CHAPTER 5

Biologically Active Organofluorine Compounds

5.1
Fluorine Effect in Biological Activity

One of the important applications of fluorinated organic compounds is in medicinal chemistry. Recent progress in organofluorine chemistry has contributed significantly to the great advances in modern medical treatments. With the aid of the known influence of a fluorine atom on physical, chemical, and biological phenomena therapeutic efficacy has been increased and pharmacological properties improved [1–3].

Resources of naturally occurring fluorinated organic compounds are limited to a small number of tropical and subtropical plants and microorganisms. They are monofluoroacetic acid, ω-fluoro fatty acids, nucleocidin, and 4-fluorothreonine, etc. (Fig. 5.1). In 1944, Marais identified fluoroacetate in the leaves of the South African shrub *Dichapetalum cymosum*, and its biomedical mechanism of toxicity in mammals was elucidated by the research of Peters [4].

In 1953, Fried published a pioneering work on the preparation of 9α-fluorohydrocortisone acetate (Fig. 5.2) [5]. Utilization of fluorination as a tool to en-

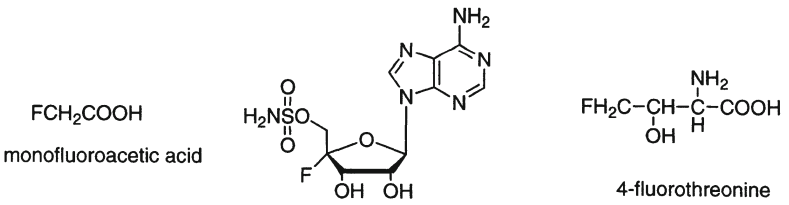


Fig. 5.1

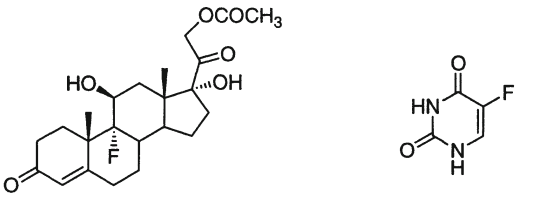


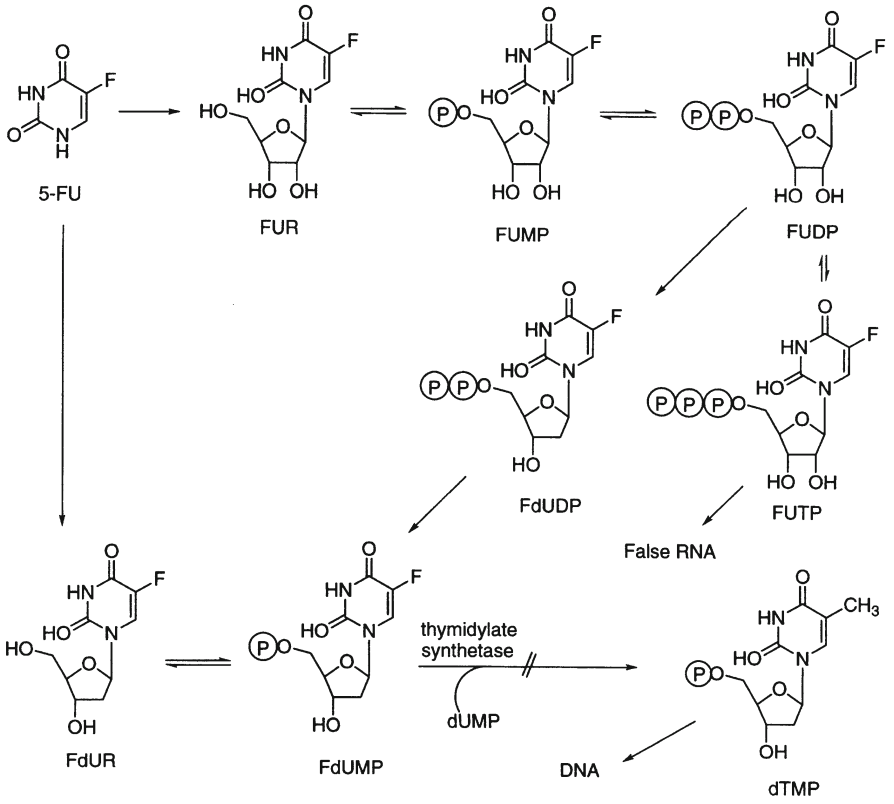
Fig. 5.2

T. Hiyama, *Organofluorine Compounds*

hance biological activity and to improve the versatility of a biologically active substance was thus clearly demonstrated. The report by Fried stimulated pharmaceutical researchers to routinely introduce fluorine as a substituent to modify original biological activity.

Another significant finding in the late 1950s was that 5-fluorouracil (5-FU, Fig. 5.2) exhibits significant tumor-inhibiting activity [6], a discovery made through the synthesis of novel nucleic acids by substituting fluorine for hydrogen in naturally occurring pyrimidines and purines. 5-FU and its nucleoside, 5-fluoro-2′-deoxy-β-uridine (FdUR), are anabolized to 5-fluoro-2′-deoxyuridylate (FdUMP), and the FdUMP competitively inhibits thymidylate synthetase, an enzyme which normally converts 2′-deoxyuridylic acid into thymidylic acid (dTMP), an essential component of DNA (Scheme 5.1). 5-FU has been employed with success for the treatment of human breast cancer and several other types of malignancies [1e].

In the 1960s and 1970s, the development of novel fluorine-containing drugs and biomedical applications became a steady stream thanks to new reagents and techniques for site-selective introduction of fluorine into organic molecules. The development of new fluorinating agents and modifications to fluori-



Scheme 5.1. Biological mechanism of 5-FU

nation procedures using conventional agents contributed greatly to the present rapid progress in this field.

An understanding of the fundamental biochemical mechanisms, coupled with knowledge of the physicochemical properties affected by fluorine substitution, has aided the rational design of many pharmaceutical drugs and pharmacological agents. Fluorinated analogs also serve as excellent probes for biochemical mechanisms. For example, many ^{19}F-NMR studies have demonstrated the utility of fluorine-labeled proteins as mechanistic tools [7]. A positron-emitting isotope of ^{18}F is also used to label a variety of organic molecules for studying biochemical transformations and distribution in the mammalian body.

A wide variety of effective fluoromedicines have been developed and put into the pharmaceutical marketplace, including steroidal and non-steroidal (NSAIDs) anti-inflammatory agents, anticancer and antiviral agents, antihypertensive agents, and central nervous system drugs for the management of mental illnesses such as depression and psychoses.

Fluorine has a small van der Waals radius of 1.35 Å (Pauling), close to that of hydrogen (1.20 Å), and thus mimics hydrogen at an enzyme receptor site with respect to steric requirement. On the other hand, the van der Waals radius estimated by Bondi is 1.47 Å, only 20% larger than that (1.20 Å) of hydrogen [8]. The C–F bond length, 1.38 Å, is comparable to that of the C–H, 1.10 Å, and C-O bond lengths, 1.43 Å. This means that such substitution will have little effect on the steric bulk of a molecule. However, the steric effect (*Es*) of a CF_3 group, according to an estimation based on the hydrolysis constant of α-substituted (*R*)-acetic acid ester, is −2.40, closer to −1.78 of an isopropyl group and larger than −1.24 of a methyl group (Table 5.1) [9, 10].

Table 5.1. Substituent constants of aliphatic and aromatic compounds

Substituent (R)	Steric effect (*Es*)[a]	Aliphatic compound hydrophobicity (π_R)[b]	Aromatic compound hydrophobicity (π_R)[b]
H	0.00	0.00	0.00
F	−0.46	−0.16	0.14
Cl	−0.97	−0.17	0.71
Br	−1.16	−0.03	0.86
OH	−0.55	−1.87	−0.49
NO_2	−1.01	−1.39	−0.28
CF_3	−2.40	0.06	0.88
CH_3	−1.24	0.54	0.56
C_2H_5	−1.31	1.08	1.02
$(CH_3)_2CH$	−1.78		
$(CH_3)_3C$	−2.78		1.98
CN	−0.51	−1.50	−0.57

[a] *Es*: Steric effect, estimated based on the hydrolysis constant of α-substituted (*R*)-acetic acid ester.

[b] π_R: Hydrophobicity; $\pi_R = \log P_R - \log P_H$, P = partition coefficient between 1-octanol and water.

Fluorine is the most electronegative element: the Pauling electronegativity is 4.0; cf. 3.5 for oxygen, 3.0 for chlorine and 2.8 for bromine. The high electronegativity of fluorine influences the electron distribution in a molecule, affecting the acidity or basicity of the neighboring group, the dipole moment within the molecule, and the overall reactivity and stability and, consequently, changes the chemical and physical properties drastically.

A C–F bond is the strongest among halogen–carbon bonds: heat of formation of a C–F bond is 456–486 kJ/mol; that of a C–Cl bond is roughly 350 kJ/mol, comparable to a C–H bond of 356–435 kJ/mol. The strong bond energy of C–F bonds contributes to the high thermal and oxidative stabilities of organofluorine compounds.

Introduction of a fluorine atom usually increases lipid solubility, enhancing rates of absorption and transport of drugs in vivo. As shown in Table 5.1, the substitution of fluorine for hydrogen slightly increases the lipophilicity. In contrast, a polyfluorinated substituent, such as a trifluoromethyl group, induces lipophilicity much more than a methyl group or a chlorine substituent [3b]. This fact often contributes to the improvement in pharmacological activity.

The electronic properties of a F–C bond and its biological effects are understood in the way discussed in Chap. 1.1.3. A fluorine atom on an sp^3 carbon causes a pronounced electron-withdrawing effect through a relay of induced dipoles along a chain of bonded atoms. This effect is called the sigma withdrawing effect, $-I_\sigma$. The electron-withdrawing effect may also be induced by a through space electrostatic interaction. This is known as a field effect. Thus, a fluorine atom in a monofluorinated molecule often acts as an acceptor of a hydrogen bond [3b] (see Fig. 1.1, Chap 1).

The electronic effect of fluorine attached directly to an sp^2 carbon in a π-system is especially complex, because unshared electrons on fluorine may be donated back to the π-system. This resonance effect is called a $+I_\pi$ repulsive interaction. Thus, the electron-withdrawing $-I_\sigma$ effect of a fluorine substituent on an aromatic ring is canceled by the electron-donating $+I_\pi$ effect particularly in an *ortho* or *para* position. Consequently, monofluorination of an aromatic compound brings little steric and electronic effect. However, since a C–F bond is stable and able to form preferentially an intramolecular hydrogen bond, fluorine substitution is considered a tool for drug design. In contrast, a trifluoromethyl group on an sp^3 or sp^2 carbon shows a strong electron-withdrawing effect.

It is well recognized that fluorine stabilizes an α-cationic center by the interaction of a vacant p-orbital of a carbocation with the filled orbitals of fluorine. However, a CF_3 group strongly destabilizes an α-cationic center in sharp contrast to a methyl group.

In general, a carbocation at a β-position of a fluorine atom is destabilized by the –I effect. Thus, it is difficult to generate a β-fluoro carbocation. This distinct substitution effect has been successfully applied to the stabilization of biomolecules otherwise unstable under neutral or physiological pH circumstances. Some examples are seen in prostaglandins and thromboxanes (see Fig. 1.4, Chap. 1).

In contrast, a carbanionic center substituted by fluorine is generally destabilized through I_π repulsive interactions, but the one that has a fluorine atom

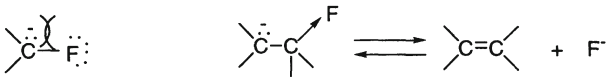


Fig. 5.3 α-Carbanion β-Carbanion

at a β-position is stabilized by an electron-withdrawing effect (Fig. 5.3); sometimes an elimination reaction may be induced and vice versa. An example accounted for by these characteristics is a suicide inhibitor such as α-fluoromethylglycine.

5.2 Strategies for Design and Synthesis

5.2.1 *Structure-Activity Relationship*

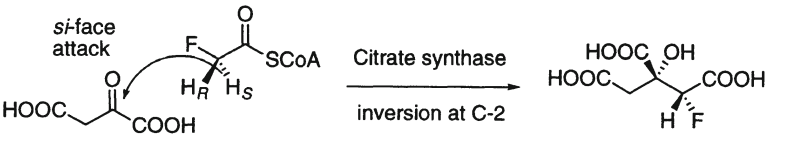
Of all the elements, fluorine is the most electronegative and forms the strongest single bond with carbon, a bond of an extremely large dissociation energy, whereas the presence of fluorine in a molecule has minor steric but potentially drastic electronic consequences.

Fatty acids having fluorine at a ω-carbon, $FCH_2(CH_2CH_2)_nCOOH$, are metabolized and degraded to fluoroacetic acid by β-oxidation in a way similar to normal fatty acids [4] (see Scheme 1.2, Chap. 1). The resulting fluoroacetic acid is incorporated into the metabolic system of mammals in a similar way to acetic acid, because the bulkiness of a fluorine atom is not discriminated. Fluoroacetic acid is first activated to fluoroacetyl-CoA by citrate synthase into (*2R,3R*)-2-fluorocitric acid, a common co-metabolite of fluoroacetic acid, arising from the condensation of fluoroacetyl-CoA with oxaloacetic acid. The biosynthetic pathway is illustrated in Scheme 1.1 in Chap. 1.

The stereochemical course of the citrate synthase reaction with fluoroacetyl-CoA is stereospecific and the 2-*pro-S* hydrogen of fluoroacetyl-CoA is abstracted exclusively. This observation demonstrates restricted rotation around the C–C bond of the fluoroacetyl moiety when bound to the enzyme. Thus, stereoelectronic control is operating during the reaction. The condensation reaction proceeds with inversion of configuration at C-2 to generate (*2R,3R*)-2-fluorocitric acid as the only stereoisomer as shown below. The enzyme of mammals distinguishes between the hydrogen and fluorine atoms and, moreover, recognizes the *pro-S* and *pro-R* hydrogen atoms.

The toxicity of fluoroacetic acid against mammals is attributed to the *lethal synthesis* of (*2R,3R*)-2-fluorocitric acid by citrate synthase; the other three stereoisomers are nontoxic [11]. (*2R,3R*)-2-Fluorocitric acid is a competitive inhibitor of aconitase, an enzyme that follows the citrate synthase in the citric acid cycle and interconverts citric and isocitric acids. Consequently, fluoroacetic acid blocks the citric acid cycle as a poison. More recently, the inhibition

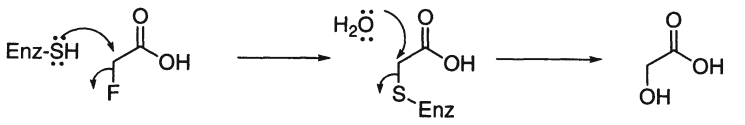
of the citrate transformation has been demonstrated to be a decisive factor in the toxicity of fluoroacetic acid [12].



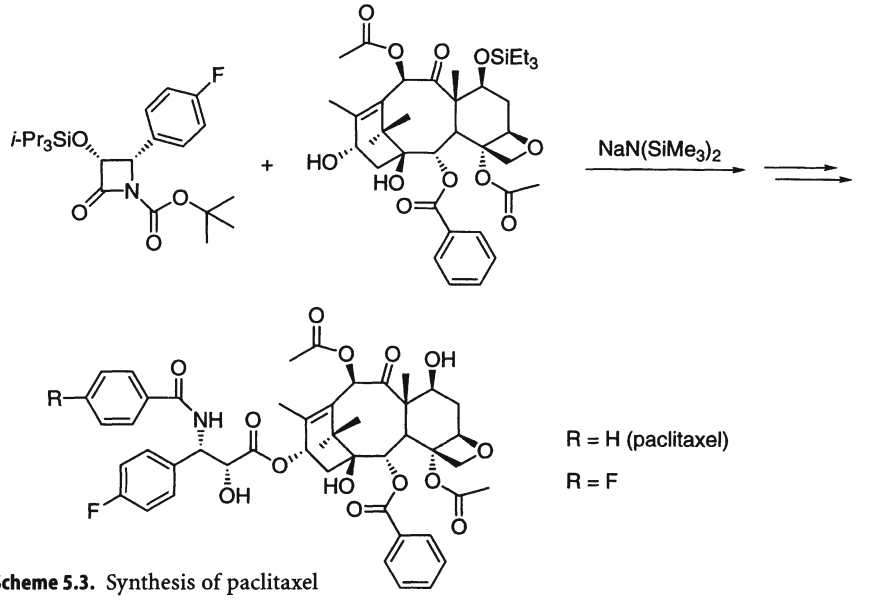
(5.1)

(2*R*,3*R*)-Fluorocitric acid

On the other hand, an enzyme that mediates the conversion of fluoroacetic acid to glycolic acid has been isolated from a number of microorganisms using fluoroacetic acid as the sole carbon source, e.g. *Pseudomonas* spp. and *Fusarium solani* [4]. A mechanism for this transformation is proposed as follows: a thiol group of the enzyme attacks fluoroacetic acid, displacing fluorine to form an α-thioacetic acid, which is subsequently attacked by a water molecule to release glycolic acid, as illustrated in Scheme 5.2.



Scheme 5.2. Metabolic transformation of fluoroacetic acid



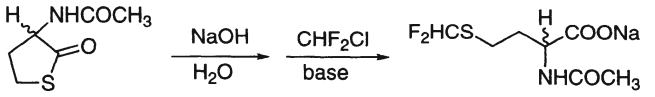
Scheme 5.3. Synthesis of paclitaxel

Replacement of hydrogen in an agent by fluorine can alter the reactivity and thus change the biological efficiency. Structural modifications in relation to biological activities, i.e. structure-activity relationships (SARs), have been studied extensively on the basis of molecular modeling and molecular mechanics calculations. There are numerous data on SARs of fluorinated agents such as quinolone carboxylic acid antibacterials [13], β-lactam antibiotics [14], vitamin D_3 analogs [15], HIV protease inhibitors [16], prostacyclins [17], angiotensin converting enzyme (ACE) inhibitors [18], and taxoids [19], etc. In particular, a series of fluorine-containing taxoids, extremely potent new therapeutic agents in the treatment of metastatic breast and ovarian cancers, have been synthesized, and the activities studied in relation to the conformation in solution (Scheme 5.3).

With respect to a central nervous system agent, a fluorine substituent in a drug may increase the lipophilicity to facilitate its transport across a blood-brain barrier, a principal diffusion barrier separating brain and blood [20] and, as a result, enhance the absorption rate.

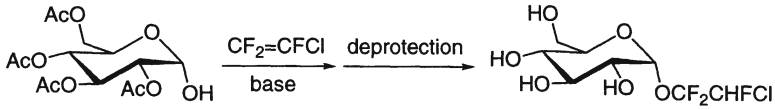
5.2.2
Commercially Available Fluorinated Materials

Thanks to the remarkable growth in the fluorochemical industry, many fluorinated organic compounds of relatively low molecular weights are now available. Examples are HCFCs (hydrochlorofluorocarbons), HFCs (hydrofluorocarbons), alternatives of CFCs (chlorofluorocarbons), and key intermediates of fluoropolymers, which are used as building blocks for the construction of a variety of desired fluorine-containing molecules [21]. Chlorodifluoromethane, for example, is employed for the synthesis of difluoromethyl sulfides and difluoromethyl ethers [22].



(5.2)

Tetrafluoroethylene (TFE, $CF_2=CF_2$) and chlorotrifluoroethylene (CTFE, $CF_2=CFCl$) are transformed to tetrafluoroethyl ethers and chlorotrifluoroethyl ethers [23], respectively. An application to glycosidation is illustrated in Eq. (5.3). Hexafluoropropene and hexafluoropropene oxide (HFPO) are versatile building blocks for the synthesis of fluorinated nucleoside analogs.



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Fluorosulfonyldifluoroacetates ($FSO_2CF_2CO_2R$) are some of the most important intermediates for the preparation of perfluorinated ion-exchange

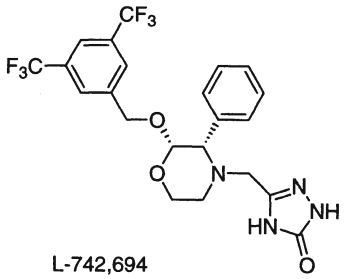


Fig. 5.4 L-742,694

membranes. The ester undergoes a trifluoromethylation reaction of aromatic halides in the presence of a copper catalyst at 80–120 °C (Chap. 3.1.1) [24, 25]. The reagent CF_3-Cu is considered to be responsible for the reaction. Difluorohaloacetates (XCF_2COOR; X=Cl, Br, I) are widely employed for the synthesis of difluorinated sugars [26], nucleosides [27], prostanoids [28], and peptide mimetics [29], etc.

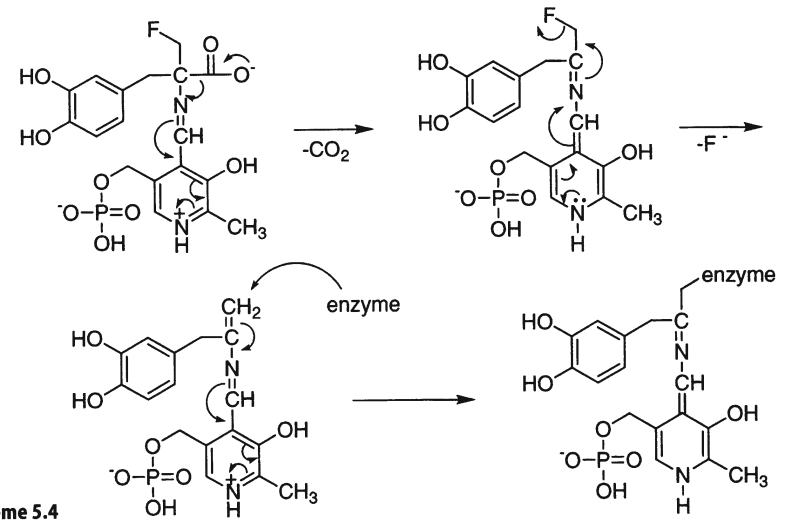
Numerous fluorinated aromatic compounds are commercially available and can be converted into many biologically active compounds [30]. Recently, a 3,5-bis(trifluoromethyl)benzyl unit has been widely used for potent pharmaceutical drugs. A typical example is the morpholine-based human NK-1 antagonist exemplified in Fig. 5.4 [31].

5.3 Fluorinated Amino Acids and Carbohydrates

5.3.1 *Amino Acids*

Elucidation of the physiological roles of a specific enzyme has led to the design of highly selective enzyme inhibitors useful for practical applications. Irreversible inactivation of an enzyme is caused by the incorporation of an inactivator into an enzyme-active site and by a normal catalysis through proton abstraction, isomerization, elimination, or oxidation leading to a reactive species which is capable of reacting irreversibly with the active site. Since the enzyme becomes inactivated by its own action mechanism, such inhibitors are referred to as *suicide inhibitors* [1–3]. Many fluorinated amino acids are potent enzyme inactivators [32, 33].

Fluoromethyl-substituted amino acids are known to inhibit an enzymatic decarboxylation reaction. Loss of carbon dioxide and elimination of a fluoride ion from an intermediate Schiff base, formed from pyridoxal phosphate and a fluoromethyl amino acid, are thought to induce an enzymatic inactivation (Scheme 5.4). Elimination of a fluoride ion generates a reactive Michael-type acceptor, which is then attacked by a nucleophilic functional group in the enzyme. The covalently bound enzyme is no longer free to bind an additional substrate.



Scheme 5.4

Amino acids substituted by a difluoromethyl group at an α-position are also effective inhibitors of decarboxylases. Difluoromethyl ornithine [34] was found to inhibit ornithine decarboxylase and intrude polyamine synthesis, a step needed for growth and development, and was implied to be an effective antigestinal, antitrypanosomal, anticoccidal, and antitumor agent. In general, the introduction of a fluoromethyl group at an α-carbon enhances the potency and efficiency of α-amino acids. α-Monofluoromethyl-dopa, for example, has selective peripheral activity (Fig. 5.5) [2].

Syntheses of fluorinated amino acids are carried out mainly by two methods. One is based on an amino acid synthesis using fluorinated building blocks, the other is the fluorination of non-fluorinated precursors. A straightforward route is an amine substitution of an α-halo acid or ester with ammonia or an equivalent such as sodium azide or potassium phthalimide (Scheme 5.5).

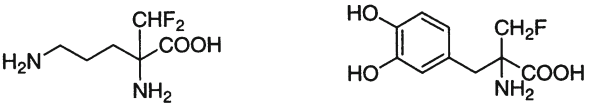
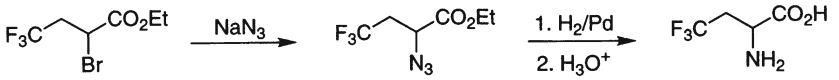
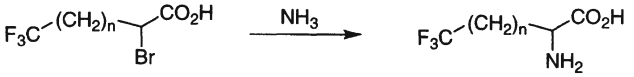


Fig. 5.5 difluoromethyl ornithine fluoromethyl dopa



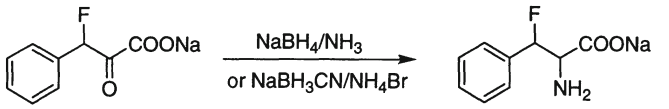
Scheme 5.5

When a substrate has a strongly electronegative CF_3 or CF_2 group at a β-position, the halogenated ester may be converted into an α-azido derivative without elimination or formation of an isomeric β-amino acid.



(5.4)

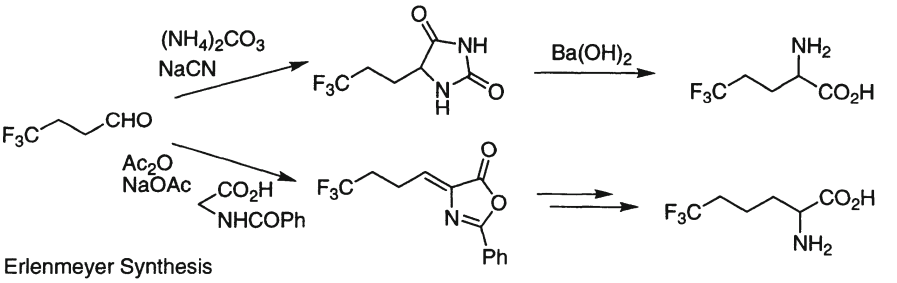
It is well known that α-keto acids are transformed to the corresponding α-amino acids by reductive amination [35]. The key intermediates [33] are imines, oximes, or phenylhydrazones. The reaction may be carried out by an enzymatic reaction using a transaminase to give optically active amino acids [36].



(5.5)

Fluorinated amino acids can also be prepared by the Strecker or hydantoin synthesis from aldehydes. The Erlenmeyer azlactone synthesis can also be applied to the synthesis of aromatic and aliphatic fluorinated amino acids under two-carbon elongation (Scheme 5.6) [33]. Enantioselective hydrogenation of dehydro amino acids in the presence of an asymmetric catalyst is now a powerful tool for the asymmetric synthesis [32, 37].

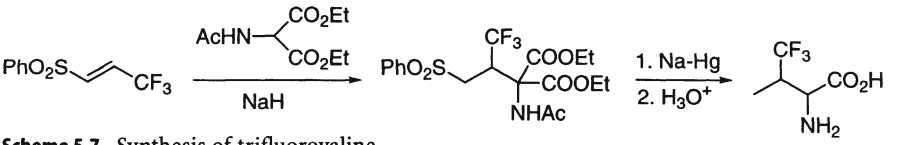
Strecker Synthesis



Erlenmeyer Synthesis

Scheme 5.6. Chemical synthesis of amino acids

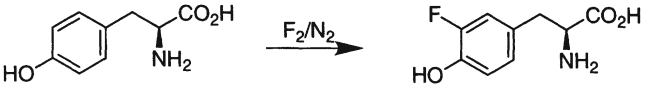
Alkylation of acetamidomalonates with a fluorinated electrophile is convenient for the synthesis of α-amino acids. For example, ω-fluoroalkyl bromides are converted into the corresponding ω-fluoro amino acids under two-carbon elongation. Conjugate addition of acetamidomalonates to a trifluoromethyl-substituted Michael acceptor, phenyl 3,3,3-trifluoro-1-propenyl sulfone, gives, after reduction, 4,4,4-trifluorovaline (Scheme 5.7) [38].



Scheme 5.7. Synthesis of trifluorovaline

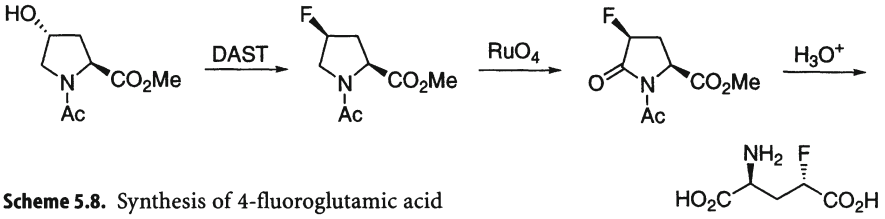
Introduction of fluorine or a fluorine-containing group into a synthetic intermediate and a natural amino acid is an alternative approach to a diversity of unnatural fluorinated amino acids. For example, alkylation of α-amino acids with fluorinated alkyl halides, such as CF_2CHCl, gives α-fluoroalkyl α-amino acids. Using an electrophilic fluorinating reagent, α-fluoro α-amino acids are easily prepared. Starting with this amino acid as a component, fluorinated oligopeptides are prepared [39].

Fluorination of tyrosine with F_2/N_2 gives 3′-fluorotyrosine exclusively [40, 41].



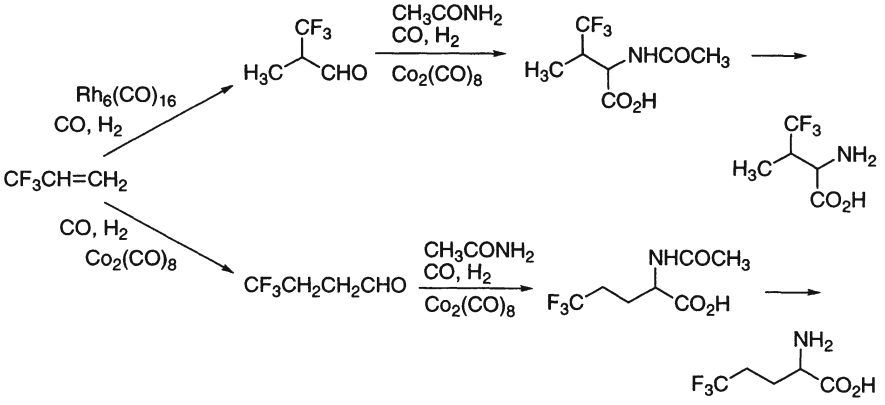
(5.6)

Treatment of a 4-hydroxyproline derivative with DAST gives a 4-fluoro derivative with inversion of configuration. This process has been applied to the synthesis of all four stereoisomers of 4-fluoroglutamic acid (Scheme 5.8) [42].



Scheme 5.8. Synthesis of 4-fluoroglutamic acid

The amidocarbonylation reaction (Wakamatsu reaction) of 2-(trifluoromethyl)propanal and 3-(trifluoromethyl)propanal gives 4,4,4-trifluorovaline and 5,5,5-trifluoronorvaline, respectively. The starting aldehydes are derived from regioselective hydroformylation of 3,3,3-trifluoropropene catalyzed by $Co_2(CO)_8$ or $Co_2(CO)_8$-$Rh_6(CO)_{16}$ (Scheme 5.9) [43]. Asymmetric syntheses of



Scheme 5.9. Synthesis of trifluoromethyl-containing amino acids from trifluoropropene

fluorinated amino acid derivatives by an aldol reaction of isocyanoacetate esters and further transformation to fluorine-containing peptides have also been achieved [32, 37, 44].

5.3.2
Protease Inhibitors

The search for a specific, orally active protease inhibitor has become an important strategy for the effective treatment of such diseases as metastatic cancer, malaria, arthritis, sleeping sickness, AIDS, etc. Introduction of fluorine is now the key to the discovery of clinical candidates, as demonstrated by several examples.

A trifluoromethyl ketone is highly electrophilic when connected to an enzyme via a hydrate form, a tetrahedral structure that mimics the transition state of an enzymatic hydrolysis. The tetrahedral intermediate is a potent reversible inhibitor. A typical example is an inhibitor of human leukocyte elastase (HLE). Serine protease, produced by neutrophiles, is closely related to the body's inflammatory defense mechanism. Imbalance of extracellular elastase levels induces many diseases such as rheumatoid arthritis, smoking-induced emphysema, and cystic fibrosis. A selective HLE inhibitor has been found that consists of a trifluoromethyl ketone moiety in addition to a tripeptide backbone containing an N-substituted glycine residue (Fig. 5.6) [45].

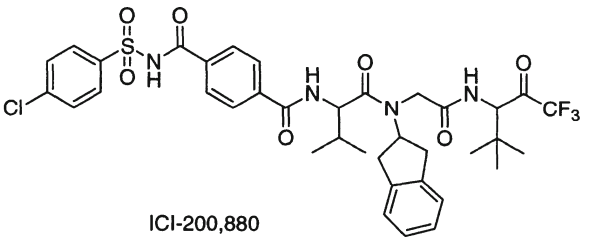
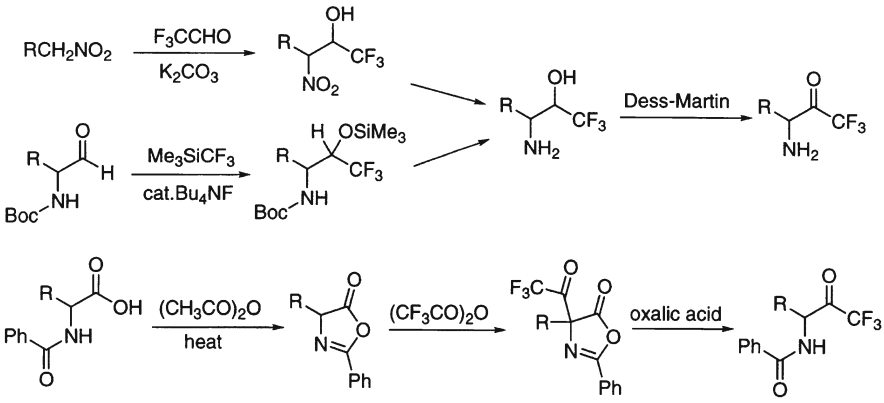


Fig. 5.6 ICI-200,880

Its key component, an α-amino trifluoromethyl ketone or its precursor trifluoromethyl α-amino alcohol, is prepared by condensation of a nitroalkane with trifluoroacetaldehyde [46], by trifluoromethylation of an α-amino aldehyde with CF_3SiMe_3 catalyzed by TBAF, or by trifluoroacetylation of oxazolidinone followed by hydrolysis (Scheme 5.10) [47, 48]. A nitro aldol condensation (Henry reaction) is also effective in the synthesis of α-amino monofluoromethyl carbonyl derivatives [49]. A hydrochloride salt of valine pentafluoroethyl ketone is prepared by alkylation of *N*-Boc valine methyl ester with pentafluoroethyllithium prepared in situ from ICF_2CF_3 and MeLi · LiBr at −78 C [50].

Aspartyl protease, called renin, cleaves the protein substrate angiotensinogen into decapeptide angiotensin I which, in turn, is cleaved into octapeptide angiotensinogen II. Highly potent inhibitors of renin are revealed to commonly contain statine, a novel amino acid present in a naturally occurring pepsin inhibitor called pepstatin. A difluorostatine-containing peptide is also



Scheme 5.10

a potent renin inhibitor, more potent than the non-fluorinated analog. Due to fluorine functionality, the carbonyl group in difluorostatone becomes much more electrophilic than statine to facilitate addition of water to form a tetrahedral species, a transition state analog, akin to the one formed during the enzyme-catalyzed hydrolysis of a peptide bond. A typical example is shown in Fig. 5.7 [51].

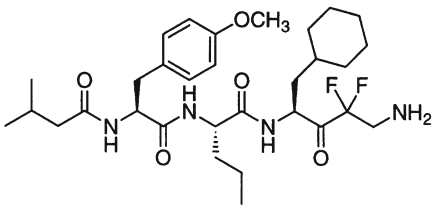
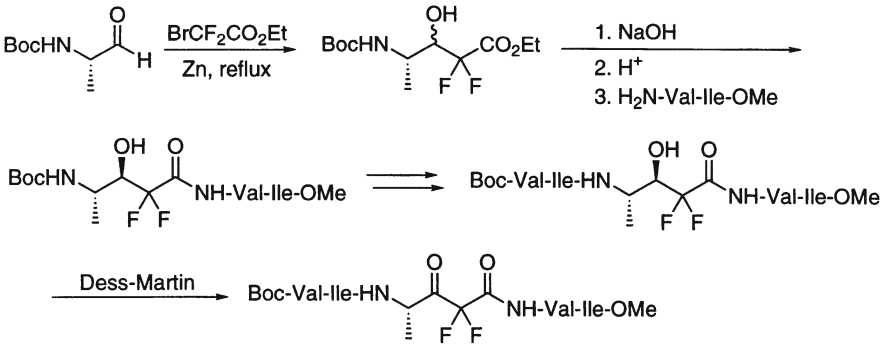


Fig. 5.7

A human immunosuppressive virus (HIV)-encoded protease, required for the post-translational processing of polyprotein gag and gag/pol gene products, has attracted enormous attention as a potential chemotherapeutic target for the treatment of HIV infection. Cellular penetration is required in the design of effective HIV protease inhibitors. New inhibitors, small and lipophilic molecules based on the difluorostatone-type transition state mimic, have been suggested [52].

A peptidomimetic having a difluoro ketone moiety has been demonstrated recently in the study of amyloid plaque formation and the pathogenesis of Alzheimer's disease. The difluoromethylene unit is prepared by a Reformatsky reaction of ethyl bromodifluoroacetate with an N-protected amino aldehyde followed by oxidation. The peptide analog of α,α-difluoro β-keto amide (see below) enhances the permeability and localization to the membrane in a cell-based assay through the retained N- and C-terminal protecting groups and selectively inhibits the production of a β-amyloid precursor protein (Scheme 5.11) [53].



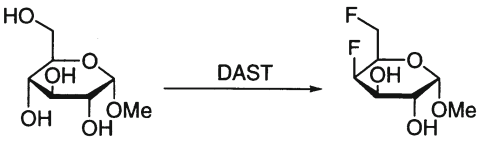
Scheme 5.11. Synthesis of fluorine-containing oligopeptides

5.3.3
Carbohydrates

Selectively fluorinated carbohydrates [54] serve as proof of biochemical mechanisms and for the modification of the glycoside activities and thus have many applications in biochemistry, medicinal chemistry, and pharmacology. The first synthesis of fluorinated carbohydrates was carried out by Moissan, the discoverer of elemental fluorine, who recorded a reaction between F_2 and glucose in his monograph in 1890 [55]. Due to the biological potency of fluoro sugars, growing interest has been focused expeditiously on fluoro sugar chemistry over the last 30 years. The activity of fluoro sugars is mostly attributed to the size (or the bond length plus van der Waals radius) 2.74 Å of a C–F bond, similar to the size of the C-O moiety of a C-OH group, 2.83 Å, and also to the capability of a C–F bond to participate in hydrogen bonding owing to the large electronegativity of fluorine. In other words, replacement of a hydroxyl group by fluorine in a carbohydrate residue causes a profound electronic effect to neighboring groups with a very minor steric perturbation of the original structure or conformation.

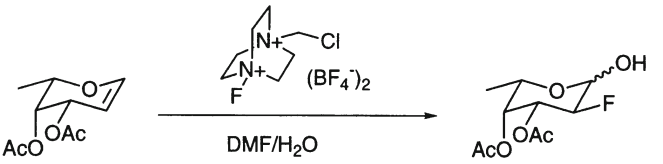
Fluorinated carbohydrates are synthesized by a sophisticated combination of modern chemical and enzymatic techniques, because requirements are strict for the stereochemical control at multiply continuing asymmetric centers. Numerous methods have been invented for the preparation of fluorinated neutral sugars, amino sugars, and branched sugars. Typical fluorination methods are a fluoride displacement reaction of sulfonate esters (reagent: KF, CsF, R_4NF), a fluorinating dehydroxylation with diethylaminosulfur trifluoride (DAST) or reagents of a similar type, epoxide or aziridine ring opening by a fluoride ion (reagent: HF, $(HF)_x \cdot$pyridine, R_4NF, KHF_2), an addition reaction of fluorine to a C=C bond (reagent: F_2, XeF_2, CF_3OF, CH_3COOF), and a fluorination reaction of >C=O groups (reagent: DAST) [54, 55]. In particular, a profound effect of neighboring group participation at a cationic center and a 1,3-diaxial or 1,2-steric effect should be considered in

these transformations. A typical example is the reaction of methyl α-D-*gluco*-pyranoside with neat DAST to give 4,6-dideoxy-4,6-difluoro-α-*galacto*-pyranoside [55].



(5.7)

Recently, a stereoselective synthesis of 2-deoxy-2-fluoro sugars was accomplished by the reaction of the corresponding glycals with a commercially available electrophilic fluorination reagent, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) [56].



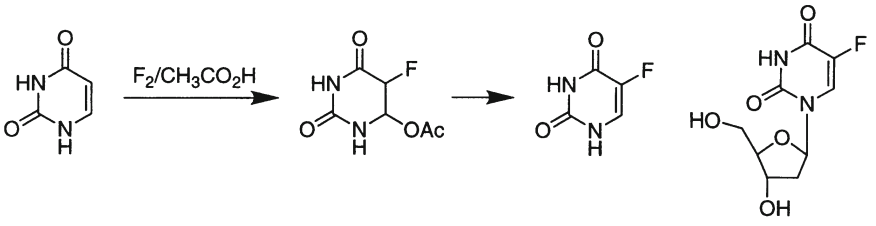
(5.8)

5.3.4 *Nucleosides*

The adenine-containing antibiotic nucleocidin (Fig. 5.1), the sole naturally occurring fluorinated nucleoside [57], displays a broad spectrum of antibiotic activities and is a particularly effective antitrypanosomal agent [58].

It is well known that substitution of a 3- or 5-hydroxyl group of a nucleoside with fluorine inhibits its transformation to a phosphonate ester, and fluorine at C-2, namely next to a glycosyl bond, generally enhances the stability of the glycosyl bond through an electron-withdrawing effect.

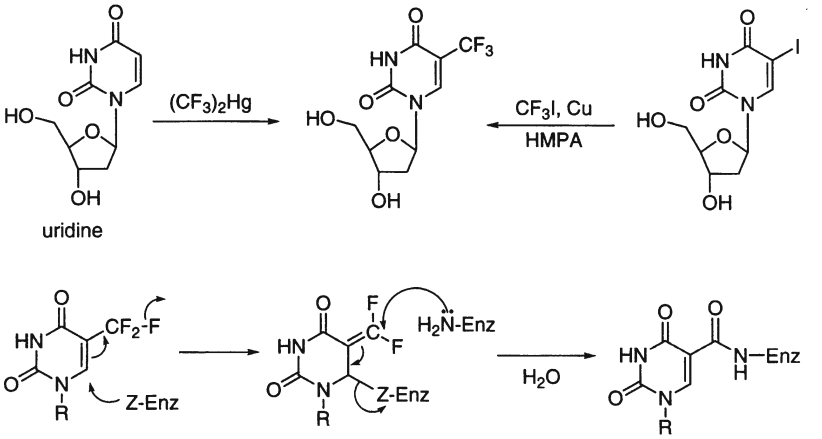
Anticancer Agents. For the treatment of leukemia and solid tumors, many fluorinated pyrimidine and purine nucleosides (and their nucleotides) have been synthesized that are less toxic and more effective than 5-fluorouracil. Presently, 5-fluorouracil is prepared by direct fluorination of uracil in acetic acid (Scheme 5.12). 2′-Deoxy-5-fluorouridine (FdUR) exhibits superior antitumor activities to its mother compound [1c].



Scheme 5.12

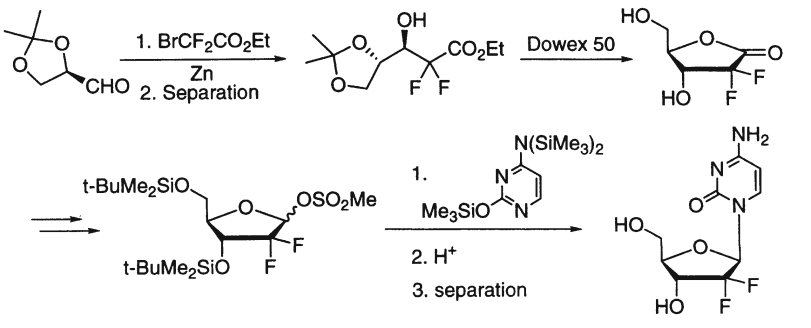
FdUR

The reaction of uridine with $(CF_3)_2Hg$ is effective for the introduction of a trifluoromethyl group to give 5-trifluoromethyluridine [59]. This is prepared conveniently by the coupling reaction of 5-iodouridine with trifluoromethyl iodide in the presence of copper powder in hexamethylphosphoramide [60]. 5-Trifluoromethyluridine exhibits antitumor and antiviral activities by irreversible amide formation with a nucleophilic site of an enzyme. A fluoroolefin is generated by the reaction with an enzyme and behaves as a Michael acceptor, as shown in Scheme 5.13 [61].



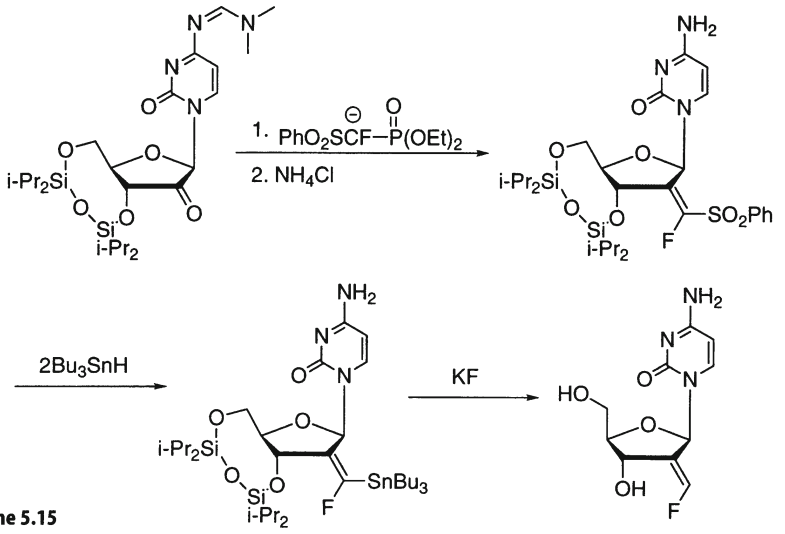
Scheme 5.13

Gemcitabine, a *gem*-difluorinated analog of deoxycytidine, was initially developed as an antiviral agent, but later was shown to exhibit a narrow therapeutic index as a drug for the treatment of human solid tumors, especially non-small cell lung and pancreatic cancer [27b]. A Reformatsky reaction of ethyl bromodifluoroacetate with (*R*)-2,3-*O*-isopropylideneglyceraldehyde affords a 3:1 mixture of α,α-difluoro β-hydroxy ester. Separation and ring closure to a lactone followed by synthetic manipulations give a mesylate which is condensed with trimethylsilylated cytosine. Subsequent deprotection and separation give the desired gemcitabine, as illustrated in Scheme 5.14.



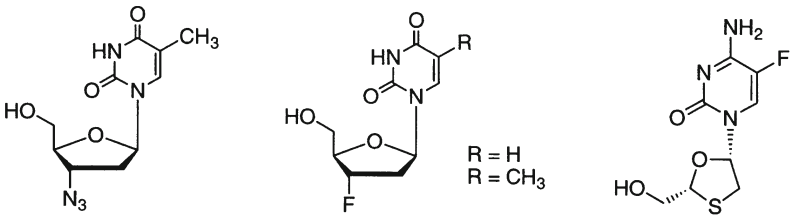
Scheme 5.14

A fluoroolefin analog of a cytidine nucleoside inhibits a ribonucleotide diphosphate reductase targeted for the treatment of tumors. This is synthesized by the introduction of a fluoroolefin using a fluorinated Horner–Emmons reagent [62]. The resulting fluorovinyl sulfone was transformed to the final (*E*)-fluoroolefin by stannylation and deprotection (Scheme 5.15).



Scheme 5.15

Antiviral Agents. Many fluorinated pyrimidine and purine nucleosides have been prepared (Fig. 5.8) in order to find an alternative to 3′-azidothymidine (AZT), an inhibitor of HIV-1 that is the putative cause of acquired immune deficiency syndrome (AIDS) [63]. Of these, 2′,3′-dideoxy-3′-fluorouridine and 3′-deoxy-3′-fluorothymidine (FLT) have been pursued extensively [64]. Another potent therapeutic agent against HIV is (–)-2′,3′-dideoxy-5-fluoro-3′-thiacytidine (FTC) that serves as an extremely potent and selective inhibitor of HIV replication in vitro and in vivo [65].



AZT

R = H: 2',3'-dideoxy-3'-fluorouridine
R = CH_3: FLT

FTC

Fig. 5.8

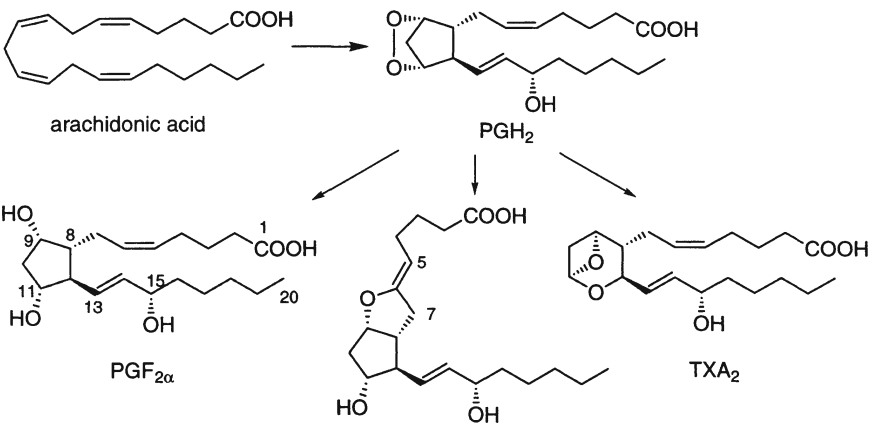
5.4
Fluorine-Containing Pharmaceuticals

Recently, it has been demonstrated that the selective substitution of fluorine for hydrogen or a hydroxyl group in a biologically active compound and the introduction of a trifluoromethyl, difluoromethyl, fluoromethyl, or fluorovinyl substituent are highly effective for the discovery of effective drugs, diagnostic agents, and biochemical probes. Accordingly, introduction of fluorine into biologically active molecules is a very powerful and versatile tool for the design of new drugs on the basis of the rational elucidation of molecular recognition processes.

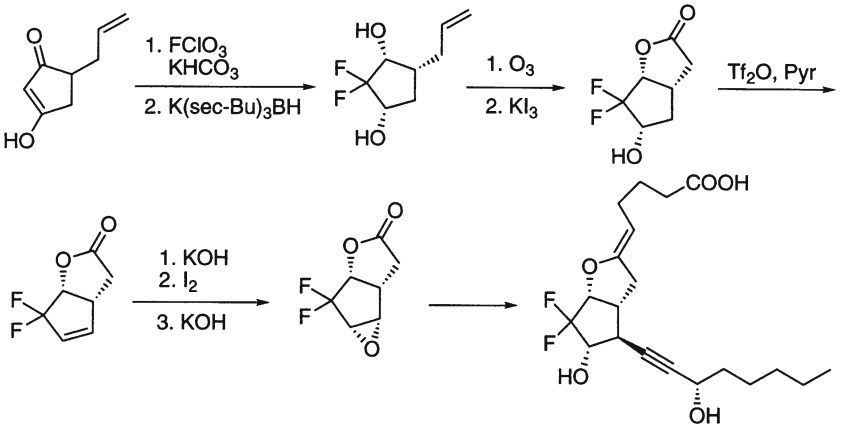
5.4.1
Prostanoids

Prostanoids, namely prostaglandins (PGs) and thromboxanes (TXs), exhibit a wide variety of biological activities at extremely low concentrations and are metabolized rapidly into inactive forms. The biosynthetic pathway of prostanoids begins with arachidonic acid which is metabolized in organs to PGH_2, $PGF_{2\alpha}$, PGI_2 and TXA_2 (Scheme 5.16). The chemical and physiological instability of prostanoids has stimulated studies on the chemical modification to improve the stability and selectivity. Selective fluorination of prostanoids has been effected at the cyclopentane ring as well as at both the α and ω side chains. Target fluorinated molecules have been prepared by means of a variety of synthetic technologies, including fluorination of synthetic intermediates and use of fluorinated building blocks [1c, 2, 66].

Prostaglandin I_2 (PGI_2), a potent inhibitor of platelet aggregation, has a half-life time $t_{1/2}$ of less than 10 min under physiological conditions and its vinyl ether moiety is easily hydrolyzed to give inactive 6-oxo-prostaglandin



Scheme 5.16



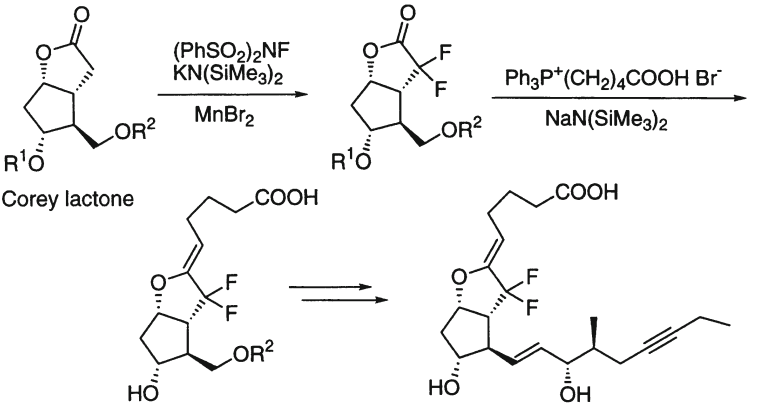
Scheme 5.17 10,10-difluoro-13,14-dehydro PGI_2

$F_{1\alpha}$. Introduction of fluorine near an acid-labile vinyl ethereal moiety results in the stabilization of the structure of PGI_2. The antiplatelet aggregatory and hypotensive effects of 10,10-difluoro-13,14-dehydro-PGI_2 are preserved with a remarkably long half-life time ($t_{1/2}$ = ca. 24 h) [67]. A key intermediate difluoro lactone is synthesized by fluorination of 5-allylcyclopentane-1,3-dione with perchloryl fluoride. The difluorinated lactone is converted into an epoxy lactone by iodolactonization followed by treatment with a base (Scheme 5.17).

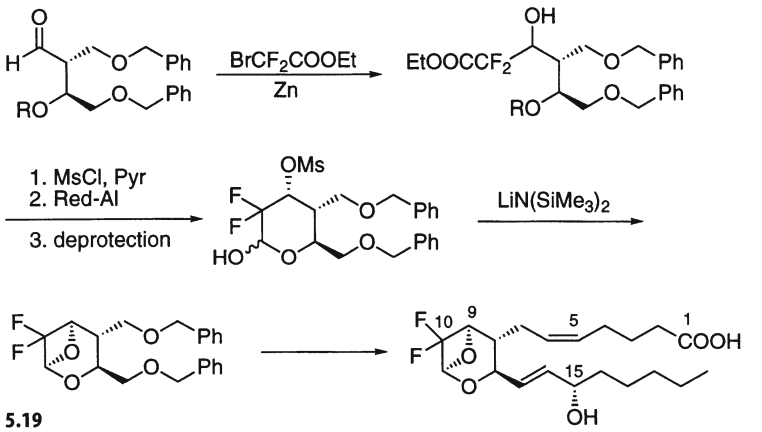
A remarkable stabilization effect by two fluorine atoms introduced at C-7 of PGI_2 is seen in 7,7-difluoro-PGI_2, which retains an extremely high inhibitory activity on platelet aggregation even in an oral administration [68]. Amazingly, its $t_{1/2}$ is more than 90 days! 7,7-Difluoro-18,19-dehydro-16,20-dimethyl-PGI_2 has been prepared by a manganese salt catalyzed electrophilic fluorination of the Corey lactone and a subsequent stereoselective Wittig reaction of the resulting difluoro lactone (Scheme 5.18).

In contrast to PGI_2, thromboxane A_2 (TXA_2) contracts the aorta and induces platelet aggregation with $t_{1/2}$ = 32 s at 37 °C under physiological conditions [69]. The short half-life time is attributed to its 2,6-dioxabicyclo-[3.1.1]heptane skeleton. However, 10,10-difluoro-TXA_2 is hydrolytically stable with four to five times more potency than natural TXA_2 with respect to stimulation of platelet aggregation. Moreover, difluorinated TXA_2 shows differential effects on platelet aggregation and aorta. The difluoro part is introduced by the reaction of a starting aldehyde with $BrZnCF_2COOEt$. Following transformations lead to a protected form of a dioxabicyclo[3.1.1]heptane intermediate (Scheme 5.19).

PGs are generally metabolized to form biologically inactive 15-oxo analogs by 15-dehydrogenase in the lung. Similarly, introduction of two fluorines at C-16 enhances the resistance to such metabolism and at the same time improves the biological selectivity. Indeed, the 15-hydroxyl group of 16,16-di-

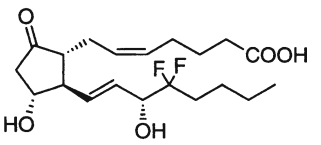


Scheme 5.18



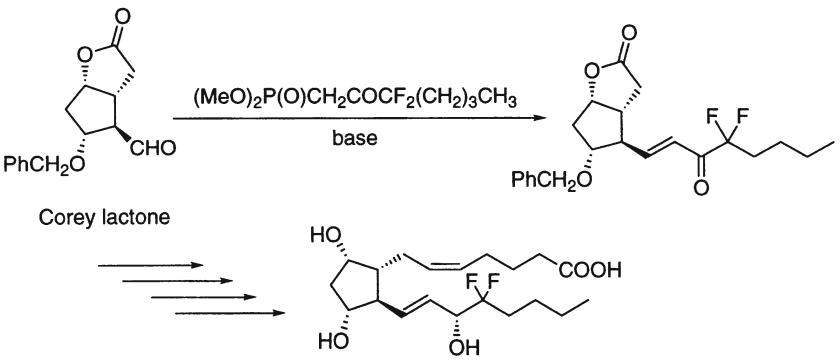
Scheme 5.19

fluoro-PGE_1 (Fig. 5.9) is not metabolized by 15-dehydrogenase. Worthy of note is that the antifertility activity of 16,16-difluoro-$PGF_{2\alpha}$ is enhanced with a side effect being suppressed against smooth muscle contraction. The difluoro-$PGF_{2\alpha}$ is prepared by the reaction of a difluorinated Horner–Emmons reagent with the Corey lactone (Scheme 5.20) [70].



16,16-difluoro PGE_1

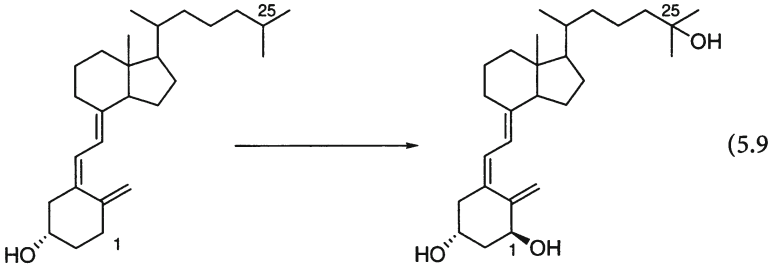
Fig. 5.9



Scheme 5.20

5.4.2 *Vitamin D_3*

Since the early work of Fried [5] it has been known that fluorinated steroids exhibit significant biological activities. Studies on vitamin D_3 have proved that a novel fluorination technique leads to improvement in the selectivity and utility of biologically active agents. Introduction of fluorine at the position where metabolic hydroxylation takes place is effective to prevent such metabolism owing to a minimal steric alternation (mimic effect) and the strong C–F bond. Vitamin D_3 is metabolized in the liver to give an activated form by hydroxylation at C-25 (25-OH D_3). Further hydroxylation at C-1 (1α) in the kidney gives active steroid hormone 1,25-$(OH)_2$ D_3. 25-OH D_3 is alternatively hydroxylated at C-23, C-24, or C-26. Among the polyhydroxy derivatives of vitamin D_3, 1,25-$(OH)_2$ D_3 is the most active; the hydroxylation at the side chain is a deactivation process leading to excretion.



(5.9)

A fluorinated derivative of 1,25-$(OH)_2$ D_3 with fluorine at C-25 and C-1 tolerates the hydroxylation reaction. This fact manifests the role of these hydroxyl groups in various aspects of the activity of vitamin D_3. 1,25-$(OH)_2$ D_3 with fluorine at C-23, C-24, or C-26 blocks further hydroxylation reactions, a process of metabolic deactivation of vitamin D_3 (Fig. 5.10) [58].

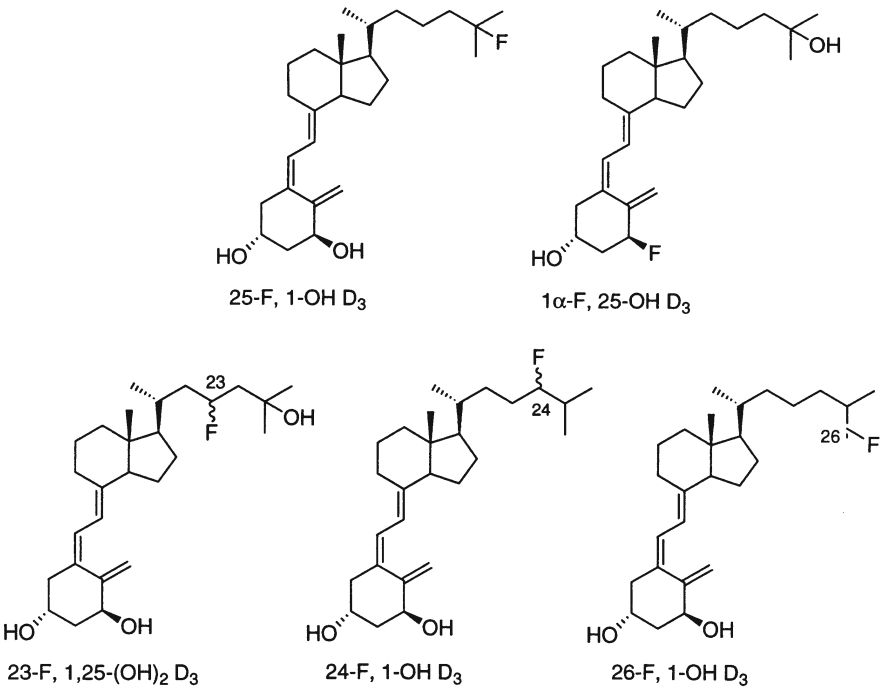


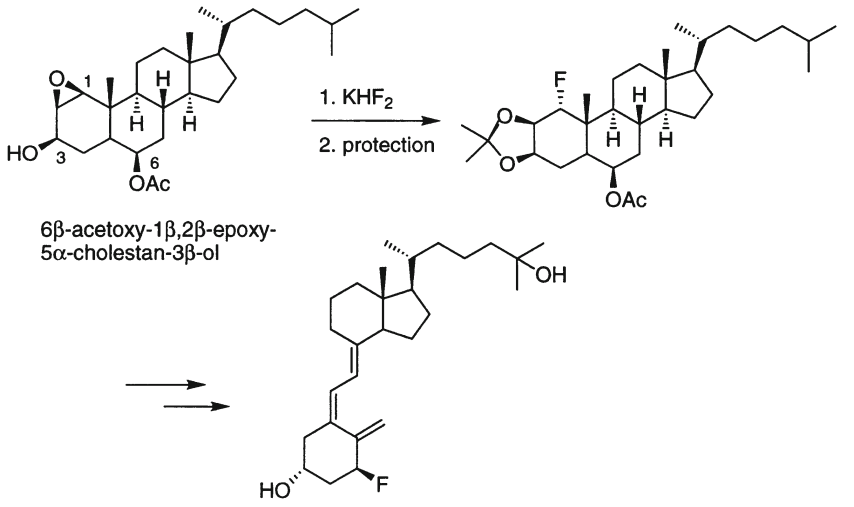
Fig. 5.10

A fluorinated D_3 derivative, 1α-fluoro-25-hydroxy-vitamin D_3, was prepared by a regio- and stereoselective ring-opening reaction of 6β-acetoxy-1β,2β-epoxy-5α-cholestan-3β-ol with potassium hydrogen fluoride [71] followed by protection to give an acetonide, which was further transformed to 1α-F,25-OH D_3 by synthetic manipulations including reductive removal of the 2β-hydroxyl group, a photochemical cyclohexadiene-hexatriene reaction, and a 1,7-hydride shift (Scheme 5.21).

1,25-$(OH)_2$ D_3 with fluorine at C-24, C-26, or C-2 adjacent to the 25- or 1-hydroxyl group (Fig. 5.11) is useful for determining the role of the hydroxyl group at C-25 or C-1 during the interaction with a hydrogen-bond donor or acceptor in a receptor [58].

The fact that 1α,25-dihydroxy-26,26,26,27,27,27-hexafluoro-vitamin D_3 (26-F_3, 27-F_3-1,15-$(OH)_2$ D_3) is more active than 1,25-$(OH)_2$ D_3 means that the hexafluoro derivative binds the receptor less tightly. A condensation reaction of a phenylsulfonylated starting material with hexafluoroacetone followed by desulfonylation gives a key intermediate, a 25-hydroxyhexafluorocholesterol derivative, which is deprotected and oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford a cross-conjugated triene. This is then transformed to the hexafluoro analog of 1,25-$(OH)_2$ D_3 (Scheme 5.22) [72].

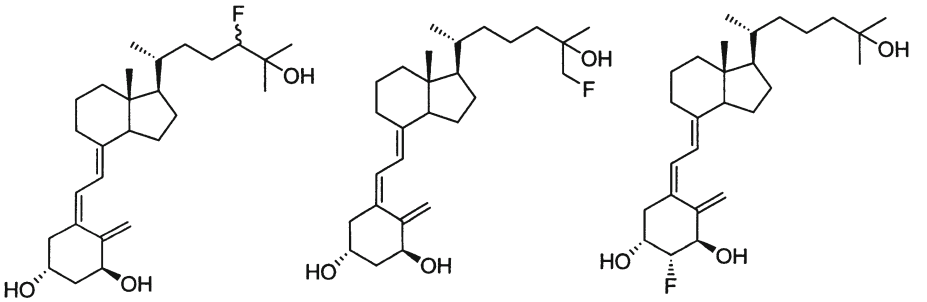
Other fluorinated examples are a 16-ene-23-yne analog of 26-F_3, 27-F_3, 1,25-$(OH)_2$ D_3 that possesses potential pharmacological properties for the treatment



6β-acetoxy-1β,2β-epoxy-5α-cholestan-3β-ol

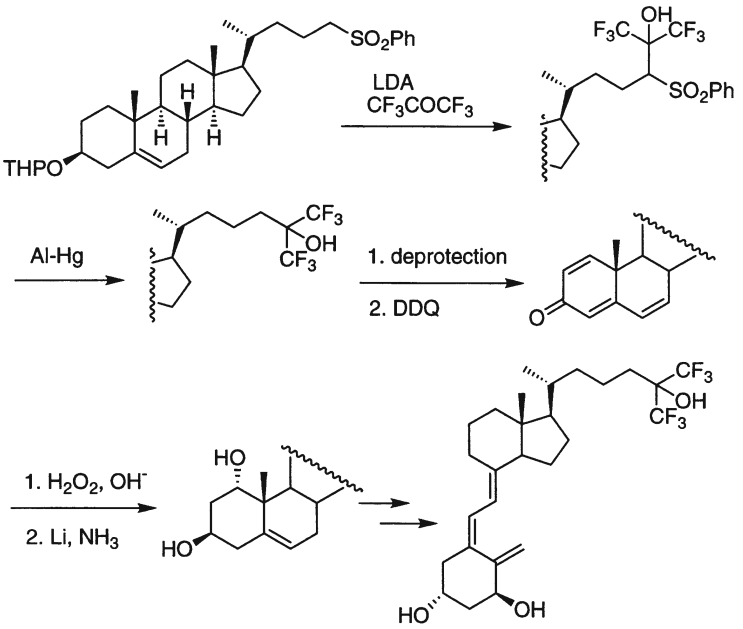
1α–F, 25-OH D_3

Scheme 5.21



24-F, 1,25-$(OH)_2$ D_3 26-F, 1,25-$(OH)_2$ D_3 2-F, 1,25-$(OH)_2$ D_3

Fig. 5.11



Scheme 5.22 26-F_3, 27-F_3, 1,25-$(OH)_2$ D_3

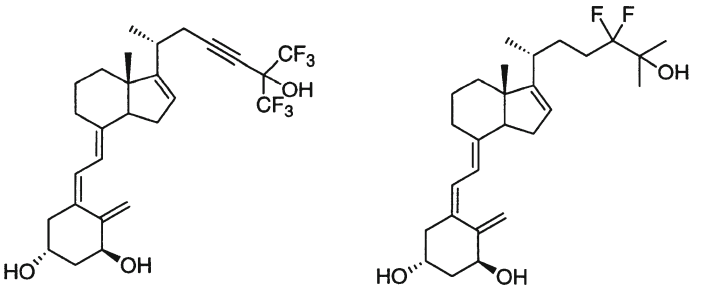


Fig. 5.12

of proliferative and immunological diseases and a 16-ene-24,24-difluoro analog of 1,25-$(OH)_2$ D_3 (Fig. 5.12) [73].

5.4.3
Central Nervous System Agents

A great success in the development of new fluorine-containing agents is highlighted in the treatment of disorders of the central nervous system (CNS). As the lipid solubility of fluorinated aromatic compounds is significantly improved, the rate of absorption and transport of a drug across the blood-brain barrier is greatly enhanced by a fluorine substituent [74].

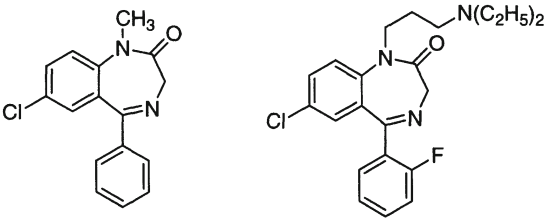


Fig. 5.13 diazepam

The most important popular prototype drug is diazepam (Fig. 5.13) which has a 1,4-benzodiazepine structure and is prescribed as a sedative and tranquilizer, controlling mild to moderate degrees of anxiety and tension. An *ortho*-fluorophenyl derivative is shown to increase the hypnotic activity of diazepam.

Fluorine-containing pharmaceuticals have played a key role in the treatment of a major debilitating illness. These agents selectively inhibit re-uptake of serotonin. Fluoxetine [75] was launched in 1986 as a very efficient and successful antidepressant. Paroxetine [76], introduced in 1991, exhibits activity similar to fluoxetine (Fig. 5.14) but with a shorter duration of action.

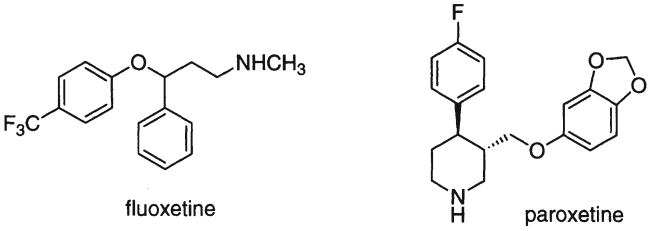


Fig. 5.14 fluoxetine paroxetine

5.4.4 *Antibacterials and Antifungals*

New antibacterials, fluoroquinolone carboxylic acids [77, 78], are essential to combat infections caused by microorganisms resistant to the traditional antibacterials: penicillins, cephalosporins, and tetracyclines. In the early days, fluorine-containing agents were limited to flucloxacillin (vide infra), a penicillinase-stable penicillin [79], and β-fluoro-D-alanine [80]. Since the introduction of norfloxacin in the early 1980s, fluoroquinolone carboxylic acids have been competitively developed, and new more effective members have emerged (Fig. 5.15). Fluoroquinolone and naphthyridine carboxylic acids inhibit a DNA gyrase bacterial enzyme, exhibiting a broad spectrum of activity against various aerobic and anaerobic gram-positive and gram-negative bacteria. Norfloxacin, enoxacin, ciprofloxacin, sparfloxacin, and tosufloxacin contain fluorine at C-6 and a piperazyl group (except for tosufloxacin) at C-7 to increase the activity. Levofloxacin, an (*S*)-isomer of ofloxacin, is especially effective in lowering respiratory, urinary tract and prostate infections, and in treating sexually transmitted diseases.

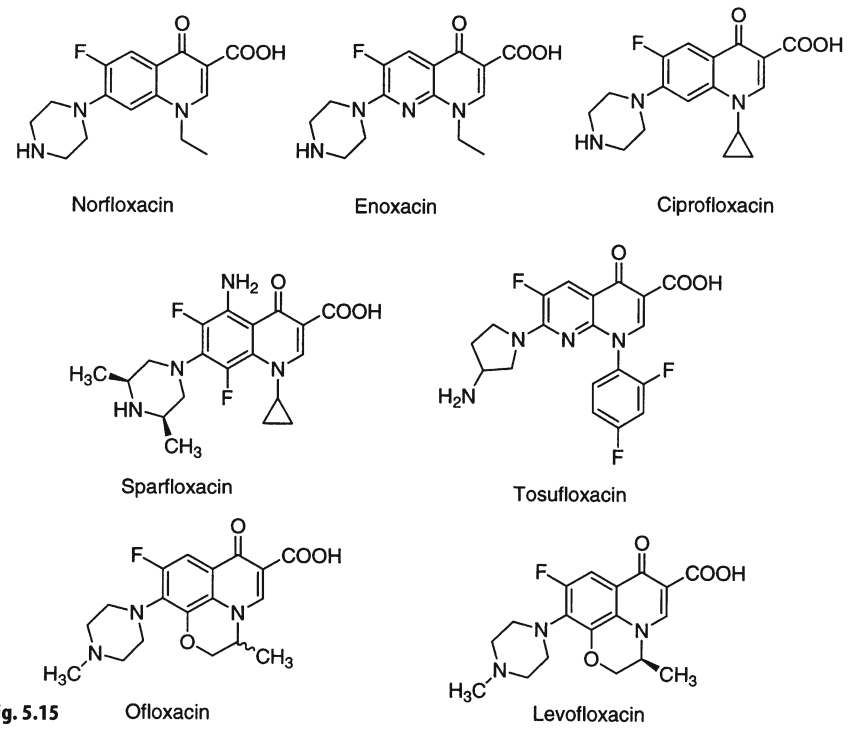
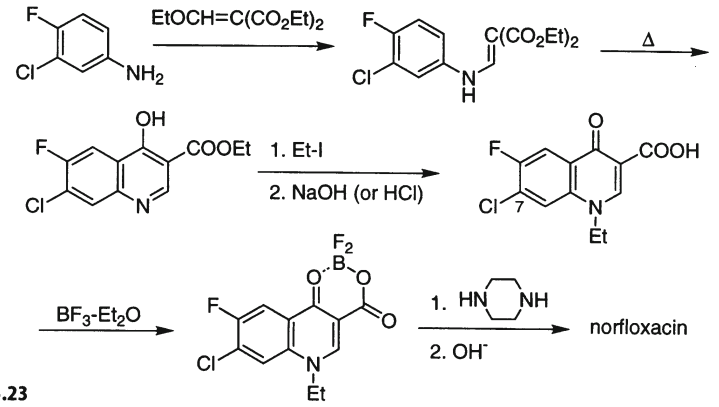
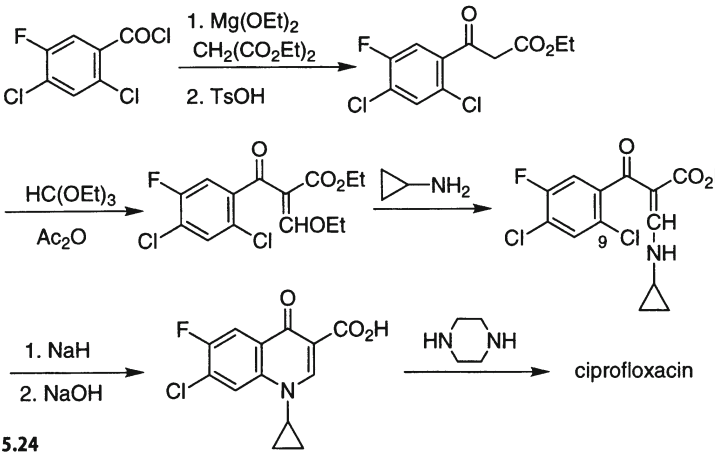


Fig. 5.15

Norfloxacin is prepared as follows: reaction of 3-chloro-4-fluoroaniline with ethoxymethylenemalonate and cyclization (Gloud–Jacobs reaction) give hydroxyquinoline carboxylate. After N-ethylation and saponification, chlorine at C-7 is substituted by piperazine by activation with boron trifluoride (Scheme 5.23).



Scheme 5.23

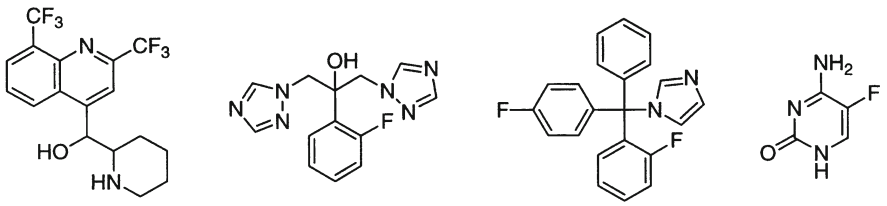


Scheme 5.24

On the other hand, the quinoline ring of ciprofloxacin can be constructed in an alternative manner by a nucleophilic substitution of Cl at C-9 with an aminocyclopropyl group. A key intermediate enamino ester is prepared by the reaction of the ethoxymethylene derivative with cyclopropylamine (Scheme 5.24).

Malaria is caused by parasitic protozoa, primarily *Plasmodium falciparum*. The antiprotozoal drug mefloquine (Fig. 5.16) [81] is one of the main agents for the current treatment of malaria, used singly or in combination with chloroquine. Since no useful vaccines are yet available, the compound still plays a significant role in the treatment.

Stable, orally active, and topical antifungal agents have recently emerged which have a 2-fluorophenyl(triazolyl)methane moiety in common. In particular, bistriazole fluconazole, launched in 1988, is effective against dermal, vaginal, and other infections, inhibiting fungal ergosterol synthesis. A new antifungal, flutrimazole, exhibits significant activity, being used singly or in combination with fluconazole or flucytosine (Fig. 5.16).



mefloquine fluconazole flutrimazole flucytosine

Fig. 5.16

5.4.5
β-Lactam Antibiotics

A very large number of β-lactams have antibacterial activities by disrupting bacterial cell wall synthesis and inhibiting one or more penicillin-binding proteins (PBPs) that catalyze, as transprotease, the crosslinking reactions of D-alanylpeptides on peptidoglycan strands of a growing cell wall. The β-lactam ring acts as an acylating reagent to inhibit transpeptidases. Typical examples of β-lactam antibiotics are penicillins, cephalosporins, cephamycins, carbapenems, and monobactams. Some fluorinated compounds, e.g. flucloxacillin [79b] and flomoxef [82] (Fig. 5.17), are already commercially available.

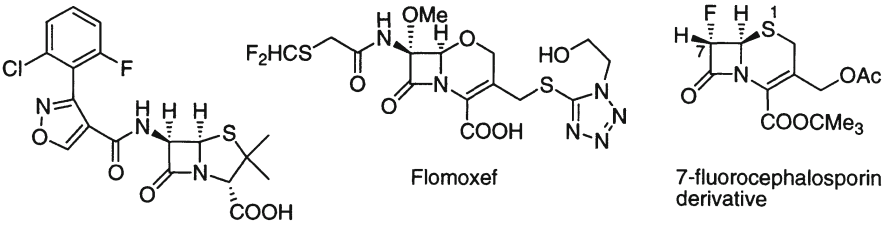


Fig. 5.17

Introduction of fluorine at C-6 of a penicillin structure is carried out on the basis that the replacement of hydrogen by fluorine does not induce any significant steric consequences at β-lactamase binding sites. However, fluorine raises the acidity of the geminal C-6 hydrogens and thus the vicinal β-lactam carbonyl group becomes readily acylated. Following a similar strategy, fluorine can be introduced at C-7 of the cephalosporin structure.

5.4.6
Anesthetics

In the 1950s, fluoroxene and halothane (Fig. 5.18) became available as anesthetics. Whereas fluoroxene is flammable at high concentrations and induces nausea, halothane is nonflammable with relatively minor side effects. The introduction of halothane has influenced the practice of anesthesia and contributed to major advances in medical treatment and health care. A new generation of fluoro anesthetics, desflurane and sevoflurane (Fig. 5.18), are now widely used [83]. Sevoflurane has properties of fast uptake and elimination.

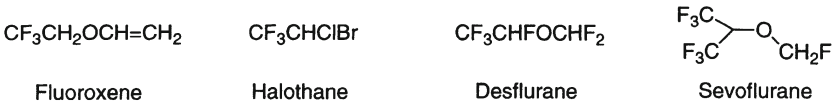


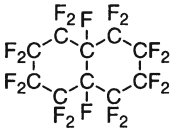
Fig. 5.18

5.4.7
Artificial Blood Substitutes

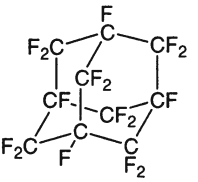
Blood is a fluid which consists of many components and has a variety of functions, namely, transport of metabolic substrates and removal of metabolic products, maintenance of ion balance, and regulation of the immune system. The most important role is the transport of oxygen to tissues and the removal of carbon dioxide from the tissues. Gas exchange by blood, a function of blood corpuscles, can be carried out by artificial blood substitutes [84].

In 1966, Clark demonstrated that a mouse submerged in perfluoro 2-butyltetrahydrofuran could survive for up to ten minutes [85]. The animal could receive a sufficient amount of oxygen from the liquid and, after removal from the liquid, did not show any apparent ill effects, exhibiting the high oxygen carrying capacity and low toxicity of perfluorocarbons (PFCs). However, intravenous infusion of liquid PFCs causes the death of animals because of the immiscibility in water and blood. Therefore, the PFC must be dispersed as fine particles for use of an artificial blood substitute.

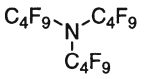
Examples of PFCs, consisting of carbon, fluorine and, in some cases, of such heteroatoms as oxygen or nitrogen, are illustrated in Fig. 5.19. PFCs are chemi-



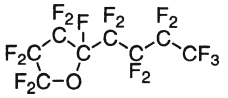
Perfluorodecalin



Perfluoroadamantane



Perfluorotributylamine



Perfluoro-2-butyltetrahydrofuran

Fig. 5.19

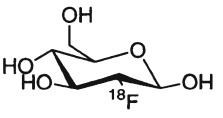
Table 5.2. Solubility of oxygen and carbon dioxide in CFCs

Compound	Temp. (°C)	Solubility (ml/100 ml)	
		Oxygen	Carbon dioxide
ethanol	25	24.2	247.9
water	25	2.9	75.9
	37	2.4	57.0
perfluorodecalin	37	45.0	134.0
perfluorotributylamine	37	38.9	142.0
perfluorotetrahydrofuran	37	58.0	160.0

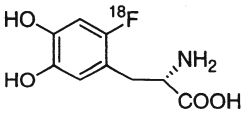
cally extremely stable and are excreted by animals without being metabolized. Boiling points of PFCs are relatively low (perfluorodecalin: 142 °C) and they exhibit low surface tensions, 9–16 mN/m, compared with those of alkanes and alcohols, 25–35 mN/m. Generally, the surface tension of a liquid relates well to the solubility of a gas in the liquid (Table 5.2). The gas exchange functions of blood corpuscles can be carried out by artificial blood substitutes. An emulsion consisting of perfluorodecalin and perfluoroisopropylamine has already been launched for the oxygen-carrying agent.

5.4.8
^{18}F-Labeled Tracers for Positron Emission Tomography

Fluorine-18 is a positron-emitting isotope of fluorine and has a long half-life of 110 min. Positron emission tomography (PET) [86], in conjunction with appropriate radiotracers labeled with fluorine-18, has been used to study biochemical transformation, drug pharmacokinetics, and pharmacodynamics in the human and animal body. Typical agents are 2-deoxy-2-[^{18}F]fluoro-D-glucose (a PET tracer for 2-deoxy-D-glucose) and 6-[^{18}F]fluoro-L-DOPA (a PET tracer for L-DOPA), as shown in Fig. 5.20. Recently, PET has also been used to assess the functional and neurochemical parameters in a normal and diseased human brain. Thus, a rapid and effective method for the introduction of ^{18}F is a great concern to current synthetic organofluorine chemistry.



a PET tracer for
2-deoxy-D-glucose



a PET tracer for L-DOPA

Fig. 5.20

5.5
Fluorine-Containing Agrochemicals

Agrochemicals are indispensable for the large-scale production of high quality crops and for an improvement in the harsh labor conditions in the fields. Because use of large amounts of chemicals may cause problems associated with safety and the environment, use of small amounts of highly potent, selective, and negligibly nontoxic agents are desirable that are effective only for a certain period and then will be decomposed rapidly to totally nontoxic compounds. To this end, many novel agrochemicals have been developed that allow applications in much smaller amounts. Fluorine has played a key role in the design of novel highly potent agrochemicals [87–91].

The fluorine effect in agrochemicals is understood in terms of an increase in lipophilicity, mimic effect, electronic effect and block effect, as described in previous sections of this chapter.

5.5.1
Insecticides

A typical class of fluorine-containing insecticides is *N*-2,6-difluorobenzoyl-*N'*-arylurea and its derivatives. Some examples are listed in Fig. 5.21. The agents inhibit chitin biosynthesis and are often called insect growth regulators (IGRs). As chitin does not affect mammals, the insecticides are selective to specific kinds of insects and nontoxic to mammals and much less influential against their natural enemies and honey bees.

A typical example is diflubenzuron, developed as a fluorine analog of 2,6-dichlorobenzoyl urea TH-6038 (Scheme 5.25) [91]. Triflumuron was designed

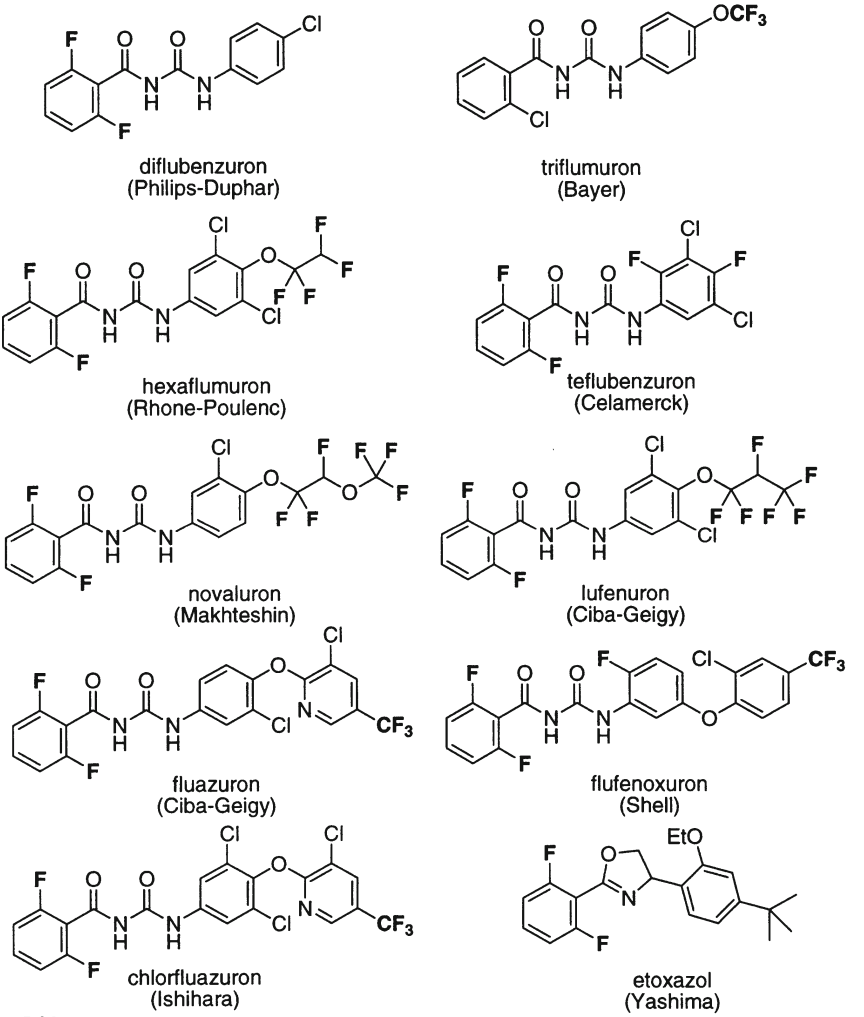
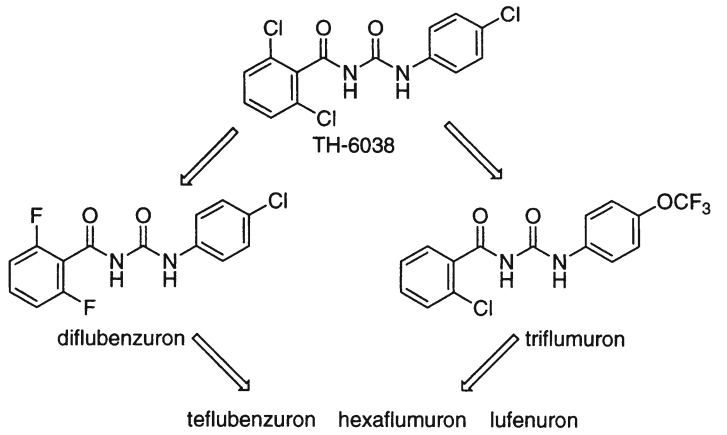


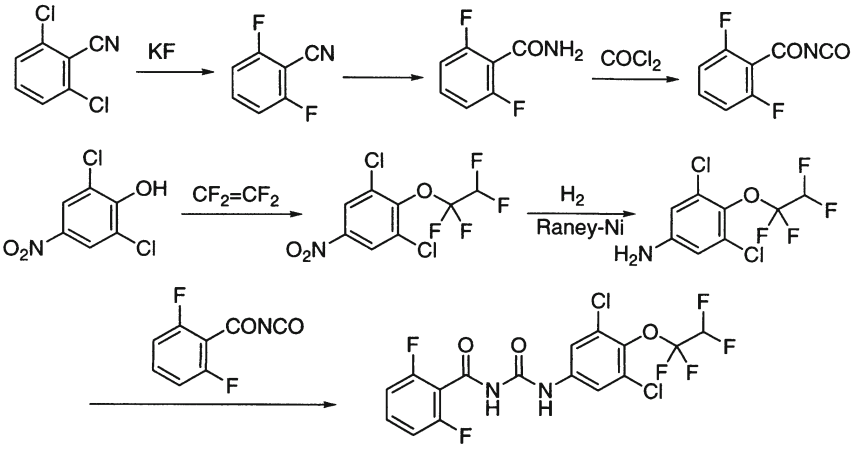
Fig. 5.21



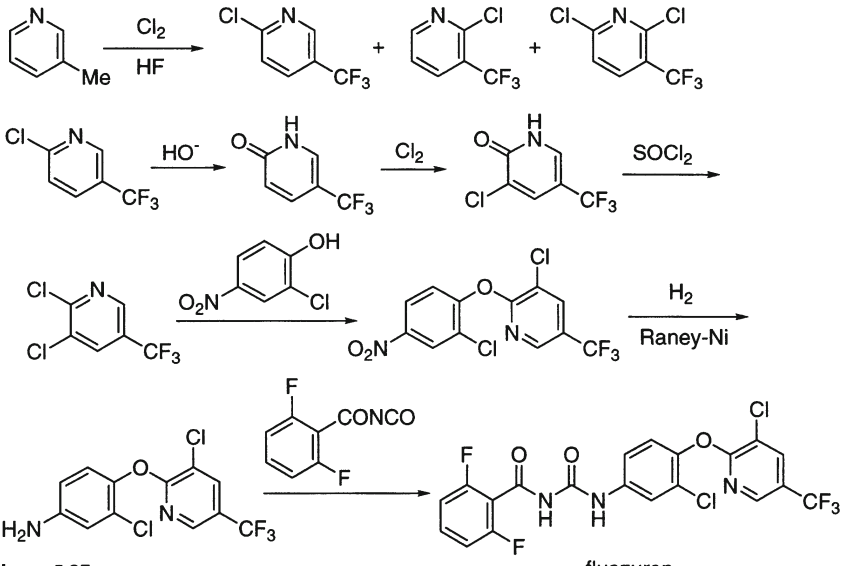
Scheme 5.25

by replacing chlorine in an aniline moiety of TH-6038 with a trifluoromethoxyl group [92]. Fluorine functional groups, like a fluorine atom, polyfluoroalkoxyl, and 3-trifluoromethylpyridin-2-yloxy groups were further introduced into the aniline moiety of diflubenzuron, as illustrated in Scheme 5.25. The resulting insecticides are now commercially available.

The synthetic route to hexaflumuron [93] is shown in Scheme 5.26. The 2,6-difluorobenzoylurea part is prepared by (1) nucleophilic fluorine substitution of 2,6-dichlorobenzonitrile, (2) hydrolysis of the nitrile to an amide, and (3) reaction of the amide with phosgene to give 2,6-difluorobenzoylisocyanate. The aniline part of hexaflumuron is prepared by nucleophilic addition of



Scheme 5.26



Scheme 5.27

fluazuron

2,6-dichloro-4-nitrophenol to tetrafluoroethene followed by reduction. The resulting aniline derivative is allowed to react with the benzoylisocyanate to give hexaflumuron. Use of $CF_2{=}CFCF_3$ or $CF_2{=}CFOCF_3$ in lieu of $CF_2{=}CF_2$ gives lufenuron or novaluron, respectively.

The synthesis of fluazuron starts with chlorinative fluorination of β-picoline, as summarized in Scheme 5.27 [94]. Separation of 2-chloro-5-trifluoromethylpyridine to form a mixture of regioisomers, hydrolysis to pyridone, stepwise dichlorination, nucleophilic substitution of the resulting dichloropyridine with 2-chloro-4-nitrophenol, and catalytic reduction of the nitro group followed by reaction with 2,6-difluorobenzoylisocyanate give fluazuron.

The second important class of insecticides are the pyrethroids that affect the nervous system of insects. It is known that the major components of a pyrethrum are pyrethrin I and pyrethrin II (Fig. 5.22), highly potent insecticides that are almost nontoxic to mammals. These are, however, so labile against sunlight that their activity is rapidly lost when used in the fields.

Since the use of polychlorinated insecticides is now prohibited for environmental reasons, the natural pyrethroids have been extensively modified, leading to the discovery of permethrin [95] and cypermethrin [96] that are extremely potent and stable for certain periods against sunlight but then decompose gradually. To enhance the insecticidal activity and, especially, the acaricidal activity, trifluoromethyl analogs were introduced. For example, bifenthrin [97], developed by FMC in 1982, has about 55-fold acaricidal activity in addition to an insecticidal activity comparable to permethrin [98]. Tefluthin is a tetrafluorobenzyl ester analog of biphenthrin and thus has a high vapor pressure which makes it more effective against vermin in soil [99].

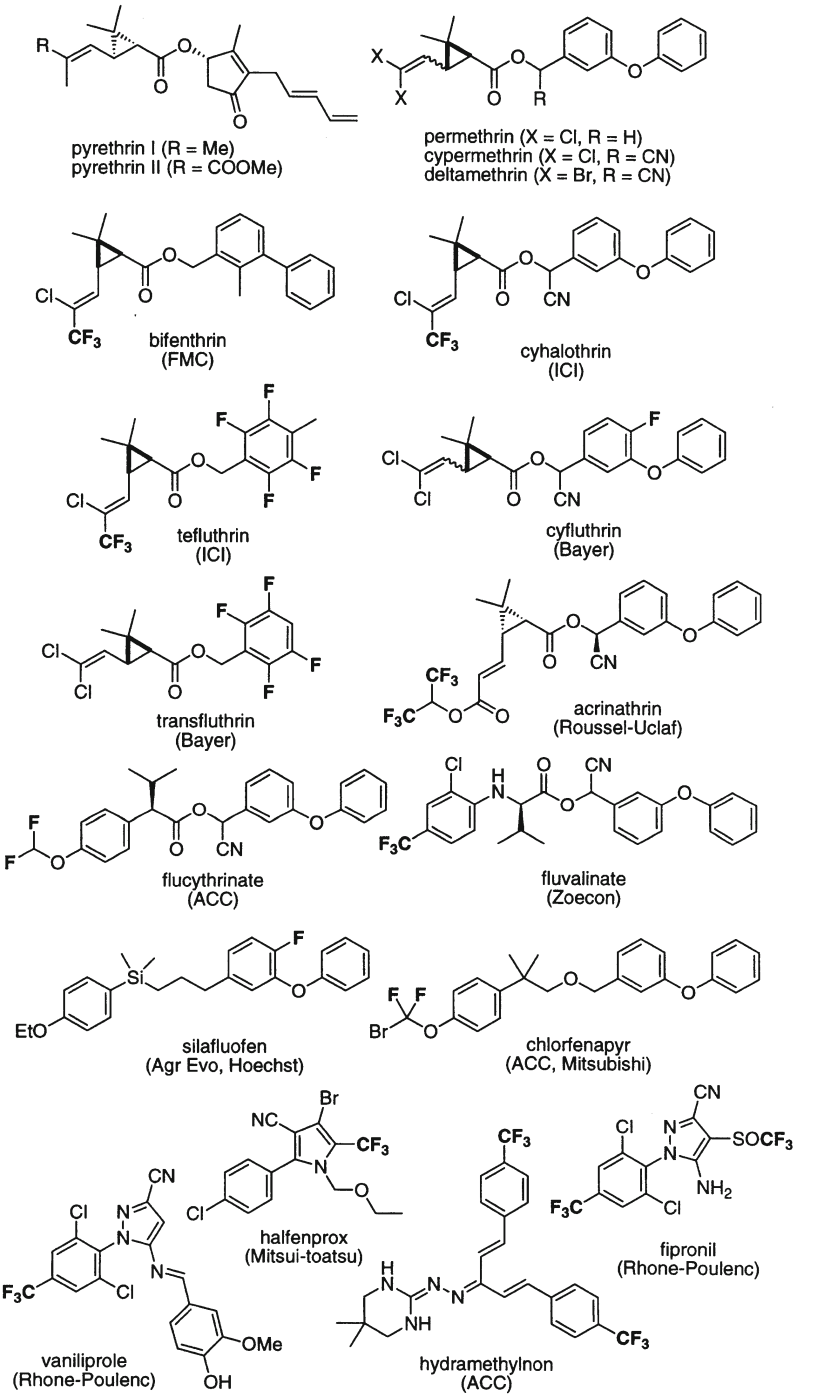
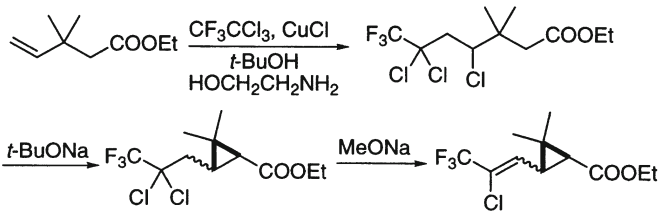

pyrethrin I (R = Me)
pyrethrin II (R = COOMe)
permethrin (X = Cl, R = H)
cypermethrin (X = Cl, R = CN)
deltamethrin (X = Br, R = CN)
bifenthrin
(FMC)
cyhalothrin
(ICI)
tefluthrin
(ICI)
cyfluthrin
(Bayer)
transfluthrin
(Bayer)
acrinathrin
(Roussel-Uclaf)
flucythrinate
(ACC)
fluvalinate
(Zoecon)
silafluofen
(Agr Evo, Hoechst)
chlorfenapyr
(ACC, Mitsubishi)
halfenprox
(Mitsui-toatsu)
fipronil
(Rhone-Poulenc)
vaniliprole
(Rhone-Poulenc)
hydramethylnon
(ACC)

Fig. 5.22

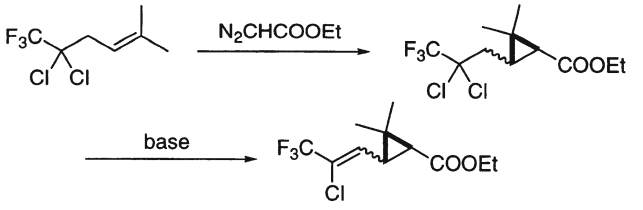


Scheme 5.28

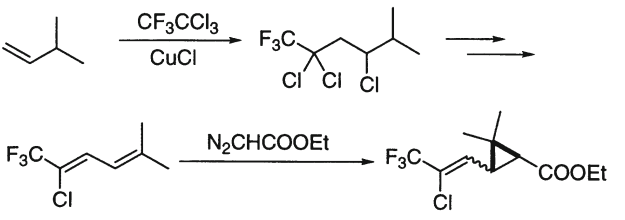
Synthesis of the trifluoromethyl-substituted pyrethroids is achieved by various methods using 1,1,1-trichlorotrifluoroethane (CFC-113a) as a CF_3 building block. The first method involves a copper(I) chloride catalyzed addition of CFC-113a to ethyl 3,3-dimethyl-4-butenoate. The resulting adduct is then treated with a base to induce ring closure and olefin formation, as summarized in Scheme 5.28 [100]. This method usually gives a mixture of *cis*- and *trans*-cyclopropanecarboxylates with ratios controllable to some extent by proper choice of the base.

The second approach involves addition of ethyl diazoacetate to 3,3,3-trifluoro-2,2-dichloropropyl-substituted isobutene or 1,1,1-trifluoro-1-chloro-5-methyl-2,4-hexadiene (Schemes 5.29 and 5.30) [101]. Although straightforward and stereospecific, the reaction is not necessarily effective due to the electron-deficient nature of the olefinic moiety.

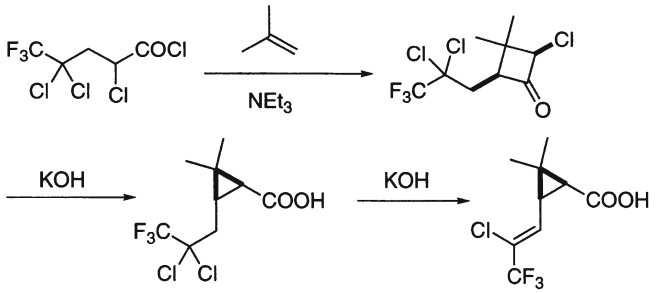
Ring contraction is the third method. Cycloaddition of a ketene with isobutene gives a cyclobutanone which, upon treatment with a base, undergoes a Favorskii rearrangement to give preferentially a *cis*-cyclopropanecarboxylic acid. The sequence of the reactions is illustrated in Scheme 5.31 [102].



Scheme 5.29



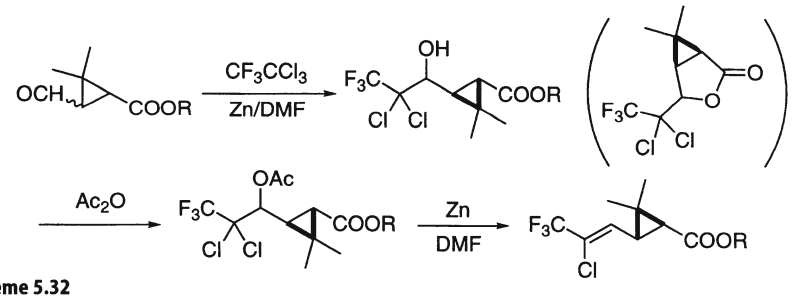
Scheme 5.30



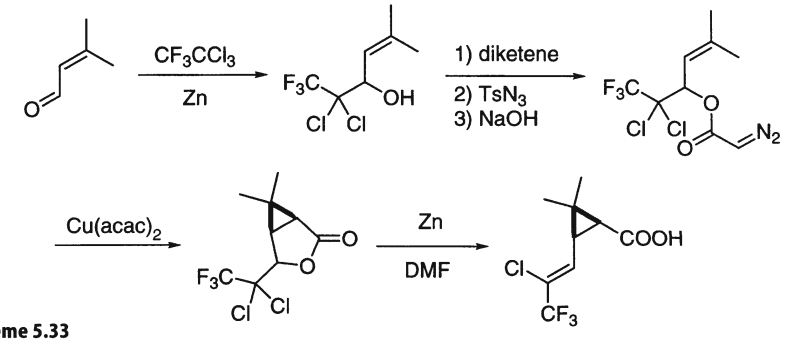
Scheme 5.31

The last approach is carbonyl addition of a zinc carbenoid derived from CFC-113a. The resulting adduct is acetylated and then reduced with zinc dust to give the target ester (Scheme 5.32). Since an adduct derived from *cis*-Caron aldehyde forms a lactone ring and is easily separated, only *trans*-cyclopropanecarboxylate results [103].

Selective synthesis of more potent *cis*-cyclopropanecarboxylates than the *trans*-isomers is stereospecifically achieved by addition of the same zinc carbenoid to 3-methyl-2-butenal, diazoacetylation, and intramolecular carbene addition, followed by zinc reduction, as shown in Scheme 5.33 [103].



Scheme 5.32



Scheme 5.33

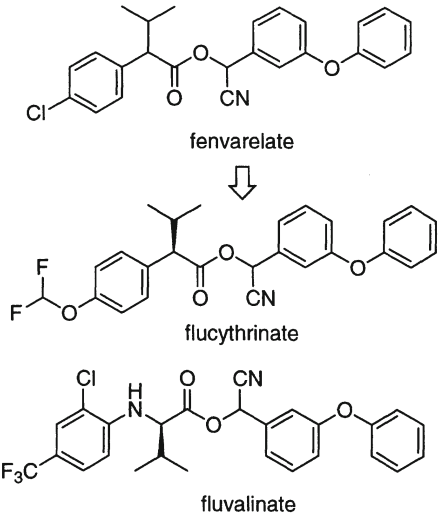


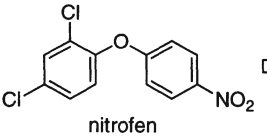
Fig. 5.23

Further design of synthetic pyrethroid insecticides has led to novel structures that lack a cyclopropane ring. A typical example is fenvarelate [104], illustrated in Fig. 5.23. The chlorine in fenvarelate is replaced by a difluoromethoxyl group to give flucythrinate (Fig. 5.22) [105]. Further modification of 4-chlorophenyl in fenvalerate to 2-chloro-4-trifluorophenylamino gives fluvalinate [106]. Whereas fenvarelate was patented as a mixture of 4 diastereomers, these new compounds have been patented as a diastereomeric mixture with the configurations of the carbon α to the ester carbonyl being both *R*. Fluvalinate is as active as fenvalerate against the tobacco moth and the house fly and has an acaricidal activity seven times higher.

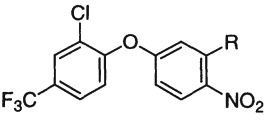
Later, it was revealed that the insecticidal activities were retained in the absence of the ester carbonyl group of fenvalerate. Thus, silafluofen [101] and halfenprox (Fig. 5.22) were designed and patented. Silafluofen was designed by replacing a CMe_2 group in fenvalerate with $SiMe_2$. Although synthetic pyrethroids are generally toxic to fish, silafluofen is much less toxic and can be applied to rice fields.

5.5.2 *Herbicides*

A typical class of herbicides are the diphenyl ethers, including nitrofen, shown in Fig. 5.24. This type of compounds inhibits the protection mechanism for the biosynthesis of chlorophyll and allows singlet oxygen generated by sunlight irradiation to oxygenate lipids in membranes of weeds and/or forbs to wither them [87]. A chlorine substituent in nitrofen can be replaced by a CF_3 group to give nitrofluorfen, to which various substituents can be introduced at a position *ortho* to a nitro group. Of these, acifluorfen, fomesafen, and lactofen are post agents against forbs of soybeans.

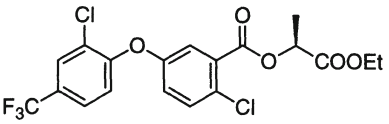


nitrofen

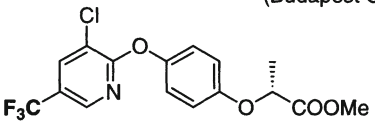


R =		
	H	nitrofluorfen
	OEt	oxyfluorfen (Rohn & Hass)
	COONa	acifluorfen-Na
	$CONHSO_2Me$	fomesafen (ICI)
	COOCHMeCOOEt	lactofen (PPG)

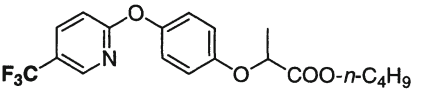
Fig. 5.24



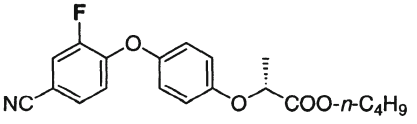
ethoxyfen-ethyl
(Budapest Chem. Works)



haloxyfop-*R*-methyl
(Dow Elanco)



fluazifop-*p*-butyl
(Ishihara)



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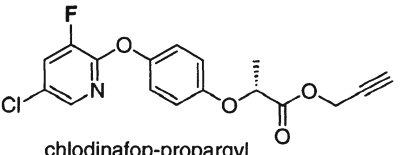
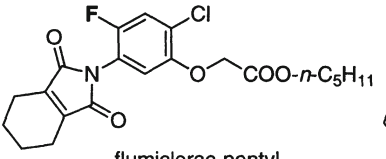
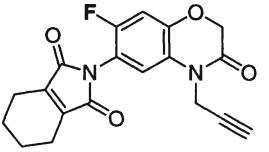


chlodinafop-propargyl
(Ciba-Geigy)

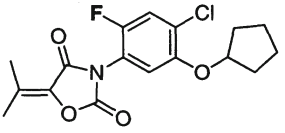
Fig. 5.25



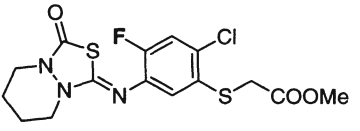
flumiclorac-pentyl
(Sumitomo)



flumioxazin
(Sumitomo)

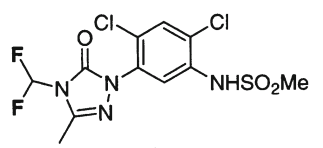


pentaoxazone
(Kaken)

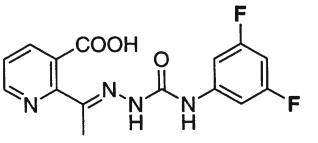


fluthiacet-methyl
(Kumiai)

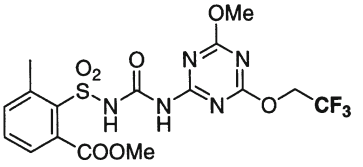
Fig. 5.26



sulfentrazon
(FMC)



duflufrnzopyr
(BASF)



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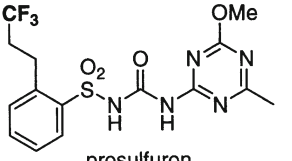
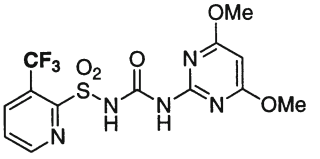
(Du Pont)



prosulfuron
(Ciba-Geigy)



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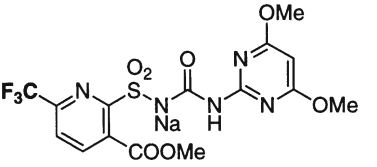
(Ishihara)



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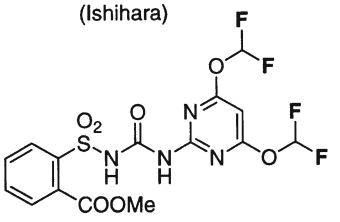
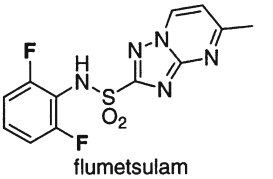
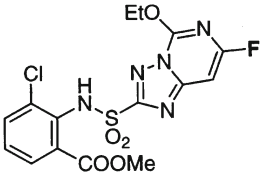
(Du Pont)



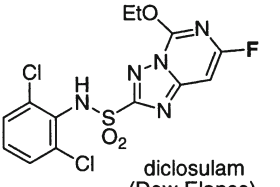
primisulfuron-methyl
(Ciba-Geigy)



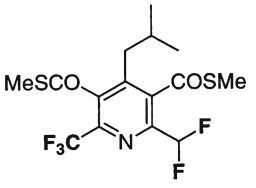
flumetsulam
(Dow Elanco)



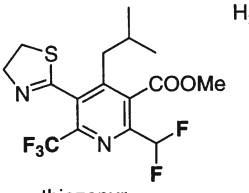
cloransulam-methyl
(Dow Elanco)



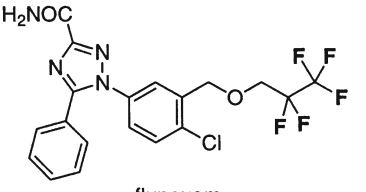
diclosulam
(Dow Elanco)



dithiopyr
(Monsanto)

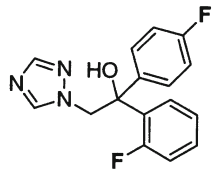


thiazopyr
(Monsanto)

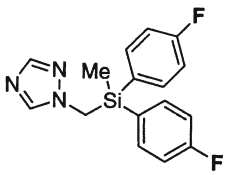


flupoxam
(Kureha)

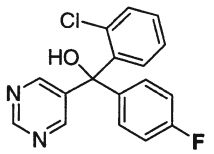
Fig. 5.27



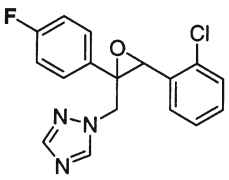
flutriafol
(ICI)



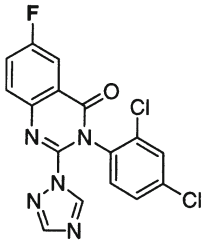
flusilazole
(Du Pont)



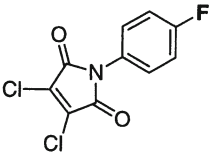
nuarimol
(Eli Lilly)



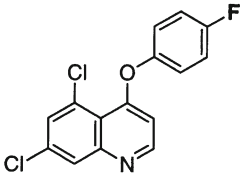
epoxiconazole
(BASF)



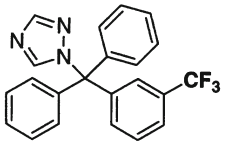
fluquinconazole
(Schering)



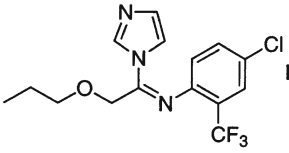
fluoroimide
(Mitsubishi-kasei)



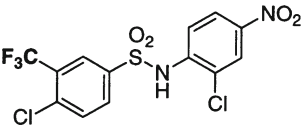
quinoxyfen
(Dow Elanco)



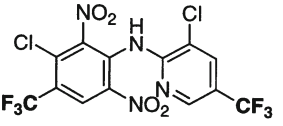
fluotrimazole
(Bayer)



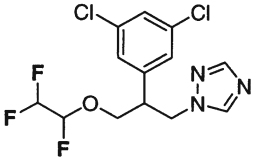
triflumizole
(Nihon-soda)



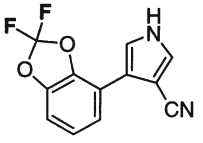
flusulfamide
(Mitsui-toatsu)



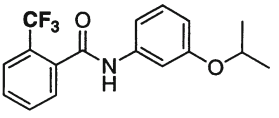
fluazinam
(Ishihara)



tetraconezole
(Isagro-Ricerca)



fludioxonil
(Ciba-Geigy)



flutolanil
(Nihon-noyaku)

Fig. 5.28

An analog of lactofen is ethoxyfen-ethyl (Fig. 5.25) which contains a lactic acid moiety [107]. This structural modification led to a general structural class of 2-(4-aryloxy)phenoxypropionates that show high and selective herbicidal activity against grasses. Of these, haloxyfop-*R*-methyl [108], cyhalofop-butyl [109] and chlodinafop-propargyl [110] have been launched.

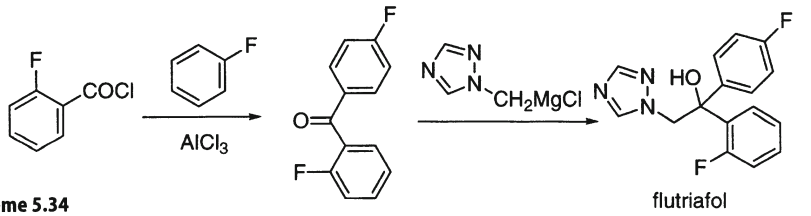
Another type of photochemical herbicides are cyclic imides such as flumiclorac-pentyl [111], flumioxazin [112], pentaoxazone [113], and fluthiacet-methyl [114]. A common structural feature is a 4,5-disubstituted 2-fluorophenyl group substituted to an imide nitrogen or the isomers, as illustrated in Fig. 5.26.

The third important class of herbicides are sulfonylureas and triazopyrimidines that inihibit acetolactate synthetase. Examples [86] that contain a fluorine, difluoromethoxyl, or trifluoromethyl group are listed in Fig. 5.27.

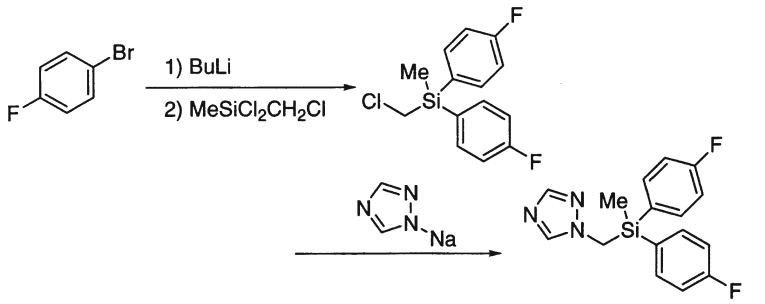
5.5.3
Fungicides

Few fungicides are known that contain a fluorine functionality. Some examples are listed in Fig. 5.28. A synthetic route to flutriafol is shown in Scheme 5.34. The Friedel–Crafts reaction of fluorobenzene with 2-fluorobenzoyl chloride gives difluorobenzophenone, which is then allowed to react with a Grignard reagent to give flutriafol that is active against mildew of wheat.

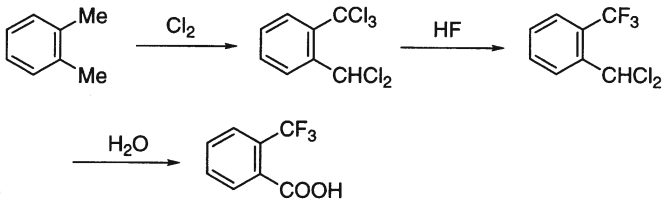
Flusilazole is prepared by the route summarized in Scheme 5.35. 4-Bromofluorobenzene is lithiated and silylated with dichloro(chloromethyl)-methylsilane to give $Cl(CH_2)SiMe(4\text{-}F\text{-}C_6H_4)_2$ which is then reacted with sodio-



Scheme 5.34 flutriafol



Scheme 5.35 flusilazole



Scheme 5.36

triazole to give flusilazole. This compound can be applied to wheat, apples, grapes, peanuts, and sugar beet [87].

The *o*-trifluoromethylbenzoic acid moiety of flutolanil is prepared on a large scale by pentachlorination of *o*-xylene, fluorine substitution, and hydrolysis (Scheme 5.36).

The design and synthesis of agrochemicals have been carried out by replacing a substituent in a prototype lead compound with a fluorine functional group, e.g. CH_3 to CF_3, Cl to CF_3, CF_3O or $CHCF_2O$. The structure-activity relationship is now expressed in various numerical ways. Accordingly, exploitation of novel agrochemicals containing a variety of fluorine functionalities will be accelerated in the near future, and they will be marketed if the synthetic costs are reasonable.

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