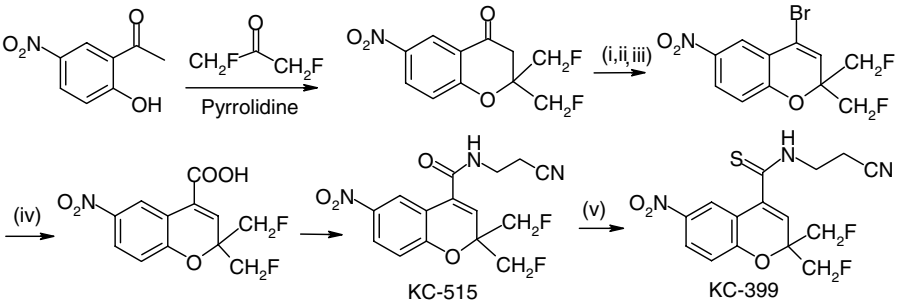


Figure 8.66 Fluorinated agonist of K^+ channel.



(i) $NaBH_4$; (ii) APTS; (iii) Br_2; (iv) CO, $Pd(OAc)_2$; (v) Lawesson reagent

Figure 8.67 Synthesis of K-515 and K-399.[73]

8.5.3 Drugs for Arrhythmias

Flecainide is a selective inhibitor of Na^+ channels and does not act on K^+ channels. It is an antiarrhythmic class I, mainly active on ventricular disorders. Flecainide is a bis-(trifluoroethyl) ether. This substituent, which brings metabolic stability and lipophilicity, is introduced by reaction of trifluoroethyl triflate on hydroquinone (Figure 8.68).

The difluoromethyl ether *AZD-7009* is in Phase II clinical trials as an atrial repolarization-delaying agent.

8.5.4 Antithrombosis and Anticoagulant Fluorinated Agents

Prasugrel (CS-747) and *R-99224* are antiplatelet agents, similar to *clopidogrel*. They are in development (Phase III) as antithrombosis agents for the treatment of stroke and acute coronary syndromes (Figure 8.69). *Cangrelor sodium* is being developed as a short-acting antiplatelet agent and is currently in Phase II clinical trials.

Antithrombolitic effects of *razaxaban* (an inhibitor of coagulation factor Xa) are currently being evaluated in Phase II trials.

SSR-182289 is a direct thrombin inhibitor, structurally related to *argotroban*. It is undergoing Phase II clinical trials for thromboembolic disease treatment.

Fluindione, a *p*-fluoro *phenindione*, is a vitamin K competitive antagonist used as an anticoagulant. The plasma half-life of phenindione is strongly increased by the fluorine substitution (from 10 to 30 h).

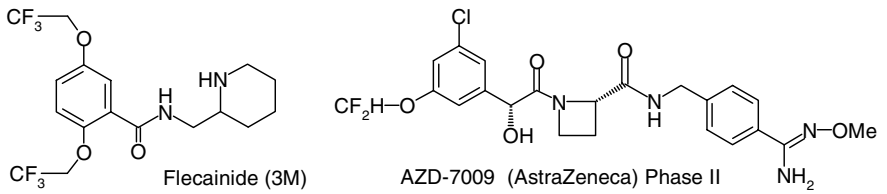


Figure 8.68 Drugs for arrhythmias.

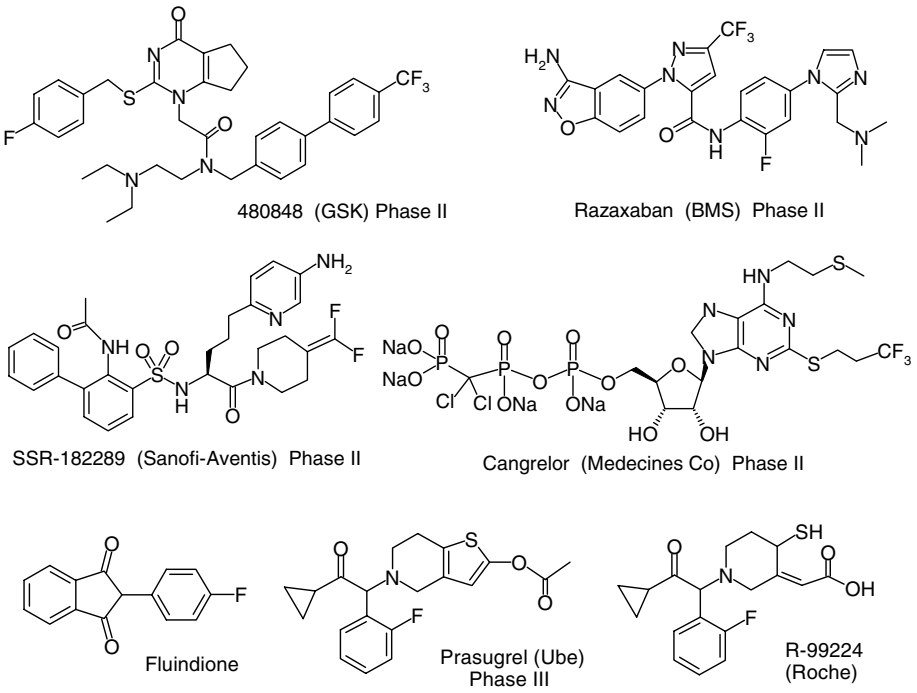


Figure 8.69 Antithrombosis and anticoagulant fluorinated agents.

480848 is an inhibitor of lipoprotein associated with phospholipase A_2 (Lp-PLA_2), an enzyme involved in the development of atherosclerotic plaques. It is planned for Phase III clinical trials for the treatment of atherosclerosis (Figure 8.69).

8.6 DRUGS FOR GASTROINTESTINAL DISORDERS

8.6.1 Prevention and Treatment of Ulcer

Pantoprazole and *lansoprazole* are two sulfinyl-containing benzimidazoles. They are close analogues of *omeprazole,* an irreversible inhibitor of H^+/K^+-ATPase (proton pump) of gastric parietal cells.[74] Omeprazole was the world's highest selling drug in 1997. Lansoprazole is now the leader of the very important market of drugs to treat ulcers and gastroesophageal reflux disease (GERD) (lansoprazole: 62 tons in 2001, ranked sixth in 2003 in the class of most sold pharmaceuticals). Improvements in enantioselective oxidation of sulfur to sulfoxide has made it possible to prepare pure enantiomers of omeprazole-type compounds.[75] Consequently, following the recent chiral switch of omeprazole *(esomeprazole)*, (*S*)-enantiomers at the sulfoxide center of pantoprazole and lansoprazole are also under preclinical development.

Lansoprazole contains a trifluoroethoxy group and pantoprazole has a difluoromethoxy moiety (Figure 8.70).

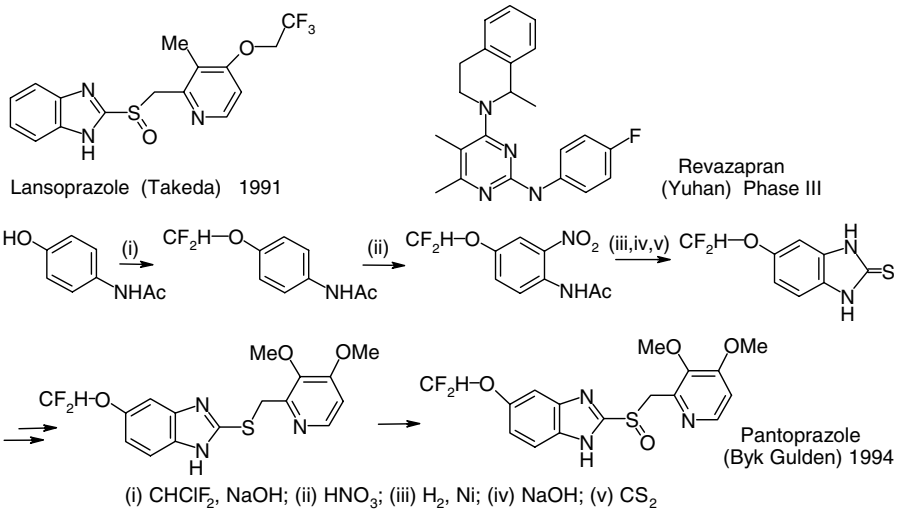


Figure 8.70 Fluorinated proton pump inhibitors.[74, 75]

Revaprazan is a reversible proton pump inhibitor. It is currently in Phase III clinical development as a treatment for peptic ulcer (Figure 8.70).

Cisapride, a nonselective 5-HT_4 serotonin antagonist, has been largely indicated as gastroprokinetic before its recent withdrawal related to severe cardiac accidents (Figure 8.71).

8.6.2 Antiemetic Agents

Mosapride is a benzamide, structurally close to *cisapride*. This 5-HT_4 receptor agonist, which is also a 5-HT_3 and D antagonist, was launched for the treatment of gastroesophageal reflux disease (GERD) (Figure 8.71).

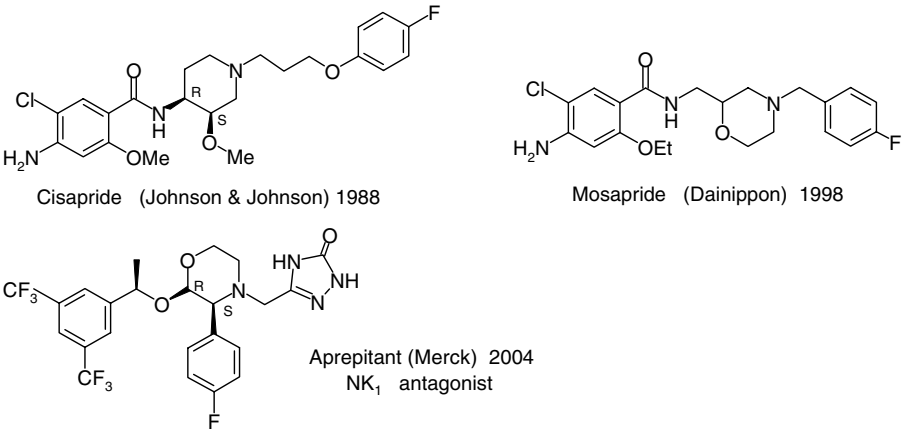


Figure 8.71 Gastric prokinetic and antiemetic agents.

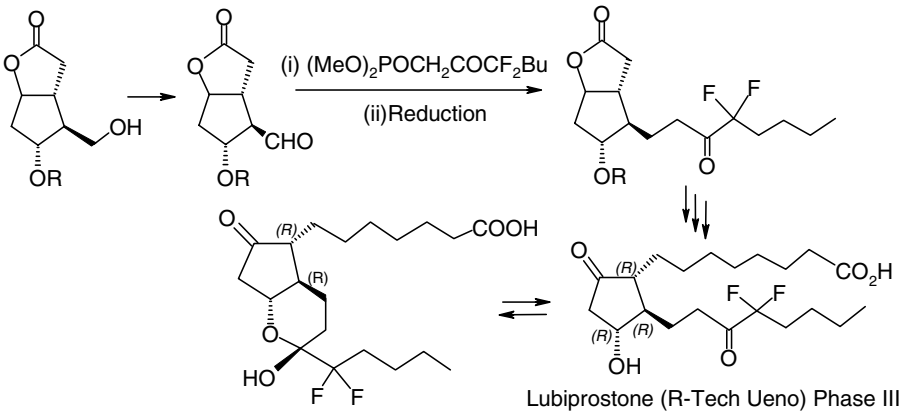


Figure 8.72 Synthesis of lubiprostone.[76]

Aprepitant is a neurokinin-1 antagonist marketed for the prevention of chemotherapy-induced nausea and vomiting (Figure 8.71).

8.6.3 Drugs for Bowel Disorders

Lubiprostone has emerged as a novel agent for the treatment of constipation. This prostaglandin analogue potently activates intestinal Cl^- channels, without altering Na^+ and K^+ balance. This difluoromethyl ketone is in equilibrium with the bicyclic hemiketalic form, which is predominant in the absence of water (Figure 8.72).[76]

8.7 DRUGS FOR ENDOCRINE AND METABOLIC DISORDERS

8.7.1 Drugs Acting on Steroid Hormone Receptors

8.7.1.1 Androgenic Receptors The antagonists of androgenic receptor, *flutamide*, *nilutamide* and *bicalutamide*, have the same *m*-trifluoromethylaniline moiety (Figures 8.73 and 8.74). They are marketed for hormone-dependent prostatic cancer treatment.[77, 78]

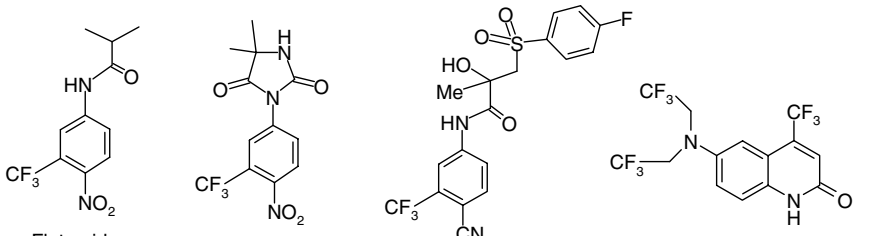


Figure 8.73 Ligands of androgenic receptor.

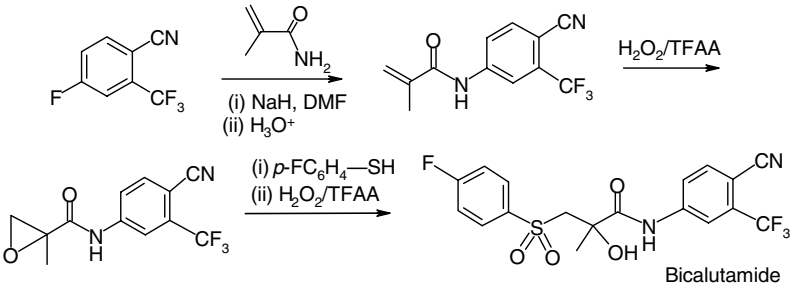


Figure 8.74 Synthesis of bicalutamide.[78]

A highly fluorinated androgen agonist, *LGD-2941*, is in early clinical development for the treatment of several indications related to the beneficial effects of the androgen receptor activation (e.g., hypogonadism).[79]

8.7.1.2 Estrogen Receptors *ERB-041* is a potent and highly selective estrogen receptor (ER)β agonist that has a binding affinity that is comparable to natural ligand (17β-estradiol). However, it is more than 200-fold selective over ER(α). ERB-041 is currently in clinical development for the treatment of endometriosis and rheumatoid arthritis (Figure 8.75).

Fulvestrant is an estrogen receptor competitive antagonist that binds to the estrogen receptor with comparable affinity to that of estradiol. Fulvestrant downregulates the estrogen receptor in human breast cancer cells. It is marketed for treatment of hormone-dependent breast cancer (Figure 8.76).[80]

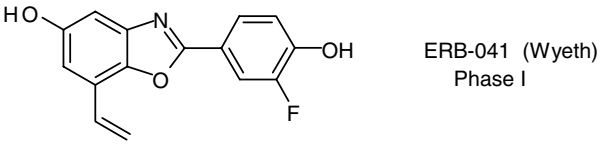


Figure 8.75 Estrogen receptor (ER)β agonist ERB-041.

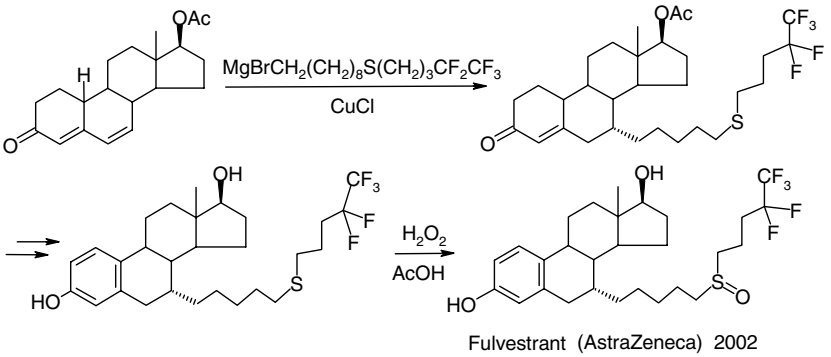


Figure 8.76 Synthesis of fulvestrant.[80]

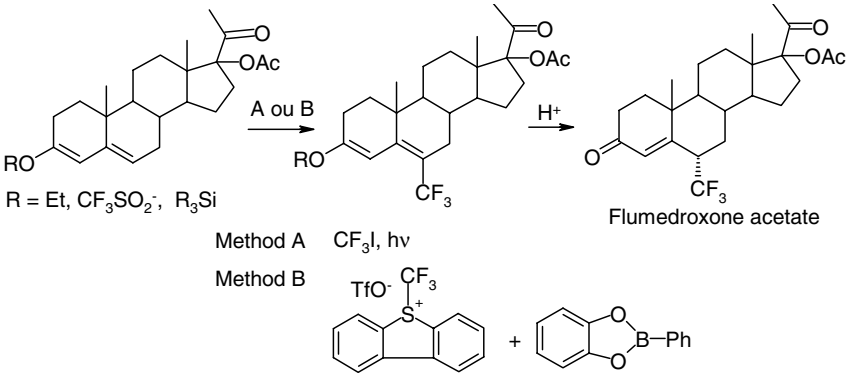


Figure 8.77 Synthesis of flumedroxone.[81c]

8.7.1.3 Progesterone Receptors *Flumedroxone*, a progestative agent, is a pregnane derivative substituted at C-6 by a trifluoromethyl group. This group is introduced by radical trifluoromethylation or by electrophilic trifluoromethylation of enol with the Umemoto reagent (Figure 8.77).[81]

Antiprogestine (*ZK-230211*) is a progesterone receptor antagonist developed for treatment of breast tumors. It is substituted at C-17 by a hydroxyl (17β) and a C_2F_5 group (17α), which is introduced with pentafluoroethyllithium, prepared *in situ* from pentafluoroethyl iodide and butyllithium (Figure 8.78).[82]

8.7.1.4 GnRH Receptor (Gonadotropin-Releasing Hormone) *Sufugolix* (TAK-013) is a nonpeptidic gonadotropin-releasing hormone (GnRH) antagonist in development for the treament of sex-dependent diseases, such as endometriosis (Phase II).

8.7.2 Drugs for Benign Prostatic Hypertrophy (BPH)

Dutasteride inhibits both type 1 and type 2 5α-reductase, which is the enzyme responsible for converting testosterone to dihydrotestosterone in the prostate. It has

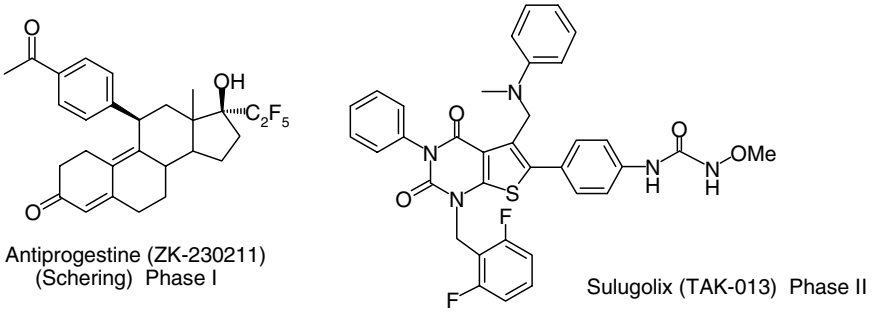
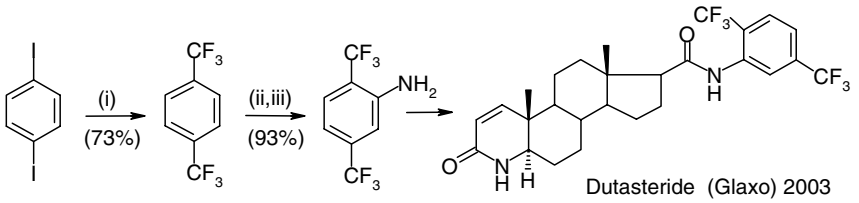


Figure 8.78 Antiprogestine and sulugolix.



(i) CF_3COONa, CuI, NMP; (ii) HNO_3, H_2SO_4; (iii) H_2, Ni, *i*-PrOH

Figure 8.79 Synthesis of dutasteride.[83]

been introduced for the treatment of BPH. The starting 2,4-ditrifluoromethylaniline is prepared by trifluoromethylation from the corresponding diodoaniline (Figure 8.79).[83]

Elocalcitol (*BXL-628*) is the fluoro analogue of the D_3 metabolite that inhibits the growth factors involved in benign prostatic hyperplasia (BPH); it is without direct androgenic effects and does not cause hypercalcemia. It is in Phase II development for the treatment of BPH and overactive bladder (cf. Chapter 4).[84]

Finrozole is a nonsteroidal competitive aromatase inhibitor that is being evaluated in Phase II trials for the treatment of lower urinary tract symptoms associated with a reduced androgen/estrogen ratio in aging males associated with BPH.

Silodosin is an α_1-adrenoceptor antagonist that is being marketed for the treatment of urinary disturbances associated with BPH (Figure 8.80).

8.7.3 Drugs for Other Urologic Disorders

NS-8 and *ZD-0947* are calcium sensitive potassium channel openers, that have no effects on the cardiovascular system. They are currently being developed for the treatment of bladder hyperactivity (Phase II) (Figure 8.81).

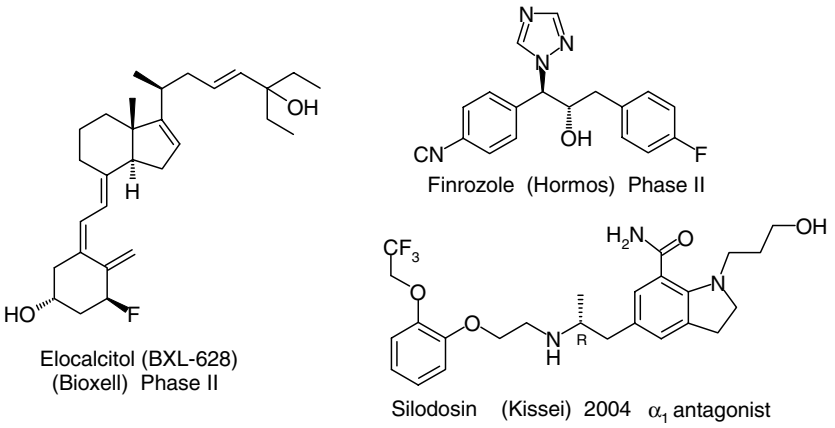


Figure 8.80 BPH treatment agents.

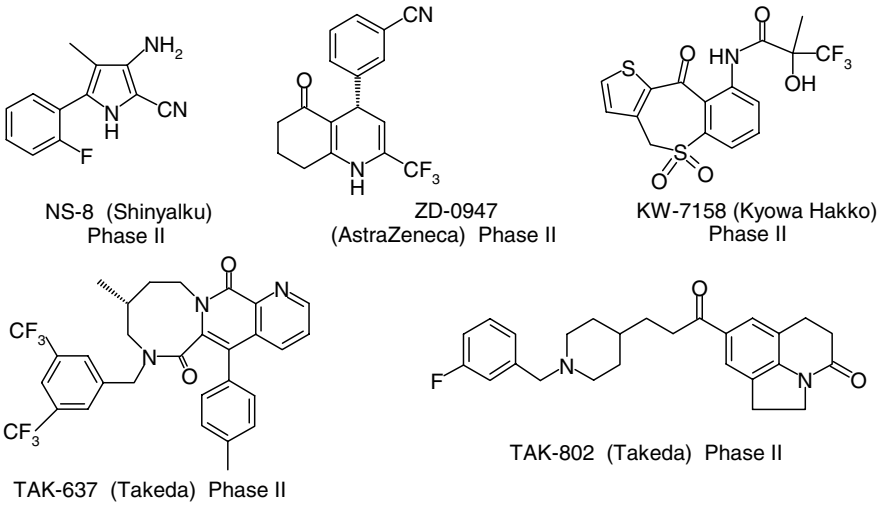


Figure 8.81 Drugs for other urologic disorders.

KW-7158 is a noncholinergic agent that acts on sensory nerves in the bladder. Phase II trials are under way for incontinence associated with bladder hyperactivity (Figure 8.81).

TAK-637 is a potent and selective neurokinin NK_1 antagonist being studied (Phase II) for its potential in the treatment of urinary incontinence (Figure 8.81).

TAK-802 is an acetylcholinesterase inhibitor in Phase II testing for the treatment of hypoactive bladder (Figure 8.81).

8.7.4 Drugs for Calcemia Disorders

Falecalcitriol is a fluoro analogue of calcitriol (dihydroxy vitamin D_3). It acts as a hypercalcemiant agent, and it is marketed for the treatment of hypocalcemia, rachitis, and osteomalacia. Trifluoromethyl groups both increase affinity of falecalcitriol-receptor complex for ADN and decrease affinity for the protein binding vitamin D. Moreover, due to the presence of CF_3 groups, metabolic oxidation is slowed down and, consequently, the plasma half-life is prolonged (cf. Chapter 4) (Figure 8.82).[85]

Cinacalcet is a calcimimetic agent that modulates the response of the calcium-sensing receptor on the parathyroid gland, and thus may lead to a reduction in the levels of calcium. It is marketed to treat hypercalcemia (Figure 8.83).

8.7.5 Drugs for Diabetes

Several fluorine-containing drugs are currently in development for the treatment of diabetes. These are peroxisome proliferator-activated nuclear receptor (PPAR) agonists, aldose reductase, and dipeptidylpeptidase IV (DPP-IV) inhibitors.

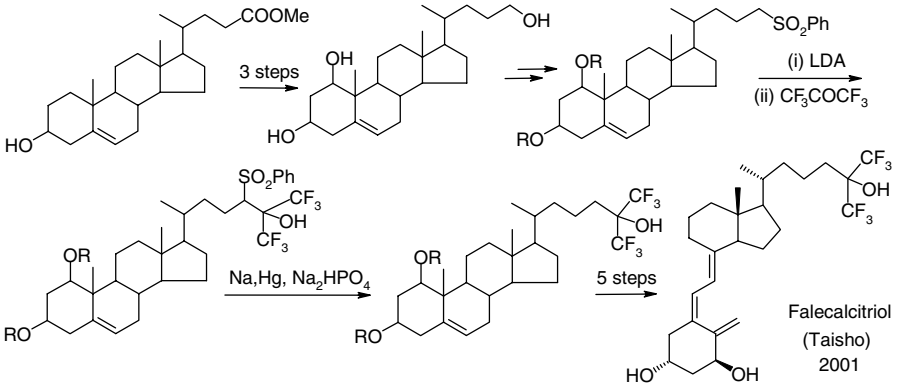
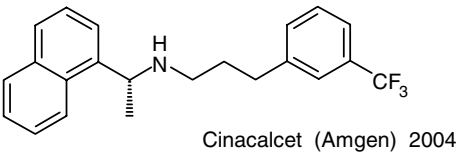


Figure 8.82 Synthesis of falecalcitriol.[85]

Netoglitazone is an insulin sensitizer currently in Phase II clinical trials. It is able to modulate both PPAR-α and PPAR-γ subtypes of peroxisome proliferator-activated receptor (Phase II).[86] *Metaglidasen* (*MBX-102*) is the (−)-enantiomer of the NSAID *halofenate*. This selective PPAR-γ nuclear receptor agonist is being evaluated (Phase II) as an insulin sensitizer. It is structurally different from the currently marketed *glitazones* (Figure 8.84).[87]

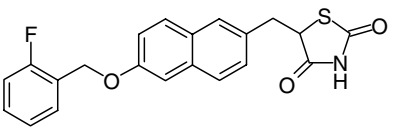
Fidarestat is an aldose reductase inhibitor. It was being developed (Phase II/III) for complications of diabetes, but it seems to have been discontinued. Two other aldose reductase inhibitors, *lidorestat* and *SPR-210*, are currently in development for the treatment of diabetes complications (Figure 8.85).

The incretin hormone glucagon-like peptide-1 (GLP-1) plays a crucial role in the regulation of insulin by acting on the pancreas to potentiate glucose-induced insulin secretion. GLP-1 is rapidly cleaved by serine protease dipeptidylpeptidase IV. The inhibitors of DDP-IV are new drugs for the oral treatment of type 2 diabetes.

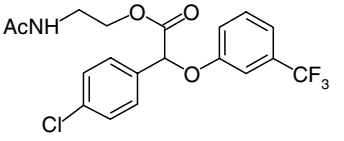


Cinacalcet (Amgen) 2004

Figure 8.83 Cinacalcet.



Netoglitazone (Mitsubishi Pharma) Phase II



Metaglidasen (MBX-102) (—) Halofenate
(Metabolex) Phase II/III

Figure 8.84 PPAR-γ agonist an insulin sensitizer.

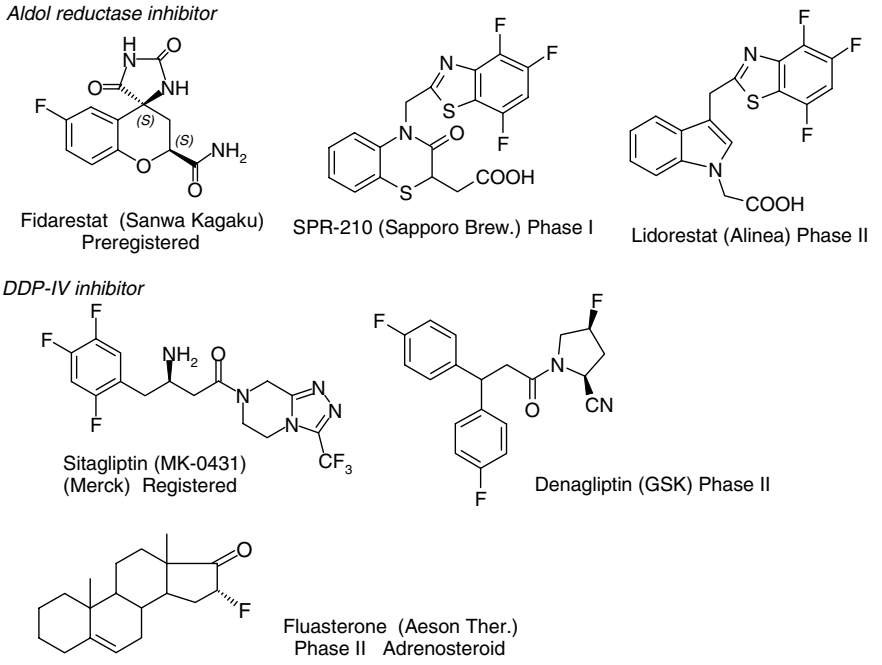


Figure 8.85 Other drugs for diabetes.

Sitagliptin (*MK-0431*) and *denagliptin* are registered and in Phase II development trials (Figure 8.85).

Fluasterone is a stable adrenocortical steroid analogue of *prasterone* (dehydroepiandrosterone (DHEA)) fluorinated at C-16α (Figure 8.85). It is currently being developed (Phase II) for the treatment of metabolic syndrome (i.e., insulin resistance). Electrophilic fluoration with NF type reagent is well adapted for the synthesis of such as α-fluoroketone (95%, α:β 95:5).[68]

8.7.6 Drugs for Hepatic Disorders

Nitisinone is an inhibitor of 4-hydroxyphenylpyruvate dehydrogenase (4-HPPD). Originally studied as a herbicide, it is now marketed to prevent hepatic damage caused by hereditary tyrosinemia type I. This genetic disease is due to the absence in the body of fumarylacetoacetase, which ensures the last step of tyrosine degradation (Figure 8.86).

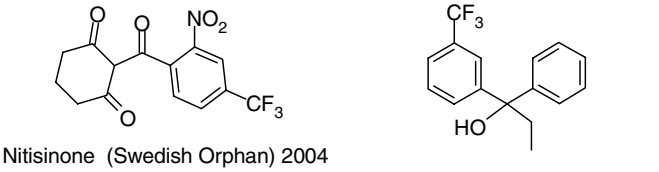


Figure 8.86 Drugs for hepatic disorders.

Flumecinol is an inductor of cytochrome P-450 enzymes, which has been used as a hepatoprotector. Its development seems to have stopped.

8.8 MISCELLANEOUS

8.8.1 Drugs for Ophthalmic Disorders

Travoprost and *tafluprost* are ester prodrugs of a fluorinated analogue of prostaglandin $PGF_{2\alpha}$ (cf. Chapter 4) (Figure 8.87).[88] These full agonists of prostaglandin F (FP) receptor are used to lower the elevated intraocular pressure that causes glaucoma.

Difluorophate (diisopropyl fluorophosphate) is an irreversible inhibitor of cholinesterase. It has been used in the treatment of glaucoma (Figure 8.87).

A vitronectin ($\alpha_v\beta_3$ integrin) antagonist, *267268*, is currently undergoing clinical trials for the treatment of age-related macular degeneration.

8.8.2 Drugs for Genetic Disease

ICA-17043 is a novel inhibitor of the Gardos channel (a calcium-dependent potassium channel). This drug is indicated for the treatment of a hematologic genetic disease (sickle cell disease) (Phase II) (Figure 8.88).

8.8.3 Contrast and Diagnostic Agents

Altropane and *ioflupane* bind L-dopamine transporter protein. They are being developed, respectively, as potential contrast agent for radioimaging and imaging

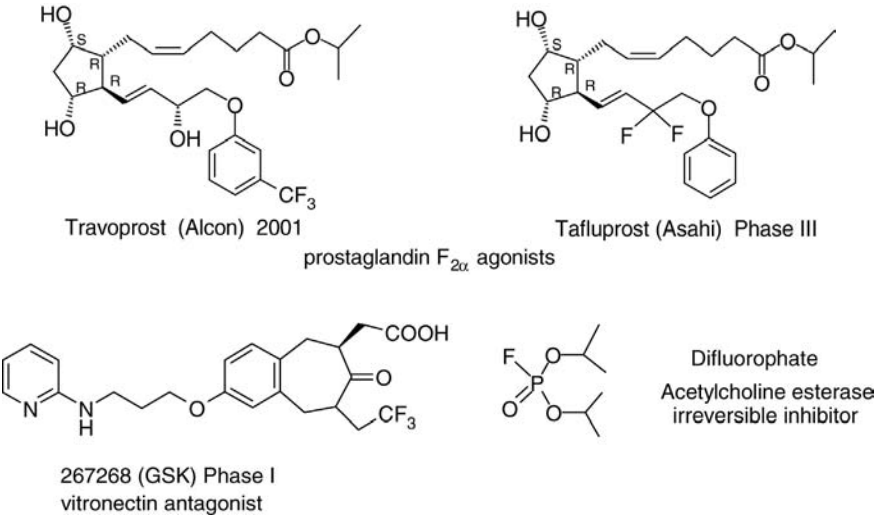


Figure 8.87 Fluorinated drugs for the treatment of ophthalmic desorders.

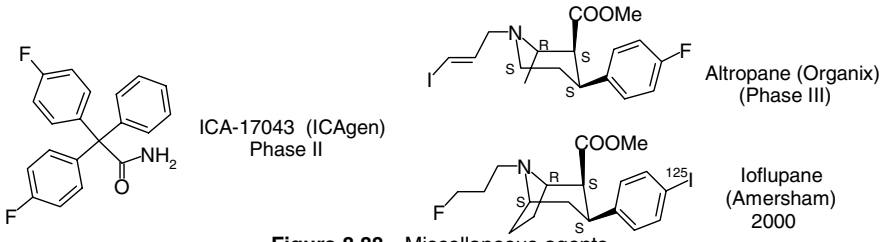


Figure 8.88 Miscellaneous agents.

probes for PET (positron emission tomography) and SPECT (single photon emission computed tomography), for the early diagnosis of Parkinson disease and attention deficit hyperactivity disorder (Figure 8.88).[89] Altropane is currently in Phase III clinical trials.

8.9 HIGHLY FLUORINATED COMPOUNDS WITH CLINICAL USES

8.9.1 General Anesthetics

In the 1950s *halothane* (a perhalogenoethane) began to replace diethyl ether, vinyl ethyl ether, and ethyl chloride in general anesthesia. Halothane exhibits clear advantages: it is much safer (noninflammable and nonexplosive compound) and more metabolically stable than previous anesthetics. Halothane is now being abandoned in favor of highly fluorinated ethers (Figure 8.89). These latter compounds exhibit the same benefits as halothane, but they are much more metabolitically stable (Table 8.2).[90] Moreover, these fluoroethers are relatively poorly soluble in blood (Table 8.2): the more unsoluble an anesthetic is, the faster is both anesthesia and

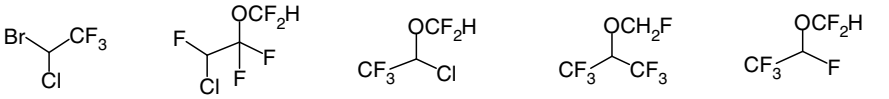


Figure 8.89 General anesthetic agents.

Table 8.2 Fluorinated general anesthetic agents data[90]

Agent	bp (°C)	Blood–gas Partition Coefficient	Muscular Coordination Recuperation Time (min)	Metabolism %
Halothane	50	2.35	47.2	20–45
Enflurane	56	1.91		2.4
Isoflurane	48.6	1.4	23.2	0.2
Sevoflurane	58.6	0.63	14.2	5–10
Desflurane	23.5	0.42	4.7	<0.1

awakening. These latter features are the two conditions required for good quality anesthetics.[90]

Four highly fluorinated ethers with low boiling points are currently used in anesthesia: *enflurane*, *isoflurane*, *sevoflurane,* and *desflurane* (Figure 8.89).[91] Desflurane and sevoflurane are now the most used (sevoflurane is especially used in pediatrics). They exhibit the lowest blood–gas partition coefficients, the lowest ratio of toxic metabolites, and the lowest solubilities in lipids. These features limit the retention and, consequently, the metabolism is delayed (Table 8.2).

The metabolism of halothane leads to trifluoroacetyl chloride, which can acylate hepatic endoplasmic reticulum proteins into immunogenic ones; thus, it can lead to immunoallergic hepatitis (Figure 8.89). Conversely, the metabolism of fluoroethers is low. This is due to the steric and electronic protecting effect of fluorine. Moreover, metabolites (trifluoroacetic acid and fluoride anion) do not have appreciable toxicity. Even sevoflurane, which undergoes nonnegligible metabolism, provides hexafluoroisopropanol, which is cleared as glucuronide (Figure 8.90).[92]

Fluoroether anesthetic agents have few adverse cardiac effects. However, they are potent peripheral vasodilators and they often provoke shivers upon awakening.

The main difficulty in the preparation of fluorinated anesthetics is to obtain the desired compound with the required degree of purity: these fluorinated molecules are gaseous or very volatile and have a poor polarity. Some examples of the synthesis of these compounds are given in Figure 8.91.[90, 91, 93]

It was believed that these lipophilic fluoroethers act as anesthetic agents through nonspecific interactions with cerebral lipids. Actually, data show that the anesthetic properties of fluoroethers come from specific interactions with some proteins.[94] Fluoroethers can possibly potentiate binding of GABA on its receptor, and thus facilitate chloride channel opening. They could also inactivate other receptors, for instance, glutamate receptor. Such a hypothesis would imply that the absolute configuration of the fluoroether should be a key factor for the potency of the anesthetic, since affinity for the target depends on the absolute configuration of a ligand. This is the reason why pure enantiomers of halothane, isoflurane, and desflurane have been synthesized (Figure 8.92).[90, 95, 96]

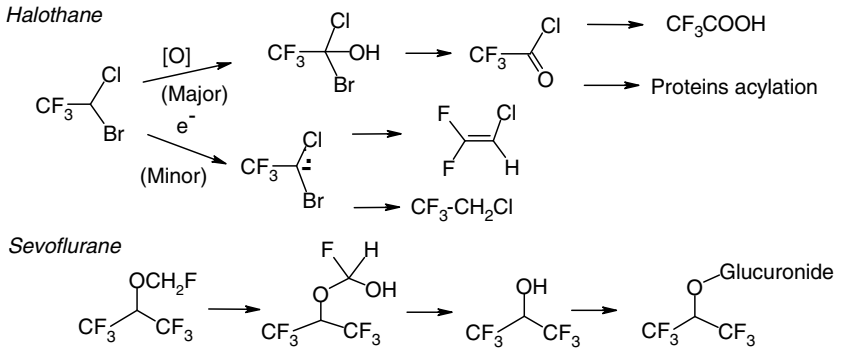


Figure 8.90 Metabolism processes of halothane and sevoflurane.[92]

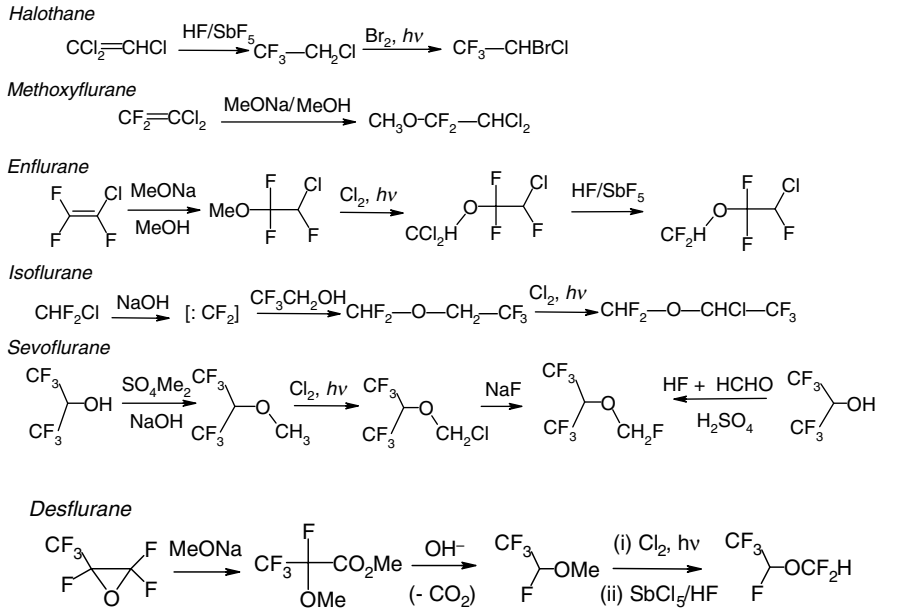


Figure 8.91 Synthesis of fluoroethers as anesthetic agents.[90,91,93]

No difference has been observed in the interactions of the two enantiomers of isoflurane with lipid bilayers. But the (*S*)-enantiomer of isoflurane is two times more active than the (*R*)-enantiomer toward a calcium channel receptor, that is sensitive to volatile anesthetic agents, while nodifference in activity has been observed toward an anesthetic nonsensitive receptor.[97] The (*S*)-enantiomer of isoflurane is also more active than the (*R*)-enantiomer toward acetylcholine nicotinic receptor and $GABA_A$ receptor. These data strongly suggest that fluoroethers interact not only with cerebral membranous lipids but also with receptor proteins.

Cryofluorane (ClF_2C-CF_2Cl) (Freon 114) is used as a local anesthetic agent for sport and dental uses.

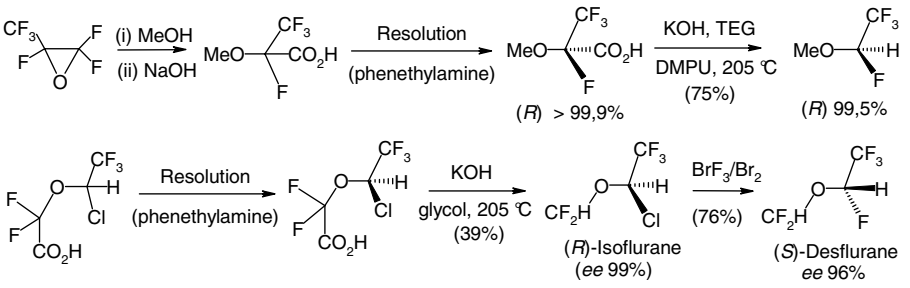


Figure 8.92 Synthesis of desflurane enantiomers.[95]

8.9.2 Therapeutic Uses of Perfluorocarbons

8.9.2.1 Propellant Gas for Spray Gaseous chlorofluorocarbons (CFCs) (CCl_3F, CF_2Cl_2, $CFCl_2CF_2Cl$) are used as propellants in the spray formulations of drugs for inhalation at controlled doses in the treatment of respiratory disorders (e.g., asthma, COPD, chronic bronchitis). Propellants should be nontoxic, nonflammable, and nonsoluble in the drug and should have a well-adapted density and a boiling point between -15 and $-30°C$.[98]

Since CFCs are being progressively banned for environmental reasons by the Montreal protocol, there is an active search for new propellants. The two best candidates are CF_3—CFH_2 (HFC-134a) and CF_3—CHF—CF_3 (HFC-227). They satisfy all the required criteria, with minimum environmental impact. However, it is difficult to apply the GMP (Good Manufacturing Practice) code to the synthesis and purification of HFCs, which are gaseous, in contrast to usual drugs.

8.9.2.2 Contrast Agents for Ultrasound Imaging More flexible and easier than other technique of medical imaging (RX, MRI, PET), ultrasound (US) imaging (e.g., echography) has become one of the most useful and most used techniques for diagnosis and functional exploration. However, as for any imaging techniques, echography requires efficient contrast agents. The role of contrast agents is to increase the signal difference between different tissues. For instance, it can allow assessment of structural and functional cardiovascular abnormalities and of solid organ lesions, including tumors.[99]

The constrast agents that have been developed and approved by health authorities for diagnostic US imaging are micron-size gas bubble products that are injected into the patient's bloodstream. Being highly compressible, gas bubbles scatter US several orders of magnitude more effectively than blood, providing powerful echo and bright contrast. These contrast agents contain a gaseous perfluorochemical that opposes rapid dissolution of the microbubbles in the bloodstream. The reasons for the use of fluorocarbon compounds as contrast agents are the "unique" combination of a very low water solubility, a high vapor pressure relative to molecular weight, and an exceptional biological inertness. When used as the filling gas of microbubbles, perfluorocarbon vapor counterbalances the surface tension and blood pressure forces that push the gases inside the bubble toward dissolution. On the one hand osmotic properties are favourable; on the other hand they are stable and nonreactive and are excreted nontransformed by the lung. Moreover, they can be obtained in high purity. The bubble wall typically consists of a 2–3 nm thick phospholipid monolayer or of thicker and more rigid membranes made from proteins (denaturated albumin) or of biodegradable synthetic polymers. Injection of 250 μL of emulsion is enough (PFC represents about 20% of the mass of emulsion).[99]

The commercially available perfluorocarbon-based contrast agents for diagnosis for liver and heart echography include *sonovue*, a suspension of microparticles of galactose with surface microbubbles of air or sulfur hexafluoride (SF_6); *optizon,* a suspension of perfluoropropane encapsulated in microspheres of albumin; and *sonazoide*, based on perfluorobutane (Phase III). Other formulations of perfluorobutane

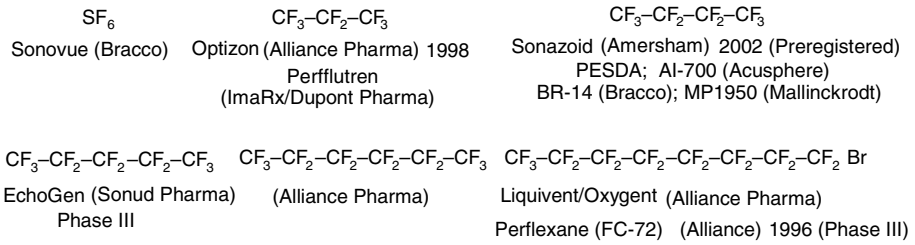


Figure 8.93 Perfluorochemicals used for microbubble products.

(*PESDA*, *AI-700*, MP 1950) and of perfluorooctyl bromide (***liquivent*** and ***perflexane***) are under clinical development (Figure 8.93).

8.9.2.3 Blood Substitutes and Oxygen Carriers Because of their aptitude to dissolve gases, in particular, oxygen, emulsions of perfluorocarbons have found applications as liquid carriers of oxygen with many applications as temporary blood substitutes and as oxygenation liquids for tissues during organ transplantations or in ocular surgery.[100–103] Numerous reviews have recently been published on these applications, and so they are not considered in this book.

Several formulations based on perfluorodecalin, perfluoropropylamine, and perfluorobutylamine are marketed or in development (*fluorosol*, *perfluoran, fluxon*, *oncosol*, *oxyfluor*, *oxygent*).

8.10 FLUORINATED FUNCTIONS AND MOTIFS IN MEDICINAL CHEMISTRY

In most of cases, the fluorine atom(s) or the CF_3 group(s) is borne by aromatic rings. Synthesis of these compounds for the optimization of "hits" as well as for parallel synthesis is done using the numerous fluoro aromatic or heterocyclic compounds that are commercially available. These latter compounds generally come from aromatic fluorination or trifluoromethylation reactions (especially the Balz–Schiemann reaction) and from heterocyclization reactions. However, fluoroaliphatic chains and fluorofunctionalities are more and more present, because of their pharmacological properties. Some examples are given in this section.

While the average number of fluorine atoms in drugs is generally between 1 and 4, it is worth noting that there are also some molecules with more fluorine atoms (5 or 6). Even more fluorinated drugs are in development, such as *torcetrapid* (9 fluorines), *SC-71952,* and *tafluposide* (10 fluorines). Considering the influence of fluorine on the log *P* value, this is rather surprising.

8.10.1 Fluorinated Ethers

While the O—CH_2CF_3, O—CF_3, O—CHF_2, S—CF_3, and S—CHF_2 moieties are very often found in pesticides and herbicides, they have been introduced now in medicinal

chemistry. Trifluoroethyl ethers are much more stable than the corresponding ethyl ethers toward oxidative metabolism;[104] they are also more lipophilic. The same is true for the difluoro or trifluoromethyl ethers of phenols and thiophenol: they are much more stable and lipophilic, more than one log *P* unit for O—CF_3 compare to O—CH_3.

Ar—O—CF_3 and Ar—O—CHF_2 type compounds are now accessible through the desulfurization–oxidative fluorination of dithiocarbonates and dithiianes.[105] Introduction of a O—CHF_2 group can also be performed by adding the corresponding difluorocarbene onto the phenolic hydroxyl (cf. Chapter 2).[105]

Flecainide (Figure 8.68), *lansoprazole* (Figure 8.70), and *sidolosine* (Figure 8.80) are ethers of trifluoroethanol. The only ether of hexafluoroisopropanol is the anesthetic *sevoflurane* (Figure 8.89). The trifluoroethyl phosphonate of *alamifovir* is a prodrug (Figure 8.6).

Among the difluorinated ethers of Ar—O—CF_2H type, some fluoroquinolones are found (*garenoxacine, garefloxacine, BMS-284756*; Figure 8.18), and also other drug types such as *roflumilast* (Figure 8.51), *AZD-7009* (Figure 8.68), and *pantoprazole* (Figure 8.70). Some anesthetics are ethers of difluoromethanol and of another fluorinated alcohol (*sevoflurane*, *desflurane*, *enflurane* and *isoflurane*, Figure 8.89). The two sole ethers with the motif Ar—O—CF_3 are *riluzole* (Figure 8.36) and *Syn-2869* (Figure 8.23).

The S−CF_3 moiety is not found in drugs although it is frequent by used in agrochemistry. However, there is an antibiotic with the S—CF_2 moiety (*flomorex*; Figure 8.22) and a fluorocorticoid with a S–CH_2F group (*fluticasone*; Figure 8.43). The NH—CF_3 group is present in a fluoroquinonlone in preclinical development (Figure 8.18).

8.10.2 Fluorinated Alcohols and Amines

Fluoroalcohols are found in some steroids: *falecalcitriol* (Figure 8.82), *CCD-3693*, (Figure 8.38), and *antiprogestine* (Figure 8.78) and in the calcemic inhibitor *KW-7158* (Figure 8.81). Fluoroalcohols permit strong hydrogen bonds, due to the electron-withdrawing effect of fluorine. It has been suggested that such bonds could enhance the affinity of the drug for the target.

SS-750 is a difluoroalcohol with a sulfonyl group in α (Figure 8.23); it is currently in development. *Efavirenz* is the cyclic ether of a chiral trifluoromethyl alcohol (Figure 8.11).

Some fluoroamine moities are now present in drugs such as *halazepam* and *quazepam* (Figure 8.34) and *LGD-2941* (Figure 8.73). Fluoroamines are less basic and cannot be protonated at physiologic pH (cf. Chapter 3).

8.10.3 Fluorinated Ketones

Despite the numerous enzymology studies with fluoroketones as inhibitors of hydrolytic enzymes, only a few of them have become drugs (cf. Chapter 7). Among them, we can cite a monofluoroketone (*fluasterone*, Figure 8.85), a difluoroketone

(*lubiprostone*, Figure 8.72), and a peptidyl trifluoromethyl ketone as an inhibitor of HLE (*AE-3763*, Figure 8.53).

8.10.4 Fluoroalkyl Groups

For a long time, medicinal chemistry has only focused on monofluorinated and trifluoromethylated compounds. It is only recently that other fluorinated substituents, such as CH_2F, CF_2H, C_6F_5, or C_2F_5, have appeared in medicinal chemistry.

8.10.4.1 C—CH2F and C—CF2H Groups The CH_2F group is found in *aflaquone* (Figure 8.38), *fleroxacin* (Figure 8.18), and *ioflupane* (Figure 8.88). It is also present in *KC-399* and *KC-515* (Figure 8.66) under the geminal form of a *bis*(-mono-) and bis(difluoromethyl).

There are only rare examples where the CF_2H group is the substituent of a carbon, despite its ability to donate hydrogen bonds (cf. Chapter 3), or as a precursor of reactive species (cf. Chapter 7). This group is found in *SC-71952* (Figure 8.61) and *eflornithine* (Figure 8.27).

8.10.4.2 Perfluoroalkyl Groups The pentafluoroethyl group has just begun to be used in drugs. It is found as an alcohol substituent in *antiprogestine* (Figure 8.78) and at the end of a chain in *fulvestrant* (Figure 8.76). In this latter case, the C_2F_5 group protects the chain from metabolic oxidation, just like a CF_3 does (e.g., *cangrelor*, Figure 8.69).

8.10.4.3 Perfluoroaryl Groups While tetra- and pentafluorinated groups have a specific ability for π-stacking and have a favorable effect on the metabolic stability and log *P* values (close to those of a CF_3), they are rarely found in drugs.[106] Only two pentafluorophenylsulfamides (*T-138067* and *T-900607*, Figure 8.9) and an *etoposide* derivative that has two pentafluorobenzoate groups (*tafluposide*, Figure 8.7) are in development.

8.10.4.4 Fluorocyclopropanes Monofluoro- and difluorocyclopropanes are new structural moieties used in medicinal chemistry.

The monofluorocyclopropane moiety is now introduced as a pure (*S*)-enantiomer on the nitrogen 1 of fluoroquinolones that are in development: *garenoxacine*, *sitafloxacine*, *DK-507k*, *DQ-113*) (Figures 8.18 and 8.20). Synthesis of the precursor (monofluorocyclopropylamine) involves a Curtius reaction. The desired enantiomer is obtained by resolution (Figure 8.20).

It has to be noted that *DQ-113*, *sitafloxacine*, and other fluoroquinolones that are in development (*olamufloxacine*) also have a structurally sophisticated 3-fluoropyrrolidine in position 7 (Figures 8.19 and 8.20).

The difluorocyclopropane motif is found in *zusuquidar*, an inhibitor of the efflux pump (Figure 8.10).

8.10.4.5 Vinylic Fluoride In spite of numerous studies on the inhibition of enzymes by fluorovinylic compounds, six compounds are in development. These are *tezacitabine*, an irreversible inhibitor of RDPR (Figure 8.3; see also Chapter 7), a fluoroquinolone (Figure 8.18), and an epothilone, *ZK-EPO* (Figure 8.7). *SSR-182289* (Figure 8.69) and *Seletracetam* (Figure 8.35) are difluorovinylic compounds. However, except for tezacitabine, the fluorinated moiety does not play an essential role in the inhibition.

APPENDIX: INN AND TRADEMARK NAMES

Only main trademarks are reported. Some of these drugs may have been commercially stopped or withdrawn.

ANTITUMOR AND ANTIVIRAL DRUGS

Capecitabine	Xeloda, Aracytine
Carmofur	HCFU, Mifurol, Mirafur, Yamaful
Clofarabine	Clofar
Doxifluridine	Furtulon, Furzron
Efavirenz	Sustiva, Stocklin, Stocrin
Emtricitabine	Emtriva
Fludarabine	Fludara
5-Fluorouracil	Fluoro-uracil, Efudix,etc.
Gemcitabine	Gemzar
Gefitinib	Iressa
Nilotinib	Tesigna
Socafinib	Nexavar
Tegafur	UFT
Trifluridine	Trifluoridine, Triherpine, Virophta, Viroptic, etc.
Valrubicin	Valstar, Valtaxin
Vinflumine	Javlor

ANTI-INFECTIVE AGENTS

Ciproxacine	Ciflox, Cipro, Cilab, Ciloxan, Ciproxan, etc.
Eflornothine	DFMO, Ornidyl, Vaniqa
Enoxacine	Enoxor, Penetrex, Enoxin, etc.
Fleroxacine	Quinodis Flucytosine *Ancotil*, Ancobon
Flumequine	Apurone
Flomorex	Elmox, Flomex, Floxef, Flumarin
Flubendazole	Fluvermal, Flicum, Flumoxal, Fluverval, Fluvermox
Fluconazole	Triflucan, Beagyne, Diflucan
Flurithromycin	Flurizic, Mizar, Ritro
Flutrimazole	Flusporan, Flutrim, Funcenal, Micetal, Nitral, etc.
Gatifloxacine	Gatiflo, Gaity, Tequin, Bonoq

Halofantrine	Halfan
Levoxacine	Tavanic, Levaquin, Quixin, etc.
Linezolid	Zyvoxid, Zyvox, Zyvoxa, Zyvoxam
Lomefloxacine	Logiflox, Decalogiflox, Maxilin
Mefloquine	Lariam, Mephaquin
Moxifloxacine	Izilox, Avalox, Actira, etc.
Nadiafloxacine	Acuatim, Nadixa
Norfloxacine	Noroxine, Chibroxine, Nolicin, Noflo, etc.
Ofloxacine	Oflocet, Exicine, Monoflocet,Taravid, etc.
Pefloxacine	Peflacine
Rufloxacine	Chiriax, Monos, Qari, Ruxin, Tebraxin, etc.
Sparfloxacine	Zagam, Spara
Tosufloxacine	Ozex, Toskinasin, Tosufloxacin
Tipranavir	*Aptivis*
Trovafloxacine	Alatrofloxacin, Trovan
Voroconazole	Vfend

DRUGS FOR CNS DISORDERS

Neuroleptic

Benperidol	Frenactil, Glianimon
Biriperone	Centbutindole
Bromperidol	Azurene, Bromidol, Consilium, Impromen, etc.
Droperidol	Droleptan, Inapsine, Dehydrobenzperidol
Fluanisone	Sedalande
Fluphénazine	Moditen,Trancin, Permitil
Flupentixol	Fluanxol,Deanxit
Haloperidol	Haldol, Vesadol, Serenase, etc.
Isofloxythépine	Isofloxythépine
Melperone	Buronil, Aplacal, Eunerpan, Flubuperone, etc.
Moperone	Sedalium, Luvatren
Oxaflumazine	Oxaflumine
Penfluridol	Semap
Pimozide	Orap,Opiran
Pipamparone	Dipiperon, Piperonyl
Risperidone	Risperdal, Risolept, Risperdal
Serindole	Serdolect
Timepirone	Tolopelon
Trifluoperazine	Terfluzine, Stelazine, etc.
Triflupromazine	Psyquil,Vestral,Vespril
Trifluperidol	Tripéridol, Psicoperidol

Antidepressant Agents

Citalopram	Seropram, Celexa, Cipramil
Escitalopram	Cipralex, Lexapro, *S*-citalopram Seroplex, Lexapro, Gaudium, *Fluoxetine* Prozac, Fluctin, Fontex, Adofen, etc.

Fluvoxamine	Floxyfral, Dumirox, Dumyrox, Faverin, Feva rin, etc.
Oxaflozane	Conflictan, Doxaflozan
Paroxetine	Deroxat, Apropax, Eutimil, Paxil, Seroxat, etc.

Anxiolytic and Sedative Agents

Cinolazepam	Gerodorm
Doxefazepam	Doxans
Flumazenil	Anexate, Lanexat, Romazicon, Mazicon
Flunitrazepam	Rohypnol, Narcozep, Hypnodorm, etc
Flutozolam	Coreminal
Flutoprezam	Flutan, Restas
Halazepam	Alapryl, Meldrin, Pacinone, Paxipam
Haloxazolam	Somelin
Ethyl Loflazepat	Victan, Meilax
Midazolam	Hypnovel, Diricum, Dormicum, Hypnovel, etc.
Quazepam	Doral, Dormalin, Dorme, Prosedar, Quazium, etc.

Other CNS Drugs

Afloqualone	Arufuto
Flupirtine	Katadolon
Progabide	Gabrene
Riluzole	Rilutek

DRUGS FOR INFLAMATION AND IMMUNITY

Fluorocorticoids

Amcinonide	Penticort, Coderm, Cycloderm
Betamethasone	Célestène, Betnesol, Diprostène, Diprosone, etc.
Clobetasol	Dermoval, Dermovate, Temovate
Desoximetasone	Topicort, Topifran (stopped in France)
Dexamethasone	Decadron, Soludedecadron, Dectancyl, Maxidex, etc
Diflorasone	Flutone, Diacort, Difulal, Florone, etc.
Fluazacort	Azacortid
Diflucortolone	Nérisone
Fludrocortisone	Fludrohydrocortisone, Alflorane, Florinef
Difluprednate	Epotopic, Myser
Fludroxycortide	Cordron, Drenison,
Flumethasone	Locacorten, Locasalene, Flucort
Flunisolide	Bronilide, Nasalide, etc.
Fluocortolone	Ultralan, Ultralanil, Ultraproct
Fluclorolone acetonide	Topilar (stopped)
Fluocinonide	Topsyne
Fluocortin	Vaspit
Fluorometholone	Flucon

Fluticasone	Flutinase, Flixotide, Flixonase, etc.
Halobetasol	Miracorten, Ulobetasol, Ultravate
Halomethasone	Sicorten
Halopredone	Topicon, Haloart
Paramethasone	Dilar (stopped)
TBI-PAB	Taucorten
TO-186	Antebate
Triamcinolone	Kenacort, Hexatrione, Nasacort, etc.

Antiallergic Antiasthmatic Agents

Almitrine	Vectarion, Duxil, Duxor
Astemizole	Hismanal, Histamen, Cilergil, etc.
Flutropium bromide	Flubron
Levocabastine	Levophta, Livostin, Cabastine, etc.
Mabuterol	Broncholin
Mizolastine	Mistaline, Mizollen, Izollen, etc.
Ramatroban	Baynas

NSAIDs and Other Drugs for Analgesia and Arthritis

Celecoxib	Celebrex, Algitrat X, Celabrex, Niflam, etc.
Lumiracoxib	Prexige
Diflunisal	Dolobis, Dolobid, Diflusal, etc.
Anthrafenine	Stakane
Etofenamate	Bayrogel, Flogol, Medeverine, Reumon, etc.
Floctagenine	Idarac, Duralgin, Idaron, etc.
Flufenamique (acid)	Arlef, Achless, Flunalgan, etc.
Flurbiprofen	Cebutid, Antadys, Ansaid, Flurprofen, Ocufen, etc.
Glafenine	Glifanan, Glifan, Anagil
Leflunomide	Arava
Niflurique (acid)	Nifluril, Flunir, Actol, Niflam, etc.
Sulindac	Arthrocine, Clinoril, etc.
Talniflumate	Somalgen, Lomucin
Triflusal	Aflen, Disgren, Tecnosal, Triflux
Ufenamate	Combec, Fenazol

DRUGS FOR CARDIOVASCULAR DISORDERS

Atorvastatin	Tahor, Lipitor, Atorlp, Prevencor, etc.
Benfluorex	Mediator, Benfluramate, Mediaxal, etc.
Bendroflumethiazide	Precyclam, Tensioforme, Naturine,Naturetin,. . .
Butofilolol	Cafide (retiré)
Ezetimide	Zetia, Ezetrol
Flecainide	Flécaine, Tambucor
Flunazirine	Sibelium, Vasculoflex, Vertix, etc.

Fluindione	Préviscan
Fluvastatin	Lescol, Fractal, Canef, Cranoc, Lescul, etc
Hydroflumethiazide	Leodrine (stopped in France), Saludron, Vergonil, etc.
Ketanserine	Sufrexal, Ketensin, Serepress, Aseranox
Lidoflazine	Clinium, Corflazine, Klinium, Ordiflazine
Lomerizine	Lomérizine
Nebivolol	Nebilox, Lobivon, Nebilet, Silostar, etc.
Paraflutizide	Tensitral
Pitastatin	Ribar
Rosuvastatin	Crestor

DRUGS FOR GASTRO INTESTINAL DISORDERS

Aprepitant	Emend
Cisapride	Prepulsid, Alimix (withdrawn)
Lansoprazole	*Oga*st, *Lanzor*, Agopton, Prevacid, etc.
Flumecinol	Zixoryn
Mosapride	Gasmotin
Pantoprazole	Eupantol, Inipomp, Pantorc, Pantopan, Protium, etc.

DRUGS FOR ENDOCRINE DISORDERS

Bicalutamide	Casodex
Cinacalcet	Minpara, Sensipar
Dutasteride	Avodart, Avolve
Falecalcitriol	Hornel, Fulstan, Hexafluorocalcitriol, etc.
Flutamide	Eulexin, Prostadirex, Drogenil, Flucinom, Odyne, etc.
Flumedroxone	Demigran
Floxymesterone	Halotestin, Ultrandren, Oratestin, etc.
Fulvestrant	Faslodex
Nilutamide	Anandron, Nilandron, etc.

MISCELLANEOUS

Difluorophate	Diflupyl
Iodopane	DatScan
Nitisome	Orfadin
Travoprost	Travatan, Fluprostenol

ANESTHETICS AND PERFLUOROCARBONS

Cryofluorane	Cryofluorane, Cryospray
Desflurane	Suprane
Enflurane	Alyrane, Ethrane
Halothane	Halothane, Fluotan
Hexafluorure de soufre	Sonovue
Isoflurane	Aerrane, Forene, Forane, Nederane, etc

Methoxyflurane	Penthrane
Optizon	FS-069, FS-69 (pre registered)
Perflexane	Imagent US, Imavist
Sevoflurane	Sevorane, Sevofane, Ultane

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