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Selective Fluorination in Organic and Bioorganic Chemistry

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Foreword

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Preface

INTEREST IN ORGANOFLUORINE CHEMISTRY IS GROWING at a rap pace. Fluorine as a substituent can significantly affect the properties c molecular systems. Its high electronegativity and small atomic volum have been used to probe reactivity—especially that of biologically impo tant molecules.

This book brings together works of authors who are active in theoret cal studies of organofluorine compounds, engaged in the development c new preparative methods and exploring the utility of specifically fluori nated compounds in biological systems. The volume is interdisciplinary i coverage and provides a forum for the exchange of information amon theoreticians, synthetic chemists, biochemists, medicinal chemists, an bioorganic chemists studying and using fluorine-containing compounds Readers with specialized interests will find new opportunities in thei specific areas, as well as the latest progress in other areas.

In addition to reactivity and theoretical aspects, this volume provide significant coverage of biological applications. The contributions fror industry, academia, and government laboratories emphasize the fact tha research on organofluorine compounds is far from an ivory towe endeavor and, in fact, that selective fluorination does provide a usefu alternative for the study of biological problems.

Acknowledgments

The preparation of this volume would not have been possible without th willing cooperation of both the contributors and the reviewers. I woul like to thank Professor H.-J. Hansen of the Organisch-Chemische Institut of the Universität Zürich for his hospitality and support durir the sabbatical leave where a large part of the editorial obligations assoc ated with this volume were completed. It is also a pleasure to thank Pr fessor D. Seebach for the encouragement he gave me during my sabba cal stay at the Laboratorium für Organische Chemie of the ETH Züric The symposium from which this book was derived was organized durir

the time I spent there. Finally, it would not have been possible for the symposium to have been held at all without the financial support of the Division of Fluorine Chemistry of the American Chemical Society and the Petroleum Research Fund of the American Chemical Society.

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November 5, 1990

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The Effects of Selective Fluorination on Reactivity in Organic and Bioorganic Chemistry

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The influence of fluorine on the physical, chemical and biological properties of molecules is described. A discussion of the effect of fluorination on bond lengths and bond strengths is presented in the course of an analysis of the steric demand of fluorinated substituents. These steric effects as well as electronic interactions are illustrated in a discussion of fluorinated vitamin D_3 and prostaglandin and thromboxane analogs.

The current level of interest in the preparation of selectively fluorinated compounds is indicated by the increasing number of publications and presentations in this area (*1*). It has been known for some time that fluorine can have profound and often unexpected effects on activity. Selective fluorination has been an extremely effective synthetic tool for modifying and probing reactivity. Replacement of hydrogen or hydroxyl by fluorine in a biologically important molecule often yields an analog of that substance with improved selectivity or a modified spectrum of activity (*2-21*). A number of very valuable monographs and other general reviews are available for guiding chemists in the organic chemistry of fluorine (*22-28*).

Historical Perspective

Although hydrogen fluoride was discovered by Scheele in 1771 (*23*), molecular fluorine itself wasn't prepared until 1886 by Moissan (*29*). Organofluorine chemistry really began to unfold with the work of Swarts (*30*) on the preparation of fluorinated materials by metal fluoride promoted halogen-fluoride exchange reactions. The commercial utility of organofluorine compounds as refrigerants, developed by Midgley and Henne (*31*), further accelerated the growth of the field by virtue of the economic incentives involved. Wartime requirements stimulated research on thermally stable and chemically resistant materials which led to an increased interest in highly fluorinated and perfluorinated substances. Many of the exciting developments of this period have been reviewed elsewhere (*32-34*). A synopsis of the growth of organofluorine chemistry could not be complete without recognition of the enormous impact of electrochemical fluorination techniques. The electrolysis of organic compounds in anhydrous hydrogen fluoride was discovered and developed by Simons (*35-39*).

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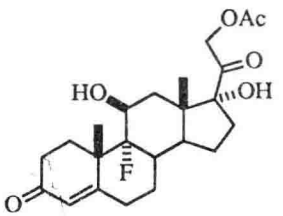
It was the pioneering work of Fried on preparation of 9α–fluoro-hydrocortisone acetate (**1**) (*40*) that led to the first significant successful application of selective fluorination for the purpose of modifying biological activity. This publication marked the beginning of a new era when medicinal chemists and biochemists routinely introduced fluorine as a substituent to modify biological activity.



9α-Fluoro-hydrocortisone acetate

1

Structure and Bonding

Fluorine is the most electronegative element with a Pauling electronegativity of 4 as compared to 3.5 for oxygen, 3.0 for chlorine or 2.8 for bromine. It is this property that is the apparent origin of many of the profound differences observed when fluorinated and non-fluorinated molecules are compared. Fluorine forms the strongest bond to carbon of the halogens, e.g., the carbon-fluorine bond energy is 456-486 kJ per mole and the carbon-chlorine bond 350 kJ per mole. For an additional comparison the carbon-hydrogen bond energy varies from 356 to 435 kJ per mole. Important also is the observation that the carbon-fluorine bond is shorter, 1.31 Å, than the other carbon-halogen bonds, for instance, the carbon-chlorine bond at 1.78 Å. Again for comparison, the carbon-hydrogen bond is 1.09 Å long and the carbon-oxygen bond measures 1.43 Å. However the bond lengths vary in an interesting manner in multipli-fluorinated methanes. With increasing fluorination the bond lengths shorten and the bond strengths increase. This phenomena is unique among the halogens (*41*).

Several alternative explanations of this phenomena have been put forth. Most simply, the contraction has been suggested to be a result of the donation of electron density from the non-bonded electron pair on fluorine into an adjacent carbon-fluorine bond (*22*). Alternative explanations have suggested that bonding with fluorine causes an increased likelihood that the p electrons of carbon will be preferentially shared with fluorine and thus the carbon fluorine bond will have more s-character and be shorter (*44*), in other words, that bonding with fluorine has greater π character. Therefore the carbon-fluorine bond in fluoromethane would be more p-rich and longer than the bond in fluoroform (*45*). The number of alternative expianations that have been put forward suggests how clouded understanding of these simple experimental observations may be. As might be expected, fluorination also has an effect on carbon-carbon bond strength. The carbon-carbon bond in 1,1,1-trifluoroethane or hexafluoroethane is considerably strengthened relative to that of ethane, 59 or 42 kJ per mole, respectively (*46,47*).

Table I. Carbon-Fluorine Bond Lengths and Bond Dissociation Energies in Halomethanes (*42-43*)

	CH_3X	CH_2X_2	CHX_3	CX_4
F	1.385 Å 456 kJ mol^{-1}	1.358 Å 510 kJ mol^{-1}	1.332 Å 535 kJ mol^{-1}	1.317 Å 543 kJ mol^{-1}
Cl	1.782 Å 350 kJ mol^{-1}	1.772 Å 339 kJ mol^{-1}	1.767 Å 325 kJ mol^{-1}	1.766 Å 301 kJ mol^{-1}
Br	1.939 Å 289 kJ mol^{-1}	1.934 Å 267 kJ mol^{-1}	1.930 Å 259 kJ mol^{-1}	1.942 Å 235 kJ mol^{-1}

Source: Adapted from ref. 22.

Another general experimental phenomenon that is particularly pronounced with organofluorine compounds is the gauche effect, the name given to the tendency of 1,2-difluoroethane to exist in a synclinal conformation as opposed to the antiperiplanar conformation, that would be expected on the basis of dipolar repulsions. Although the gauche effect is a general phenomenon that can occur with any vicinal electronegative substituents, it is most pronounced with vicinally fluorinated molecules. It is has been rationalized by invoking molecular orbital interactions between the fluorines (*48,49*).

The electronegativity of fluorine can also have pronounced effects on the electron distribution within a molecule bearing other substituents and affect the dipole moment of the molecule, the overall reactivity and stability of the compound and acidity or basicity of the neighboring groups. Fluorine can also participate in hydrogen bonds (*50,51*) or function as a ligand for alkali metals because of the available three non-bonded electron pairs (*52*).

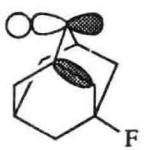
Effects of Fluorine on Chemical Reactivity.

Important differences in chemical reactivity of fluorinated compounds are based upon the difference in electronegativity between fluorine and hydrogen, on the higher carbon-fluorine bond strength versus the strength of the carbon-hydrogen bond, and on the ability of fluorine to participate in hydrogen bonding as an electron pair donor. The effects of fluorination have been thoroughly summarized by Chambers (*24*), Smart (*22*) and others (*53*).

Fluorine has a pronounced electron withdrawing effect by relay of an induced dipole along the chain of bonded atoms, a sigma withdrawing effect, I_σ, or this withdrawing may also result from a through space electrostatic interaction also known as a field effect (*54,55*). These effects are apparent when the acidity of trifluoroacetic acid (pKa 0.3) is compared with that of acetic acid (pKa 2.24). However in the gas phase, although fluoroacetic acid is more acidic than acetic acid, it is less acidic than chloroacetic acid, presumably as a result of the lower polarizability of the carbon-fluorine bond, 0.53 Å^3, relative to that for the carbon-chlorine bond, 2.61 Å^3 (*56*). This diminished charge induced dipole effect of the carbon-fluorine bond, relative to the carbon-chlorine bond, is much closer to the polarizability of the carbon-hydrogen bond. The electronic effect of fluorine directly attached to a π system can be especially complex, as electrons from fluorine may be donated

back to the π system in an I_π repulsive interaction. These repulsive interactions are most important in the reactions of α–fluorinated anions and radicals and in additions of nucleophiles to fluorinated alkenes.

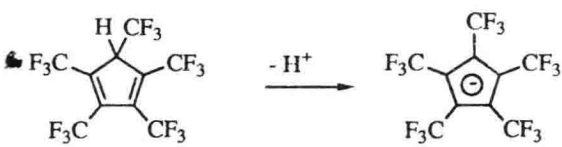
In contrast Fluorine stabilizes α–cations by the interaction of the vacant p-orbital of the carbocation with the filled orbitals of fluorine. Yet α-trifluoromethyl groups are strongly destabilizing to cationic centers relative to methyl groups. Trifluoromethyl groups have a very pronounced effect in solvolytic studies and have featured prominently in some classic studies (*57*). In recent work, it has been shown that fluorinated carbon-carbon bonds are also capable of directing the stereochemistry of reactions. The more electron deficient carbon-carbon bond (**2a**) has less electron density available to donate to a developing vacant orbital; therefore the stereochemistry of the process is controlled by the more electron rich non-fluorinated carbon-carbon bond (**2b**) (*58-61*).



2a

2b

Fluorine bonded directly to a carbanionic center is generally destabilizing by I_π repulsive interactions but when the carbanion ic atom is surrounded by trifluoromethyl groups, it is stabilized. In the case of pentakis-(trifluoromethyl)cyclopentadiene (**3**), stabilization of the carbanion accounts for a surprisingly high acidity (pKa<-2), comparable to nitric acid *(62)*.



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When speculating about the stability of α-fluorocarbanionic centers, the opposing electron withdrawing effects and I_π repulsive effects must be considered. The geometry of the system thus becomes very important in evaluating the magnitude of each of these contributions. Pyramidal α-fluorinated carbanions may be more stable than non-fluorinated pyramidal carbanions; for example, trifluoromethane is significantly more acidic than methane. If, however, fluorine resides on a planar carbanionic center, the ion is less stable; difluoroacetates form enolates less easily than acetates, presumably since the α-proton is less acidic (*63*).

Whereas fluorine bonded to a radical center may have a profound effect on the geometry of that center, the effect of fluorination on the stability of the radical is difficult to assess. However, the increased accessibility of

the carbon-fluorine bond LUMO and raised energy of the HOMO have been cleverly employed to direct the selectivity of radical reactions. A developing singly occupied orbital can be stabilized sufficiently by neighboring substituents to direct the stereochemical course of reactions, as in (**4**) (*64*).

4

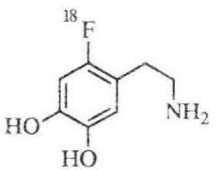
Fluorination as a Probe of Biological Reactivity

The attractiveness and utility of fluorine as a substituent in a biologically active molecule results from the pronounced electronic effects which may occur on fluorination combined with the fact that fluorine is not a sterically demanding substituent. With its small Van der Waal's radius (1.35 Å) fluorine closely resembles hydrogen (Van der Waals radius 1.20 Å). On the other hand, the carbon-fluorine bond length, 1.39 Å, is comparable to that of the carbon-oxygen bond length, 1.43 Å, which suggests that such substitutions should have little steric effect on the molecule into which they are made. However, where the Van der Waals volume of a methyl group, using a half sphere approximation, is only 19.6 $Å^3$, that of a trifluoromethyl group is 42.6 $Å^3$ more nearly that of an isopropyl group.

Fluorine can be introduced into a biologically active molecule to block metabolism, to serve as a probe of hydrogen bonding, to function as a leaving group in a enzyme inhibition or as a potent substituent for modifying chemical reactivity of adjacent functionality. Systematic substitution of fluorine for hydroxyl can help establish the effect of hydroxylation on the metabolism of a molecule. This principle has been successfully applied in the study of fluorinated vitamin D_3 analogs. The high carbon fluorine bond strength (108-456 kJ kcal/mole) renders the fluorine substituent resistant to many such metabolic transformations. Fluorine may also be employed as leaving group in addition-elimination processes where its superior leaving group ability relative to hydrogen is important. Such applications have led to the development of very effective mechanism based enzyme inhibitors. As previously mentioned, fluorine can also be a useful probe of hydrogen bonding interactions, since it may act as an electron pair donor but is otherwise unable to participate in such bonding interactions. Lastly, fluorine also has been identified as improving the lipophilicity of a molecule and hence its distribution within an organism.

The natural stable isotope of fluorine, fluorine-19 (^{19}F), with a spin of one-half and a chemical shift range of around 300 ppm, is a sensitive and useful probe in nuclear magnetic resonance (NMR) studies. Fluorine substitution may be a very effective method for studying the fate of bioactive molecules. Since there are few natural fluorinated materials to create background signals, the analyses are freed from the complications often associated with proton NMR spectroscopy (*65*). An artificially prepared useful short-lived isotope, fluorine-18 (^{18}F), decays by positron emission. Positron emission tomography (PET) is an especially useful non-invasive

technique for the survey of living tissue which complements traditional methods, such as X-ray studies, by allowing real time analysis of metabolic processes (*66*). Introduction of ^{18}F containing materials into living tissue is an essential part of PET. While other isotopes such as ^{11}C, ^{13}N, or ^{15}O have half lifetimes of twenty, ten and two minutes, ^{18}F has a convenient half life time of 110 minutes, sufficient for synthesis and for administration of the radiolabeled materials (*67*). One application of ^{18}F-positron emission tomography is in the brain imaging of Parkinsonian patients. Using ^{18}F-labeled fluorodopa (**6**), new insights into the chemistry and metabolism of brain have been revealed.



6α-[^{18}F]-Fluoro-L-dopamine

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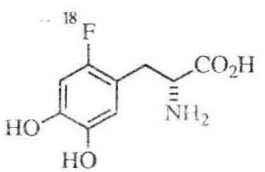

6α-[^{18}F]-Fluoro-L-dopa

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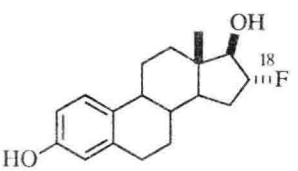
In yet another example, ^{18}F-labeled estrogen (**7**) may be useful in diagnosing breast tumors by positron emission tomography.



16α-[^{18}F]-17β-Fluoroestradiol

7

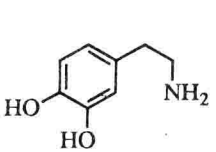
Methods for the Introduction of Fluorine

The best source of information on techniques for the introduction of fluorine into organic compounds and for information on preparative methods is the excellent treatise by Hudlicky (*23*), Houben-Weyl's Methoden der Organischen Chemie(*68*), as well as the books of Shephard and Sharts (*25*) and Chambers (*24*). More recently, methods for the fluorination of organic molecules have been reviewed by several authors (*15,69-75*). More specialized reviews discuss the synthesis of α–fluorinated carbonyl compounds (*76*), which appear quite often in biologically active molecules. An especially rapidly growing area of interest is fluorination with molecular fluorine or with reactive species prepared by means of molecular fluorine (*77-81*). Methods for the construction of more exhaustively fluorinated molecules have also been recently collated (*26*). The utility of selectively

fluorinated molecules as enzyme substrates (*82-83*) has been reviewed as has the preparation of fluorinated analogs of insect juvenile hormones and pheromones (*84*). Also progress reports on the preparation and biological activity of fluorinated analogs of vitamin D3 (*85*), on the preparation and biochemistry of fluorinated carbohydrates (*86*) and of fluorinated amino acids have appeared in the literature *(87-88)*.

Fluorination of Aminoacids and Amines. Fluorinated analogs of naturally occurring aminoacids and amines exhibit unique physiological activities. A number of fluorine containing amino acids have been synthesized and studied as potential enzyme inhibitors and therapeutic agents (*89*). β-Fluorine substituted amino acids are generally regarded as potential irreversible inhibitors of pyridoxal phosphate-dependent enzymes(*89a,b-95*). Fluorinated analogs are accepted by enzymes as substrates, as fluorine is comparable in steric demand to hydrogen, but often are not substrates for normal enzymatic transformation.

α-Monofluoromethyl and difluoromethyl amino acids have been recognized as potent enzyme-activated irreversible inhibitors of parent α-amino acid decarboxylases. Examples of the physiologically important fluorinated amines formed by decarboxylation are dopamine (**8**), 5-hydroxytryptamine (serotonin) (**9**), histamine (**10**), tyramine (**11**) and gamma-aminobutyric acid (GABA) (**12**) (*82*). The catechol amines are important in peripheral and central control of blood pressure (*96*). Elevated histamine levels are observed in diseases such as allergies, hypersensitivity, gastric ulcers and inflammation (*97*). High putrescine levels are associated with rapid cell development, including tumor growth (*98*).



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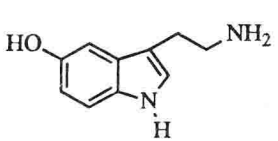

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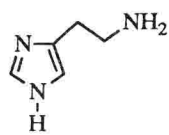

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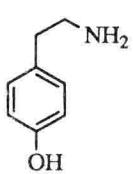

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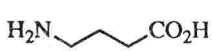

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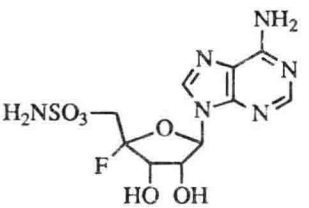
Aminoacids containing the trifluoromethyl group are also potential antimetabolites (*99*). Methyl groups may be replaced by trifluoromethyl groups in the preparation of amino acid analogs. The high electron density of the trifluoromethyl group may be important in the formation of strong hydrogen bonds with enzymes, thereby blocking enzymatic metabolism of the natural substrates. This group is also attractive since it is relatively non-toxic and somewhat more stable than the mono- and difluoromethyl analogs.

The synthesis of fluorinated analogs of biologically important amines has been explored extensively. Their direct preparation is difficult since most of the common fluorination agents can also react with the amino group. However, by the use of appropriate solvents, like liquid hydrogen fluoride which protects the amine functionality by protonation, successful fluorinations have been achieved (*100*). β–Fluorinated amines are important targets in the design of antimetabolites and drugs again since fluorine causes minimal structural changes and maximal shift in electron distribution.

Fluorinated Carbohydrates. Selectively fluorinated carbohydrates have found utility in probing biochemical mechanisms or in modifying the activity of glycosides (*86, 101-104*). These materials have many applications in biochemistry, medicinal chemistry and pharmacology. Only one naturally occurring fluorinated carbohydrate is known (*86*), the 4-deoxy-4-fluorosugar constituent of nucleocidin (**13**).



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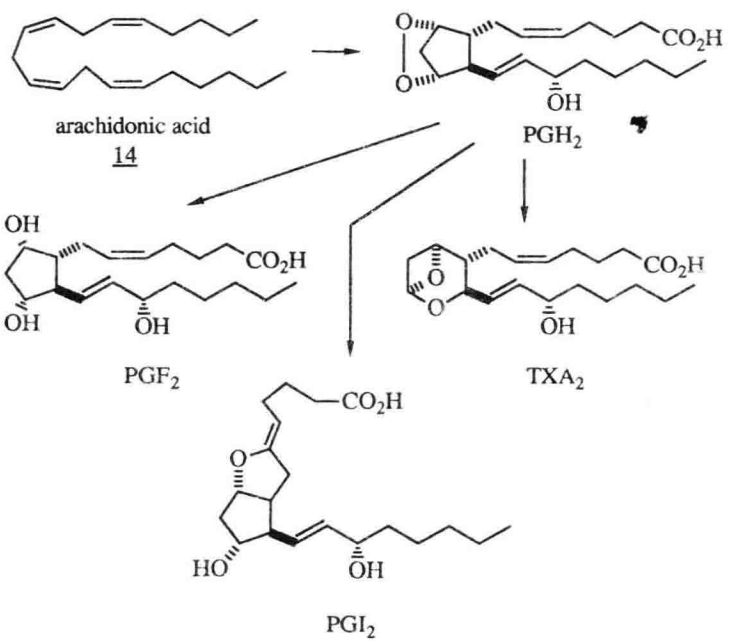
The biochemical rationale for incorporating fluorine in the carbohydrate residue is that replacement of a hydroxyl by fluorine would cause only a very minor steric perturbation of the structure or conformation while at the same time would have a profound electronic effect on neighboring groups. The substitution is possible while retaining the capacity of the position as an acceptor in hydrogen bonding. Yet these same attributes make the synthesis of fluorinated carbohydrates difficult. The synthesis of fluorinated carbohydrates offers a particularly fruitful field for the combination of modern chemical and enzymatic synthetic techniques. Total synthesis would be difficult because of the stereochemical control required at the multiple adjacent asymmetric centers of a fluorinated carbohydrate (*105*).

Fluorinated Analogs of Nucleic Acids. Fluorinated analogs of the naturally occurring nucleic acids have become established as antiviral (*106*), antitumor (*107,108*) and antifungal agents. Many fluorinated nucleosides exhibit biological activity in as much as the structures differ only slightly sterically from the naturally occurring molecules. The electronic effects of the fluorine substituent play a major role in the biological activity of the analogs. Fluorine has been employed as a replacement for both hydroxyl and hydrogen and difluoromethylene units have been employed as replacements for oxygen. The difluoromethylene group is only slightly larger than an oxygen atom, in fact there is not another functional group which can replace matches so well the steric and electronic demand of oxygen.

Fluorinated Aromatics. Fluorinated aromatics have found wide use as antibiotics, sedatives, important agrochemicals and radiochemical imaging agents. The best method is of course diazotization of an aromatic amine

followed by dediazoniation in the presence of fluoride-containing counterion. Selective electrophilic fluorination procedures are rare *(109)*. Unlike other halogens, fluorine cannot be directly introduced into specific positions of aromatic compounds using elemental fluorine. Most syntheses of bioactive materials start therefore with unfunctionalized fluorinated aromatic materials upon which the functionality is later arrayed.

Fluorine Substitution of Prostanoids. Fluorination of prostaglandins, prostacyclins and thromboxanes has led to exciting and useful modifications of activity. The biosynthetic pathway of these compounds begins with arachidonic acid (**14**).



Selective fluorination of prostanoids has been effected on the cyclopentane nucleus and on both side chains. A variety of techniques have been employed but may be arbitrarily divided into the fluorination reactions of intermediates and the use of fluorinated building blocks to prepare the target compounds. The chemistry and biology of fluorinated prostaglandins, prostacyclins and thromboxanes through 1981 has been reviewed *(110)*.

Fluorinated Steroids. The fluorination of steroids has been known to have profound effects on biological activity since the early work of Fried *(40)*. Fluorinated steroids have been described in other reviews *(111)*. The use of fluorination as a tool to enhance biological selectivity and to improve the utility of a biologically active material has been clearly demonstrated in studies of vitamin D_3.

The preparation of fluorinated analogs of vitamin D_3 has been reviewed *(112-114)*. Fluorination has been employed to prevent metabolic