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ADVANCES IN THE PREPARATION OF BIOLOGICALLY ACTIVE ORGANOFLUORINE COMPOUNDS

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1. INTRODUCTION

This review will be devoted to a description of selectively fluorinated biologically active molecules. Selective fluorination has been an extremely effective tool for modifying reactivity. Emphasis will be placed on the methods used to introduce the fluorine substituent and the effect of fluorine on the activity of the compound where it is known. Established procedures for fluorination as well as more novel approaches will be described. As an important area of research, several reviews have been published which focus on methods for fluorination or on the chemistry of a particular class of biologically active compounds which contain fluorine. This report is largely limited to work described since 1980 so as to complement those reviews.

Although the current level of interest in the preparation of selectively fluorinated compounds is indicated by the increasing number of publications in this area, it has been known for some time that fluorine can have profound and unexpected results on biological activity.[1] Fluorine is not a sterically demanding substituent, as sterically, with its small van der Waals radius (1.35 Å) it closely resembles hydrogen (1.20 Å). In molecules where conformational recognition is important minimal steric disturbance by a substituent is especially significant. Once introduced, the high carbon–fluorine bond energy renders the substituent relatively resistant to metabolic transformations. The electronegativity of fluorine (4 vs 3.5 for oxygen) can have pronounced effects on the electron distribution in the molecule, effecting the basicity or acidity of neighboring groups, dipole moments within the molecule and the overall reactivity and stability of neighboring functional groups. As a consequence of the available electron density, fluorine can function as a hydrogen bond acceptor.[2] When this observation is considered along with the fact that the carbon–fluorine bond length is 1.39 Å and the carbon–oxygen bond length 1.43 Å, it is clear that replacement of hydroxyl by fluorine in an analog may be quite successful. Systematic substitution of fluorine can help establish the effect of hydroxylation or other metabolic processes on the action of the molecule, as has been so successfully applied in the synthesis of fluorinated vitamin D_3 analogs.

Methods for the fluorination of organic molecules have been reviewed by several authors recently, focussing on the preparation of alpha-fluorocarbonyl compounds,[3] a functional relationship which appears often in biologically active molecules, and also fluorination with molecular fluorine or by reactive species prepared by *in situ* reaction of molecular fluorine where the fluorine is relayed to the target molecule.[4] Methods for the preparation of more exhaustively fluorinated molecules have also recently been summarized.[5] The utility of selectively fluorinated molecules as enzyme substrates[6] has been reviewed as has the preparation of fluorinated analogs as insect juvenile hormones and pheromones.[7] Also a progress report on the preparation and biological activity of fluorinated analogs of vitamin D_3 has been published in Japanese.[8]

This report is organized by compound classes. In the introduction to each section, the general objectives sought by specific fluorination of that class of compounds are described. Primary emphasis will be on structure, scope and synthesis with a brief description of the biological rationale for design and the biological outcome.

2. FLUORINATED AMINO ACIDS

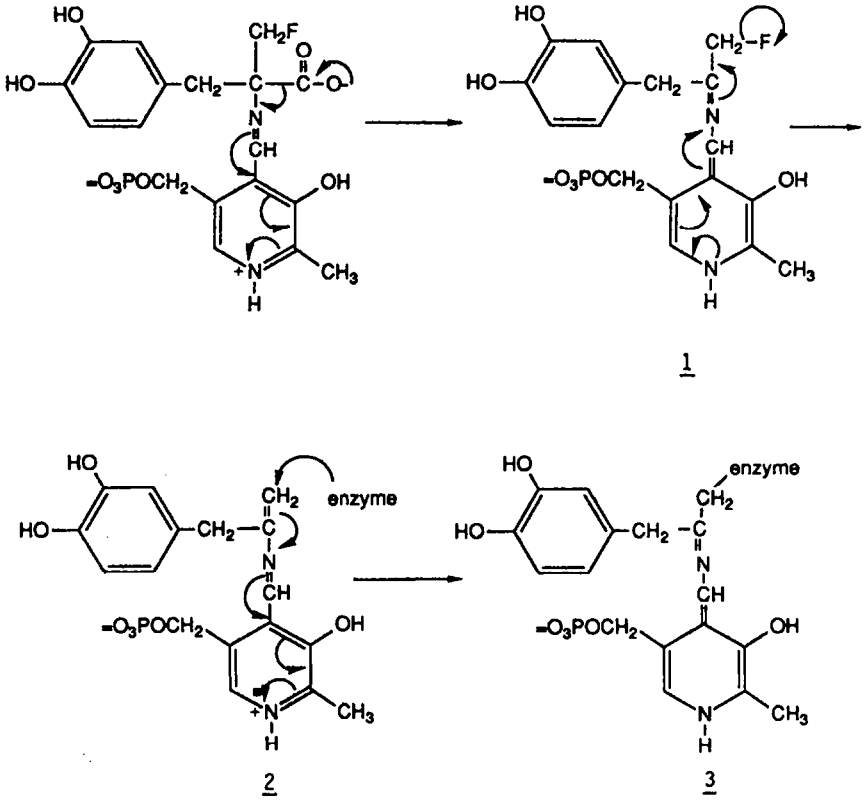
The importance of enzymatic decarboxylations of amino acids in biosynthetic pathways suggested the utility of specific inhibitors of these decarboxylation enzymes in studying these pathways. Typical of the physiologically important amines formed by decarboxylation are dopamine, 5-

Table 1. Fluoromethyl amino acid enzyme inhibitors

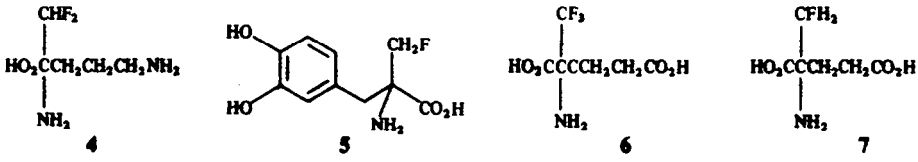
Amino acid or amine analog	Inhibited enzyme
Fluoromethylglutamic acid	Glutamate decarboxylase
Fluoromethylornithine	Ornithine decarboxylase
Fluoromethyldopamine	Dopa decarboxylase
Fluoromethyltyrosine	Dopa decarboxylase
Fluoromethylhistidine	Histidine decarboxylase(mammalian)
Fluoromethyldopa	Dopa decarboxylase
Fluoromethylhistamine	Histidine decarboxylase

hydroxytryptamine, histamine and gamma-aminobutyric acid (GABA). The catecholamines are important in peripheral and central control of blood pressure.[9] Elevated histamine levels are involved in diseases such as gastric ulcers and inflammation.[10] High putrescine levels are known to be associated with rapid cell development, including tumor growth.[11]

Fluoromethylated amino acids have been recognized as potent suicide inhibitors of enzymatic decarboxylation reactions for some time[12] (see Table 1). The enzymatic inactivation is thought to be dependent upon loss of fluoride from the intermediate Schiff base **1** formed between pyridoxal phosphate and the fluoromethyl amino acid. Loss of fluoride generates a reactive Michael type acceptor **2** which can add an enzyme bound nucleophilic functional group. The covalently bound enzyme **3** is no longer free to bind additional substrate. More recent advances in this area have been reviewed.[13] Difluoromethyl aminoacids are also very effective inhibitors of decarboxylases. In particular difluoromethyl ornithine, **4**, was found to inhibit ornithine decarboxylase and to disrupt polyamine synthesis with important implications for antigestational, antitrypanosomal, anticoccidal and antitumor agents. Difluoromethyl dopa, **5**, had selective peripheral activity and hence increased central dopa. Both trifluoromethyl and fluoromethyl glutamic acid, **6** and **7**, have been reported to inhibit glutamic acid decarboxylase, the enzyme which catalyzes formation of the inhibitory neurotransmitter GABA. Although under many conditions fluorine is relatively unreactive toward

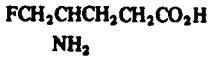


Scheme 1.



4 5 6 7

metabolism, it has been reported that all the fluorines may be eliminated sequentially from trifluoroalanine on treatment with cystathionase,[14] presumably via a similar mechanism to that invoked for formation of the active enzyme inhibitors. (See Scheme 2.) A related enzyme, GABA transaminase, which promotes catabolism of GABA, may be blocked by 4-amino-5-fluoro-pentanoic

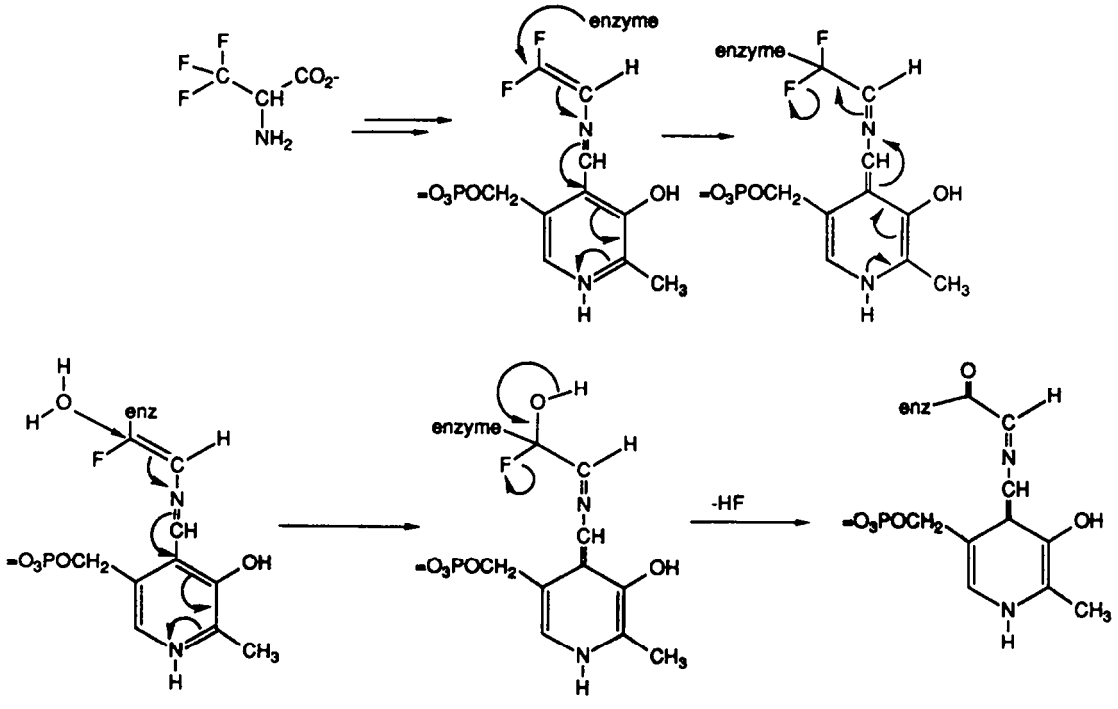


8

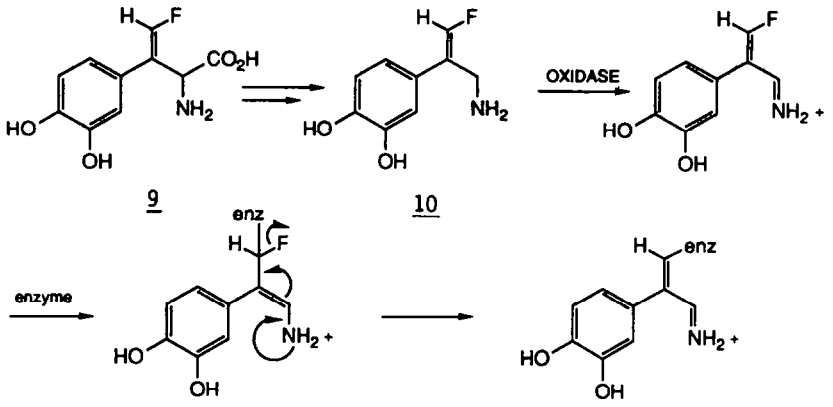
acid, **8**. It has also been reported that decarboxylation of fluoromethylene dopa, **9**, which forms fluoroallyl amine **10**, is a potent inhibitor of monoamine oxidase. Monoamine oxidase was a potential target for inhibition when it was recognized that the intermediate imine could be subject to activation if a suitable leaving group such as fluorine was present. (See Scheme 3.)

2.1. 3-*Fluorophenylalanine*

2.1.1. Erythro 3-*fluorophenylalanine*. Several attempted syntheses of 3-fluorophenylalanine via fluorinated amino acid esters have been unsuccessful because of the difficulty of hydrolyzing the amino acid ester[15] without loss of fluorine. A successful synthesis based upon treatment of the phenylpyruvate esters **11** in acetonitrile solution with fluorine[16] to form the desired fluorophenylpyruvates **12** in 50–80% yield was postulated to involve direct fluorination of the enol. Direct fluorination when enol formation was prohibited led to complex product mixtures. The esters were saponified and reductively aminated. Surprisingly, the reductive amination was very stereoselective, 95 : 5, favoring formation of the *erythro* compound **13**. It was proposed that the stabilizing interactions between the fluorine and the neighboring iminium ion favored a single conformation, **14**, for the reduction.[17]



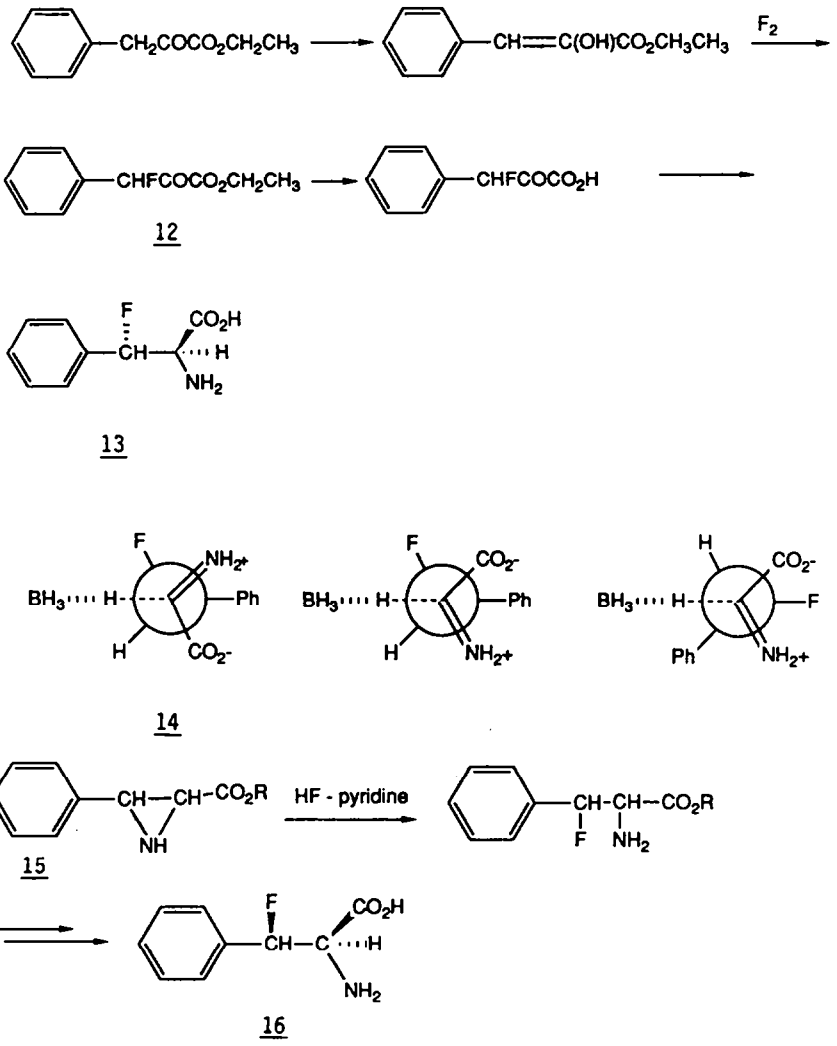
Scheme 2.



9 10

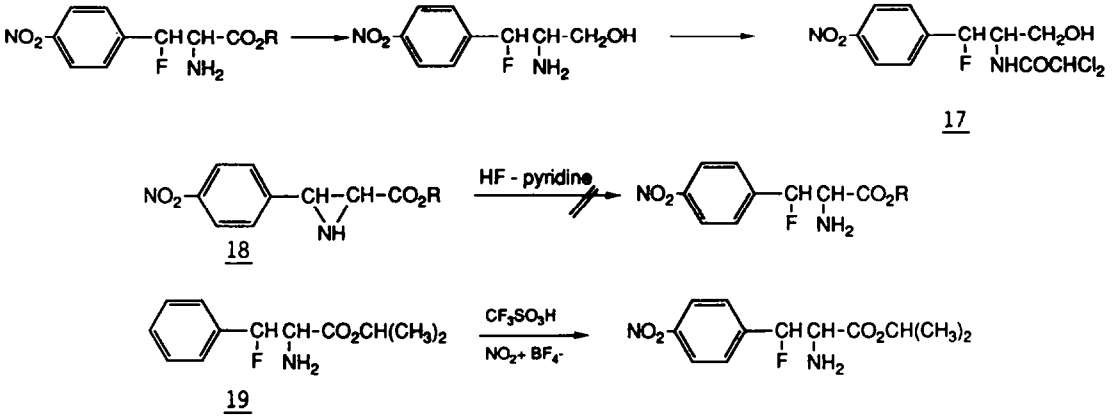
Scheme 3.

2.1.2. Threo 3-*fluorophenylalanine*. The *threo* compound, **16**, was prepared by the hydrogen fluoride–pyridine opening of suitably functionalized aziridine **15**.[18] The free amino acid was prepared by *t*-butyloxycarbonylation of the amino group and chymotrypsin catalyzed hydrolysis of the ester. The diastereochemical assignments were confirmed by NMR and single crystal X-ray diffraction studies.[19]

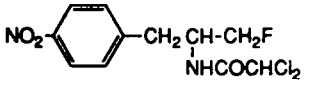


12 13 14 15 16

2.1.3. 1-*Dehydroxy*-1-*fluorochloramphenicol.* The methods developed for the synthesis of the 3-fluorophenylalanine were adapted to the preparation of 1-fluorodehydroxychloramphenicol, **17**.[20] The synthesis was completed in 30% yield by reduction of the *erythro* 3-fluoro-*p*-nitrophenylalanine prepared as described above. Direct nitration of the *erythro* 3-fluorophenylalanine was unselective in contrast to the para selectivity observed with phenylalanine. The *threo* compound could not be prepared by ring opening of a *p*-nitrophenyl substituted aziridine **18**. Therefore nitration of the *threo* 3-fluorophenylalanine **19** was unavoidable. Unfortunately neither the *threo* or *erythro* compounds



demonstrated antibacterial or antifungal activity. This is in contrast to the substitution of the 3-hydroxy by fluorine[21] which led to active compounds.

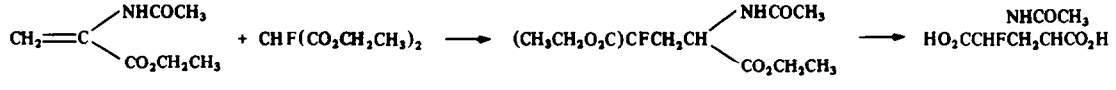


2.2. (E)-*beta*-(*fluoromethylene*)-m-*tyrosine*

Fluoromethylene tyrosine, **22**, was prepared from *m*-methoxyacetophenone, **20**, by bromination followed by fluoride displacement. Olefination, bromination, dehydrobromination and deconjugation formed the *E* bromide **21** which was converted to the amino acid.[22] (See Scheme 4.) Incubation of the fluoromethylene tyrosine with aromatic amino acid decarboxylase (AADC) formed the allyl amine **23**. Allyl amine **25** prepared independently from 3,4-dimethoxyphenylacetic acid, **24**, is a potent inhibitor of monoamine oxidase.[23]

2.3. *Fluoroglutamic acid*

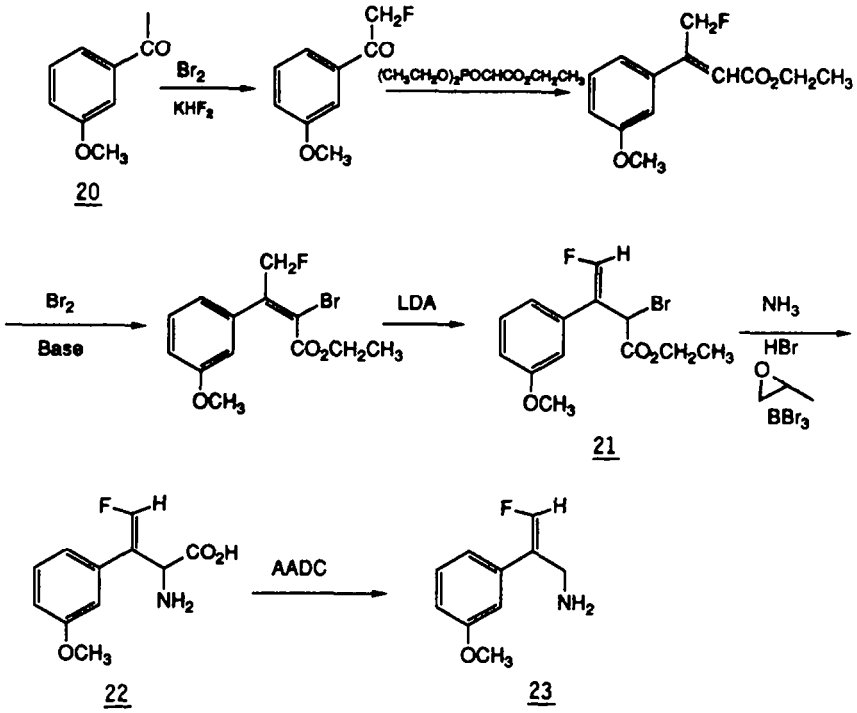
2.3.1. 4-*Fluoroglutamic acid.* 4-Fluoroglutamic acid, **28**, has been prepared by the conjugate addition of fluoromalonate **27** to ethyl 2-acetamidoacrylate, **28**. Decarboxylation yielded the desired fluoro amino acid.[24] The fluorinated glutamic acid was then incorporated into a methotrexate analog **29**. **29** is a poor substrate for folylpoly (gamma-glutamate) synthetase, the enzyme that catalyzes the biosynthesis of the highly retained, cytotoxic methotrexate polyglutamate.[24b]



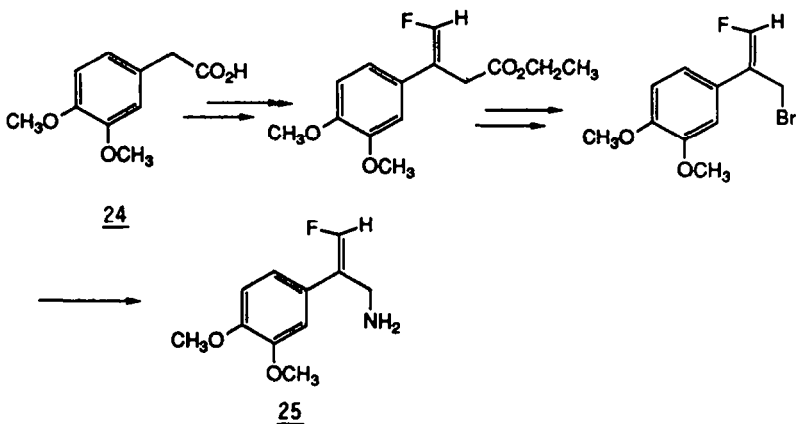
26 **27** **28**

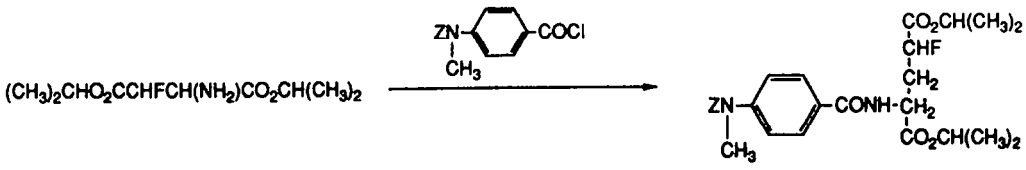
2.3.2. 2-*Difluoromethyl-glutamic acid.* 2-Difluoromethyl-glutamic acid, **31**, may be prepared by deprotonation of the Schiff base of dimethyl glutamate **30** followed by alkylation with chlorodifluoromethane. Removal of the protecting groups led to formation of a mixture of cyclic and acyclic materials. Treatment with thionyl chloride in methanol in the presence of trifluoromethanesulfonic acid yielded only the desired acyclic material **31**.

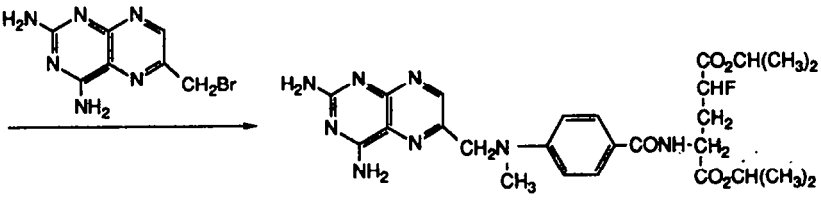
2.3.3. *3-Fluoroglutamic acid.* Fluorination of the hydroxy amino acids with sulfur tetrafluoride in hydrogen fluoride[25] lead only to the formation of fluorinated lactams **33**. Fluorination under the same conditions of the protected *N*-acetyl derivatives suppressed the formation of the lactams. As predicted, inversion of configuration occurred for both diastereomers with the proviso that inversion



Scheme 4.







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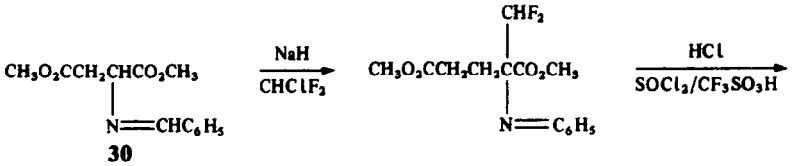

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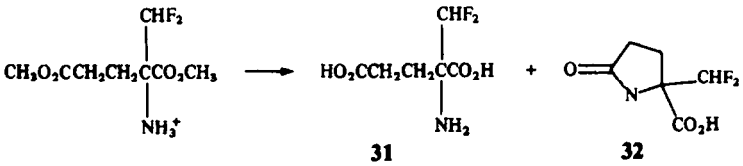

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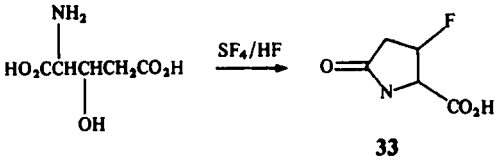

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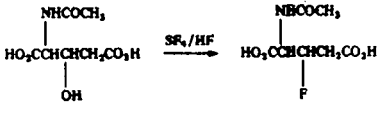
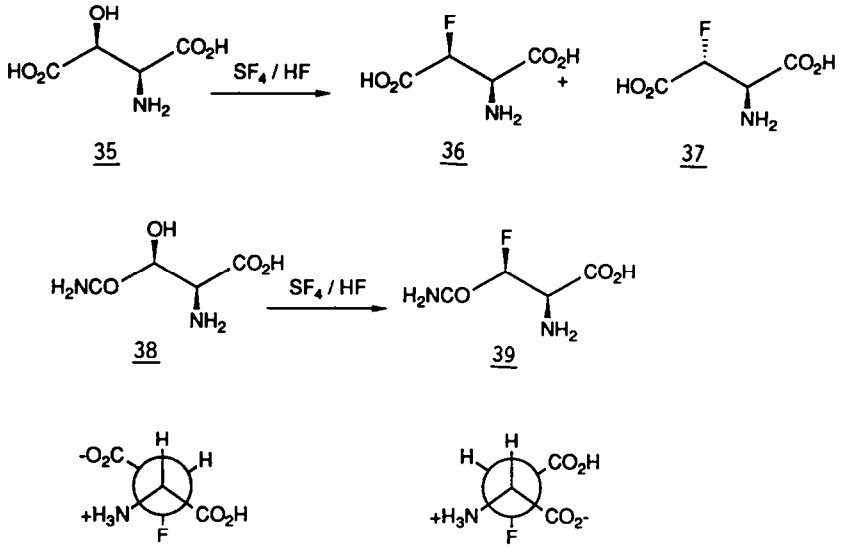


34

was more complete in the reaction of the *threo* compound, 90%, than for the *erythro*, 70%. Deacylation with acylase was selective for the L configuration of the amino acids.

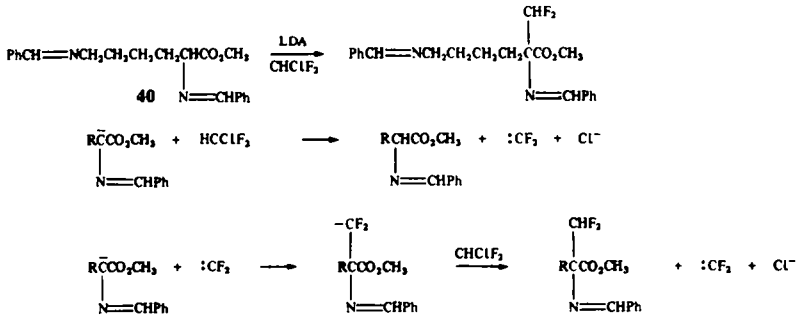
2.4. *Fluoroaspartic acid and fluoroasparagine*

Where D,L-*erythro*-beta-fluoroaspartate and beta-fluoroasparagine have not demonstrated biological activity,[26] D,L-*threo*-fluoroaspartate and fluoroasparagine have pronounced activity[27] as described later. The *threo* compound **36** was prepared by treatment of the *threo*-beta-hydroxyaspartate, **35**, with sulfur tetrafluoride in hydrogen fluoride to form a 3:2 mixture containing the *erythro* **37** as the minor component which could be separated by column chromatography. Fluorination of *threo*-beta-hydroxyasparagine, **38**, under the same conditions yielded only the *threo* fluoro product **39**. From the single crystal X-ray structure determination, in the solid state, in both the *erythro* and *threo* fluoroaspartate compounds the fluorine and the amino group are oriented in a synclinal fashion, even when in the *erythro* compound the result is steric congestion of the carboxylates. Biological studies indicate that the *erythro* compounds were considerably less active than the *threo*. *Threo* beta-fluoroasparagine was an effective inhibitor of glycosylation.[28] Three suggestions have been made to rationalize these findings; (1) as fluorine is slightly larger than hydrogen there is steric hindrance of glycosylation sites, (2) the fluoroasparagine may react with the protein, or (3) most likely fluorine electronically deactivates asparagine toward glycosylation. This inhibition was employed in an investigation of the pro-opiomelanocortin, a glycoprotein prohormone, isolated from mouse pituitary cells. Fluoroasparagine was a useful complement to tunicamycin which inhibits glycosylation by a different mechanism.[29] Significantly *threo* beta-fluoroasparagine, **39**, but not *threo* beta-fluoroaspartate, **36**, or *erythro* beta-fluoroasparagine or *erythro* beta-fluoroaspartate, **37**, showed activity against both human leukemia cells in culture and L 1210 cells in mice.[30] Apparently beta-fluoroasparagine was incorporated into protein.



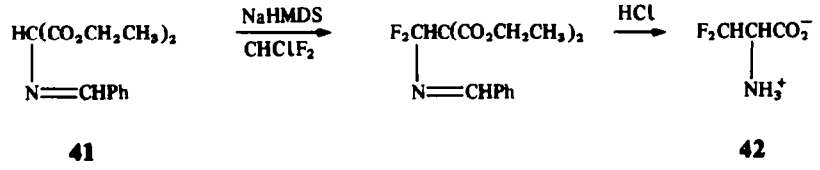
2.5. *Difluoromethyl lysine*

Difluoromethyl lysine may be prepared by reaction of the deprotonated bis-Schiff base of lysine **40** with chlorodifluoromethane. It was postulated that the reaction may proceed via the intermediacy of difluorocarbene, generated by reaction of the difluoromethyl anion species formed by the transfer of a proton from chlorodifluoromethane to the deprotonated imine in an initiating step.[31] Difluoromethyl lysine was reported to be a potent inhibitor of lysine decarboxylase,[32] blocking the biosynthesis of cadaverine which is synthesized by *Mycoplasma dispar* rather than putrescine. Inhibition of cadaverine synthesis was shown to significantly retard the growth of the organism.



2.6. *Difluoro- and trifluoroalanine*

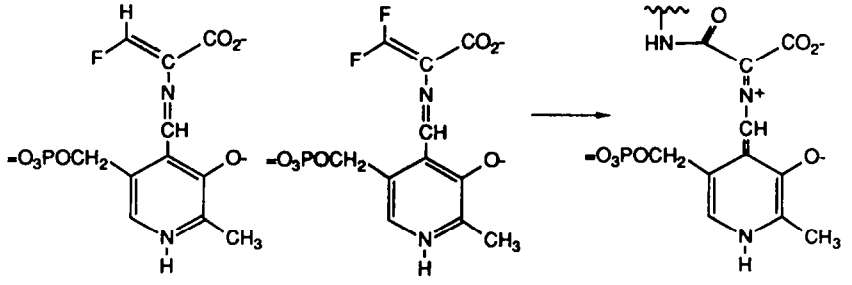
Beta,beta-difluoroalanine, **42**, has previously been prepared by photofluorination of alanine or by fluorodesulfurization of cysteine.[33] Trapping of difluorocarbene with an appropriately functionalized enolate avoids the necessity to utilize fluorine or trifluoromethyl hypofluorite as in the cited procedures. The carbanion of the Schiff base of diethyl aminomalonate **41**, prepared by deprotonation with sodium hexamethyldisilazide was treated with chlorodifluoromethane. Following saponification and decarboxylation, **42** was isolated in 36% overall yield.[34] Both difluoro- and trifluoroalanine have been found to be suicide inhibitors of alanine racemase isolated from *Escherichia coli*. Since both D and L monofluoroalanine are active inhibitors of the enzyme it follows that there might be a common intermediate. However, it was found that enzyme treated with the difluoro analog can recover its activity whereas the enzyme subject to treatment with trifluoroalanine cannot. Loss of fluoride from the Michael addition product of the enzyme can explain the failure of the trifluoroalanine compound to be reversible.[35] (See Scheme 5.) Gamma-cystathionase has been postulated to be inactivated by trifluoroalanine in a very similar manner.[36]



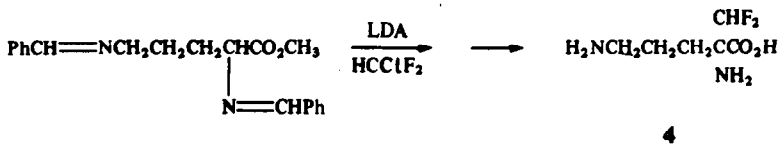
41 **42**

2.7. *Difluoromethyl ornithine*

Difluoromethyl ornithine, **4**, has been prepared by difluoromethylation with chlorodifluoromethane.[31] As was described in the beginning of this section difluoromethyl ornithine is



Scheme 5.



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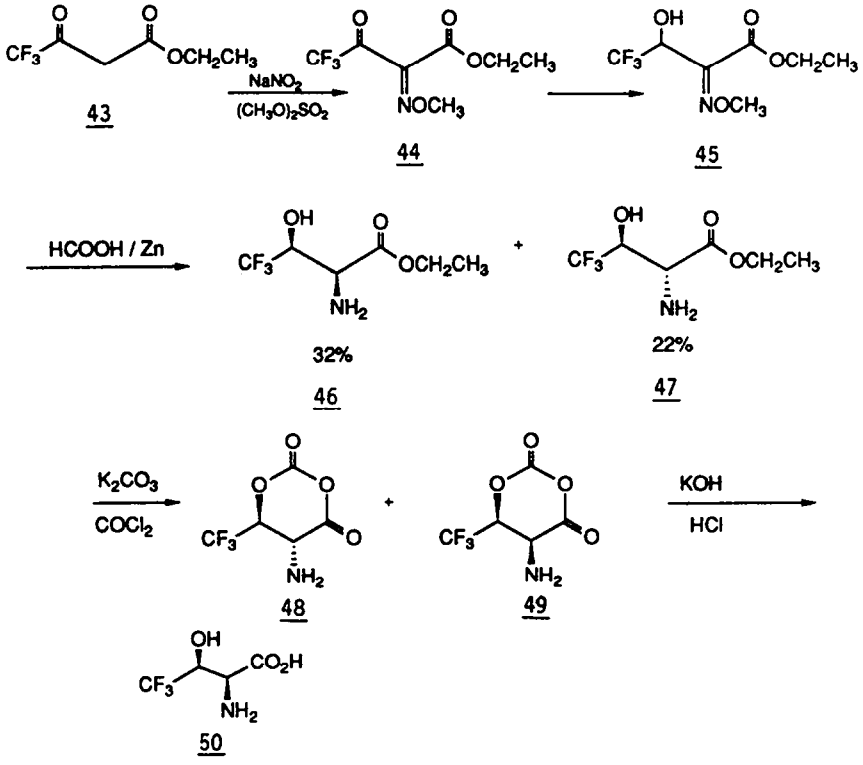
a potent inhibitor of ornithine decarboxylase, blocking putrescine synthesis and therefore reducing polyamine biosynthesis. The antitrypanosomal activity of difluoromethyl ornithine has been tied to this blockade of polyamine synthesis.[37] Inhibition of ornithine decarboxylase by difluoromethyl ornithine was a useful probe of the metabolism of a thermophilic bacterium *Clostridium thermohydrosulfuricum* and the nature of the thermally stable ornithine decarboxylase required for growth.[38]

2.8. *Fluorothreonine*

2.8.1. 4,4,4-*Trifluoro*-threo-*threonine*. Trifluoro-*threo*-threonine, **50**, was prepared by nitrosation of ethyl trifluoroacetoacetate, **43**, followed by methylation of the resultant oxime **44** and reduction with sodium borohydride to form **45**. Reduction with zinc and formic acid formed a diasteromeric mixture of the *threo* and *allo* (threonine nomenclature) materials in a 1.5 : 1 ratio. Upon saponification, these compounds were converted to the oxazolidinones **48** and **49** which could be epimerized with potassium hydroxide. Upon cleavage of the oxazolidinone only *threo* **50** remained.[39] Alternatively deprotonation of ethyl aminoacetate followed by condensation with ethyl trifluoracetate and reduction with sodium borohydride yielded the *threo* dibenzylamino hydroxy derivative **51** in 65% yield. Saponification of the ester with sodium hydroxide and hydrogenolysis of the protecting groups yielded a 2 : 1 mixture of the *allo* **52** and *threo* **50**.

2.8.2. 4-*Fluorothreonine*. 4-Fluorothreonine, **56**, was prepared from the known (2*S*),(3*R*)-3-benzyloxymethyl-2-(hydroxymethyl)-oxirane, **53**, by oxidation with sodium periodate followed by ring opening with ammonia to form, after protection and oxazolidinone formation, a 83 : 9 mixture of regioisomers **54** and **55**. Separation and deprotection followed by fluorination with diethylaminosulfur trifluoride (DAST) formed on oxazolidinone cleavage the **1** 4-fluorothreonine, **56**.



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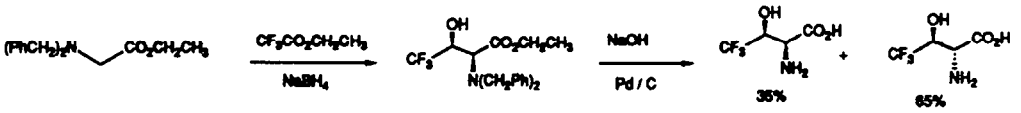

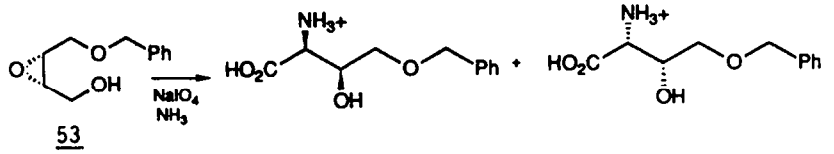

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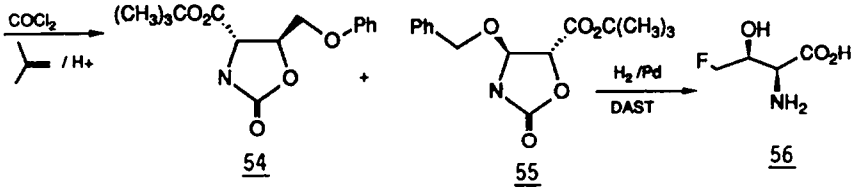
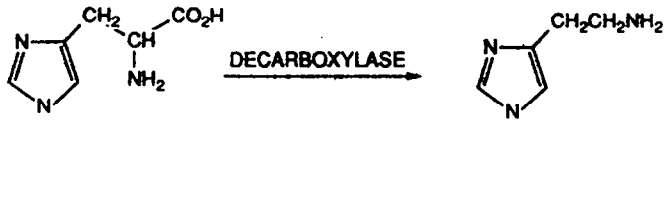
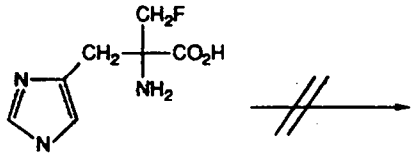


54 55 56

2.9. *Fluoromethyl histidine*

Fluoromethyl histidine, **57**, previously described in the beginning of this section as an inhibitor of histidine decarboxylase, has a pronounced *in vivo* effect on histamine levels in brain but also in the peripheral tissue of mice. It was reported that the magnitude of the induced histamine deficiencies appeared to be organ dependent.[40] More recently fluoromethyl histidine has been described as an "exquisitely selective" compound with action against histidine decarboxylase only.[41] Inhibition of histamine formation is particularly important as histamine release from gastric mucosa is often an underlying factor in the pathogenesis of gastric ulcers.



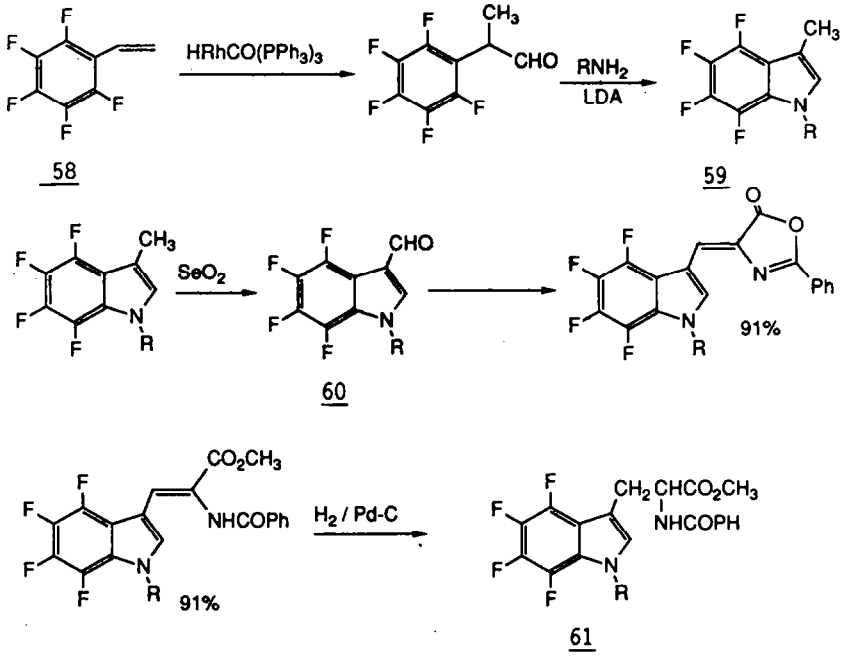


57

2.10. *Tetrafluorotryptophan*

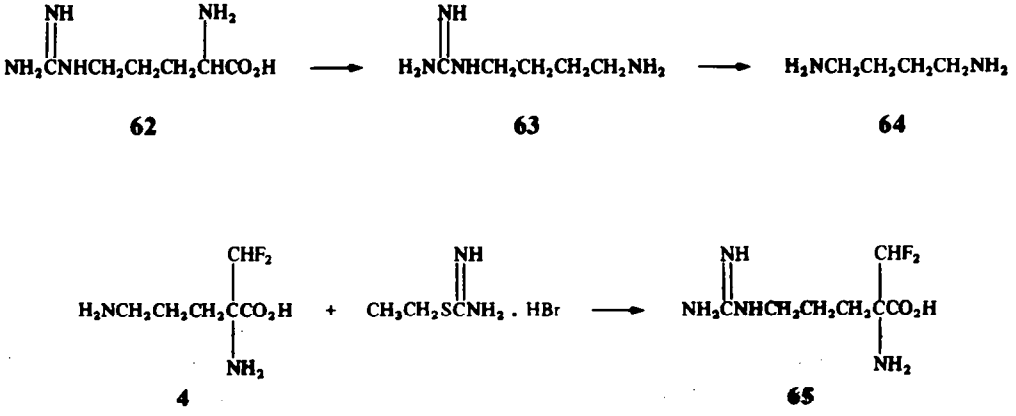
4,5,6,7-Tetrafluorotryptophan has been prepared from pentafluorostyrene, **58**, by hydroformylation with carbon monoxide and hydrogen in the presence of a rhodium catalyst.[42] Treatment of the Schiff base, formed with benzyl amine, with lithium diisopropylamide, LDA, yielded the 1-

benzyl-3-methyl-4,5,6,7-tetrafluoroindole, **59**. Following protecting group manipulation, oxidation with selenium dioxide afforded the 3-formyl indole **60** in 86% yield. Erlenmeyer's azlactone method yielded *N*-benzoyl-4,5,6,7-tetrafluorotryptophan in 79% overall yield. 4,5,6,7-Tetrafluorotryptophan is known to inhibit aminoacyl t-RNA formation.[43]



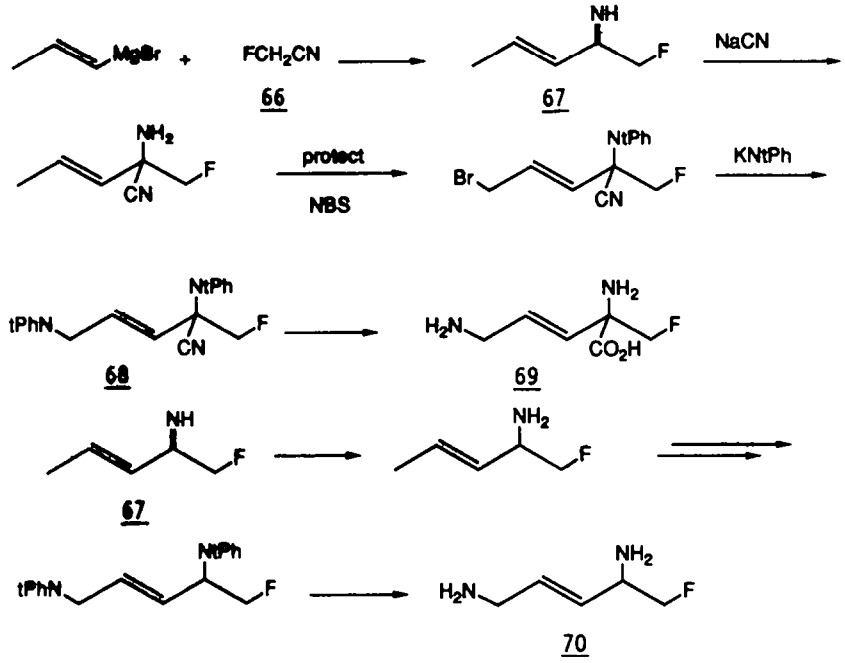
2.11. *Difluoromethyl arginine*

In order to suppress the formation of putrescine in bacteria such as *E. coli* and therefore to test the importance of such diamines in bacterial growth, it is insufficient to inhibit the direct formation of putrescine by ornithine decarboxylase because the alternate path involving the decarboxylation of arginine, **62**, to agmatine, **63**, which is further transformed to putrescine, **64**, must be interrupted also. Difluoromethyl arginine, **65**, has been found to be an effective inhibitor of both biosynthetic and biodegradative arginine decarboxylases.[44] The difluoromethyl compound may be prepared from difluoromethyl ornithine, **4**, via treatment with ethyl thiouronium hydrobromide followed by hydrolysis and purification.[31]



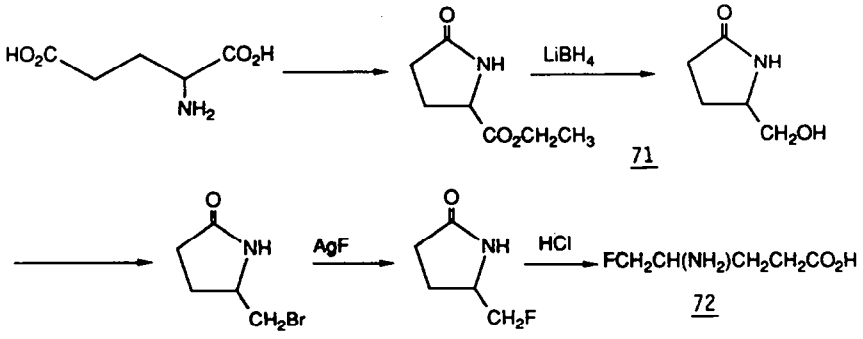
2.12. *Alpha-(fluoromethyl)-dehydroornithine*

The dehydro compound may be prepared by the addition of propenyl Grignard to fluoroacetonitrile, **66**, followed by sodium cyanide. Following protection as the phthalimide, the amine was allylically brominated with *N*-bromosuccinimide. Displacement of the bromide with phthalimide yielded the protected (*E*)-2-(fluoromethyl)-2,5-diphthalimido-3-pentenitrile, **68**. Heating the nitrile in aqueous hydrochloric acid yielded the alpha-(fluoromethyl)-dehydroornithine,[45] **69**. By reducing the addition product of propenyl Grignard to fluoroacetonitrile, **67**, with sodium borohydride, a similar set of transformations lead to the preparation of alpha(fluoromethyl)dehydroputrescine, **70**. Both these compounds very effectively inhibited ornithine decarboxylase. Whereas unsaturation has little effect on the affinity of the dehydroputrescine compound for the enzyme, it has a pronounced accelerating effect on the rate of inactivation. The affinity of alpha(fluoromethyl)dehydroornithine for the enzyme is some 30 times greater.



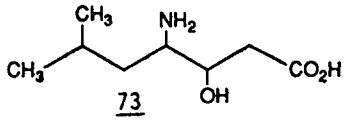
2.13 *Fluoromethyl gamma-aminobutyric acid (GABA)*

The observation that the transaminase which degrades GABA is dependent upon pyridoxal phosphate suggested that a fluoromethyl GABA analog might irreversibly inhibit the enzyme. Glutamic acid was converted to a lactam by treatment with thionyl chloride in ethanol. Lithium borohydride reduction formed the alcohol which was converted with carbon tetrabromide to the bromide. Silver fluoride treatment yielded the fluoro-lactam **71** in 85% yield. Hydrochloric acid treatment formed the desired fluoromethyl GABA,[46] **72**. Treatment of pig brain GABA transaminase with the synthetic material resulted in irreversible inhibition of enzyme activity.[47]



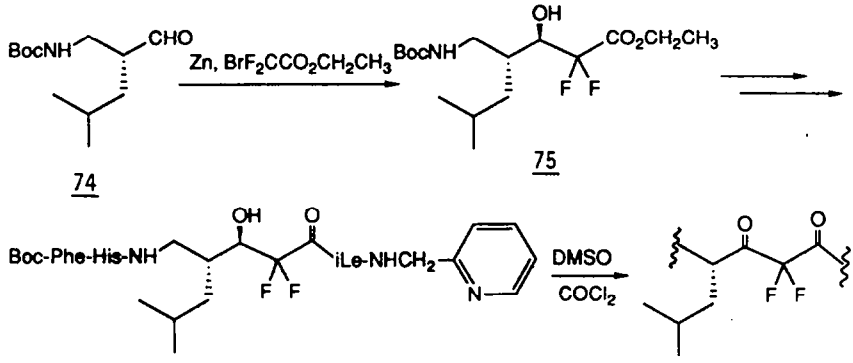
2.14. *Difluorostatine*

Cleavage of the protein angiotensinogen into the decapeptide angiotensin I, a precursor to the pressor angiotensin II, is effected by the aspartyl protease, renin. 2,2-Difluorostatine was prepared as an analog of statine, **73**, the proposed active residue of the pentapeptide aspartyl protease inhibitor pepstatine.[48] Statine has been suggested to be an effective enzyme inhibitor because it resembles the tetrahedral species formed during enzymatic hydrolysis.



73

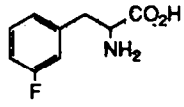
BOC-L-leucinal, **74**, was condensed with the Reformatsky reagent prepared from ethyl bromodifluoroacetate. A mixture of diastereomers, 2:1, was formed under sonicating conditions at room temperature. However under the usual refluxing conditions only a single isomer, the 3*S*-hydroxy compound **75**, was formed. After incorporation into a pentapeptide, the alcohol was subjected to Swern oxidation to form the difluoroketone **76**. Although the ketone was a less effective inhibitor of pepsin than pepstatin it did exhibit high specificity for renin.



74 75 76

2.15. m-*Fluorophenyl alanine*

m-Fluorophenyl alanine, **77**, has been incorporated in the synthesis of di- and tripeptides which easily penetrate fungal cell walls.[49] Once in the cell, the toxic agent, **77**, was released. **77** itself is completely inactive against *Candida albicans* as can be seen in Table 2 where the effect of the additional peptide residues on activity is also evident.



77

Table 2. *m*-Fluorophenyl alanine containing peptides as agents against *Candida albicans*

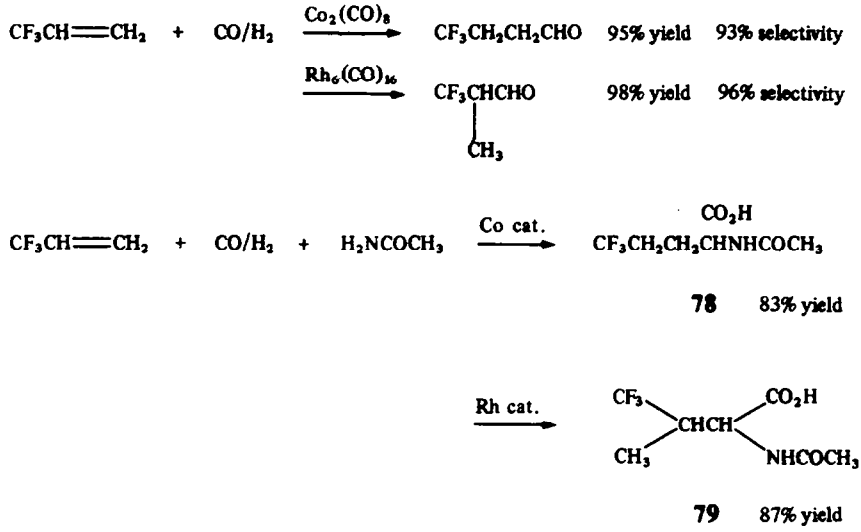
m-Fluorophenyl alanine containing compounds	MIC[a] against *C. albicans* B311	759
LmFPhe	>250	>250
LmFPhe-L-Ala	2	4
LmFPhe-L-Ala-L-Ala	0.5	2
LmFPhe-L-Met-L-Met	8	63
L-Ala-L-Ala-LmFPhe	2	63

[a] Minimum inhibitory concentration in micrograms per milliliter.

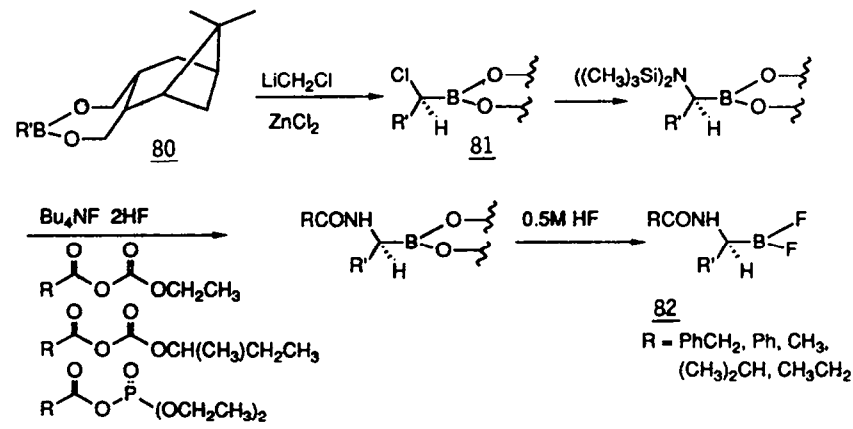
2.16. *General methods*

In addition to the procedures described above, several general synthetic methods which may be applied to the synthesis of a variety of fluorinated amino acids have also been developed.

2.16.1. *Amidocarbonylation.* Amidocarbonylation has been effectively employed to prepare 4,4,4-trifluorovaline, **78**, and 5,5,5-trifluoronorleucine, **79**, from 3,3,3-trifluoropropene, carbon monoxide, hydrogen and acetamide in presence of a catalyst.[50] The reaction presumably proceeds via the aldehyde, which can be prepared with high regioselectivity with either cobalt or rhodium carbonyl catalysts.



2.16.2. *Difluoroborane analogs.* A very different approach to the synthesis of fluorinated amino acid analogs is the synthesis of difluoroborane analogs,[51] where the boron has replaced the carboxylic acid carbon. The difluoroboron analogs were prepared from alkyl pinanediol boronates **80** which were treated with dichloromethyl lithium to form the chloromethylborates which rearrange smoothly with migration of the alkyl substituent to form **81**. The amino group is introduced by treatment with lithium hexamethyldisilazide, LHMDS. Deprotection of the amine required very dry tetra *n*-butylammonium fluoride or tetra *n*-butylammonium fluoride dihydrogen fluoride complex in the presence of an efficient acylating agent. Water and fluoride ion lead to decomposition of the amino boronate. Treatment of the boronate esters with boron trichloride followed by 0.5 M aqueous hydrogen fluoride formed the difluoroboranes **82**. The difluoroborane compounds were biologically equivalent to the boronic acids, but were much more easily purified. Several of the difluoroboranes were potent inhibitors of chymotrypsin and elastase.



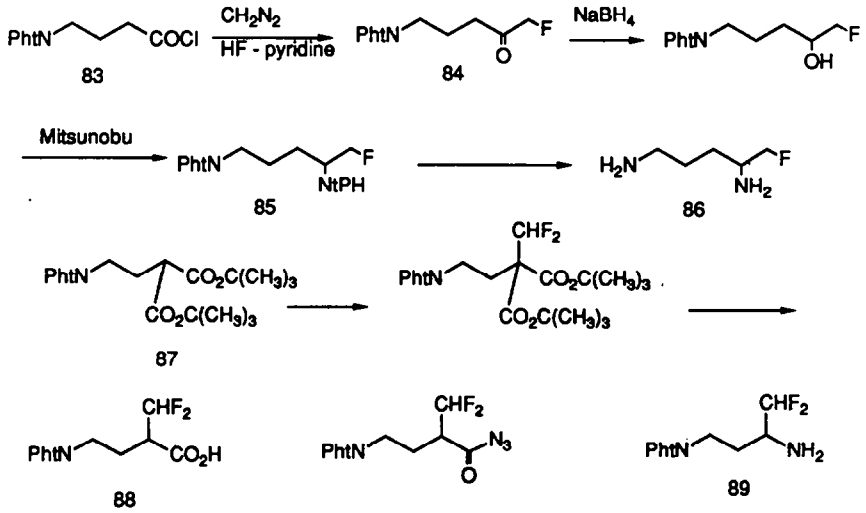
3. FLUORINATED AMINES

3.1. *Fluoromethyl putrescine*

Monofluoromethyl and difluoromethyl putrescine have been found to be potent inhibitors of ornithine decarboxylase.[52] The monofluoro compound was prepared by reaction of 4-phthalimido-l-butyryl chloride, **83**, with diazomethane to form the diazoketone which was then treated with hydrogen fluoride-pyridine solution. Reduction of the fluoromethyl ketone **84** followed by Mitsunobu reaction to form the diphthalimide **85** in 60% yield. Deprotection yielded the desired 5-fluoropentane-1,4-diamine, fluoromethyl putrescine, **86**.

3.2. *Beta, beta-Difluoromethyl putrescine*

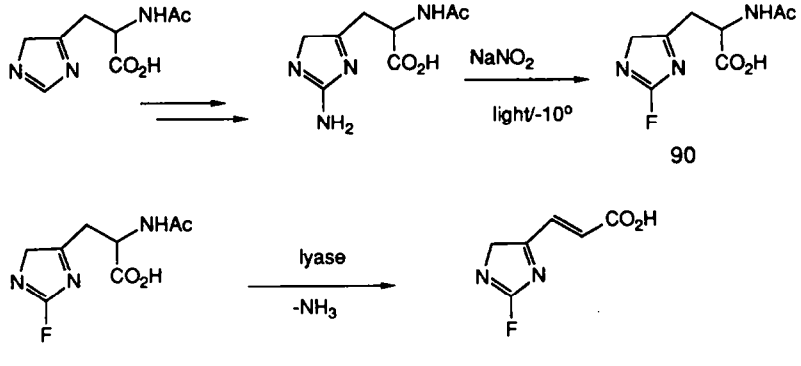
5,5-Difluoropentane-1,4-diamine was prepared by reaction of the sodium enolate of *t*-butyl 4-phthalimido-2-carbo-*t*-butoxy-butyrate, **87**, with excess chlorodifluoromethane at room temperature. Treatment with trifluoracetic acid followed by decarboxylation with glacial acetic acid yielded the 4-phthalimido-2-difluoromethyl-butyric acid, **88**. Curtius rearrangement led to formation of the desired 5,5-difluoropentane-1,4-diamine,[53] **89**. Both amines are presumed to inactivate ornithine decarboxylase by loss of hydrogen fluoride from the postulated immonium ion intermediate (see Scheme 1 for related mechanism). The resultant enamine is an active Michael type acceptor for nucleophilic portions of the enzyme.



83 84 85 86 87 88 89

3.3. *Fluorourocanic acid*

2-Fluorohistidine, **90**, which may be prepared by photolytically promoted Balz–Schiemann reaction of 2-amino-histidine. **90** has been metabolized by histidine ammonia-lyase to 2-fluorourocanic acid, **91**. 2-Fluorourocanic acid was found to be an especially potent, irreversible, inhibitor of urocanase, the second enzyme in the pathway for histidine catabolism.[54]

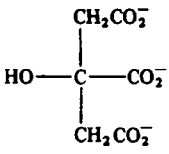


90 91

4. FLUORINATED ACIDS AND ESTERS

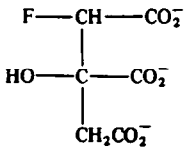
4.1. *Fluorocitrate*

Fluorinated acids and esters have been widely used as biological probes.[55] As citrate, **92**, is a central component in the primary metabolism of prokaryotes and eukaryotes, fluorinated analogs, the best known of which is 2-fluoro-citrate,[56] **93**, have received some attention. In contrast 3-deoxy-3-fluoro-citrate, **94**, cannot undergo the retroaldol type cleavage characteristic of citrate processing



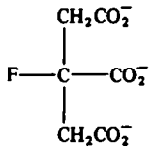
citrate

92



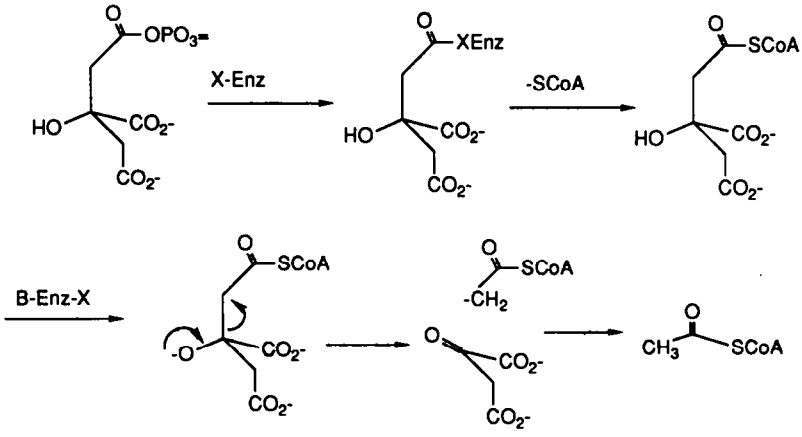
(2*R*, 3*R*) - 2 - Fluorocitrate

93



94

enzymes. 3-Deoxy-3-fluoro-citrate, **94**, is a competitive inhibitor of citrate synthase, a substrate for ATP splitting only with ATP citrate lyase, an efficient inactivator of *K. aerogenes* citrate lyase and a substrate for hydrogen fluoride elimination with aconitase. Each enzyme shows a distinct type of interaction conditioned by the nature of the enzyme and the consequences of substituting a C–F for a C–O bond.

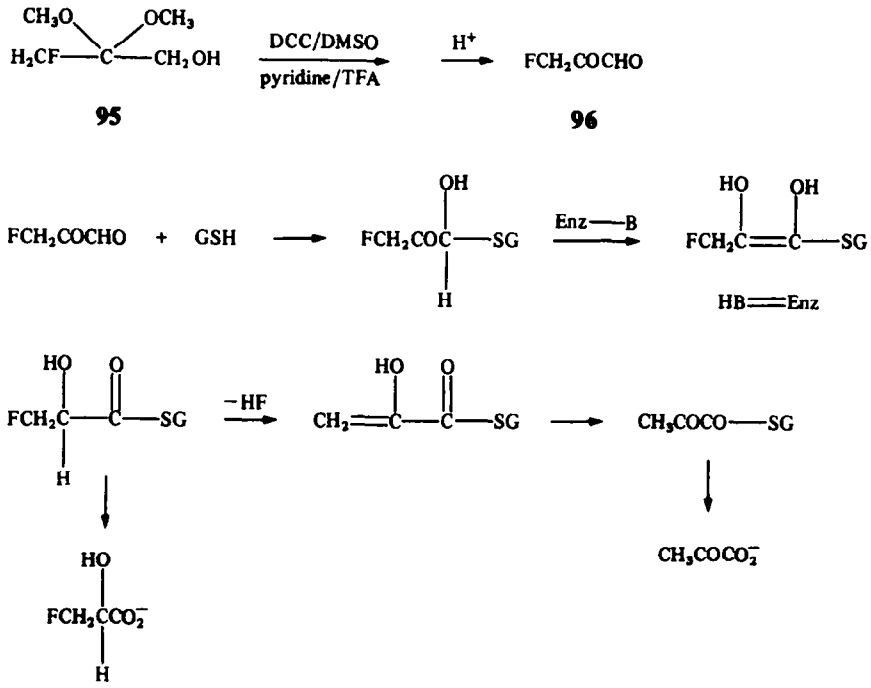


4.2. *Fluoromethyl glyoxal*

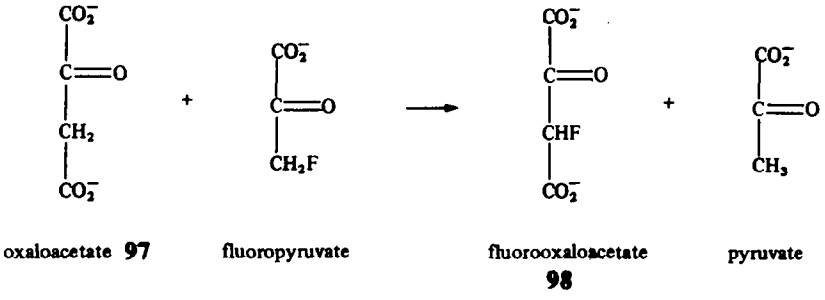
Fluoromethyl glyoxal, **96**, was prepared from the dimethylketal of fluorohydroxyacetone,[57] **95**. Following Moffatt oxidation, deketalization was extremely slow. In contrast to reactions of bromo- or chloro-glyoxal with yeast glyoxylase in the presence of glutathione, where loss of halogen predominates, there is a distinct partitioning of the intermediate with only a portion of the product suffering fluoride loss.[58] Fluoromethyl glyoxal constitutes a unique case where the typical fluoride elimination path is partially suppressed. (See Scheme 7.)

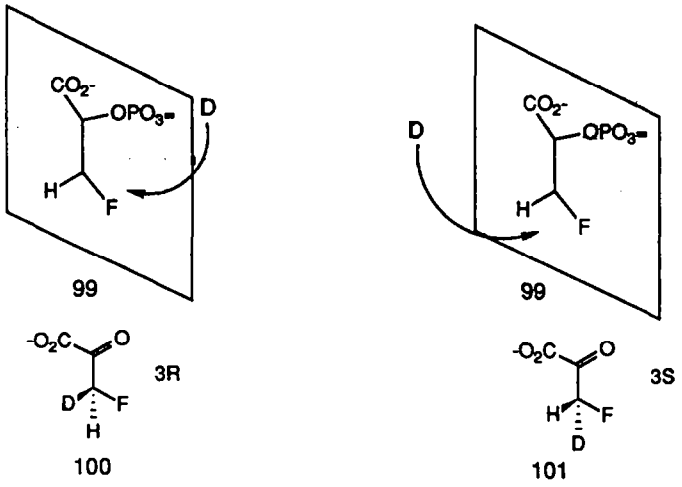
4.3. 3-*Fluoropyruvate*

3-Fluoropyruvate, **97**, has been very successfully employed in determining the stereochemistry of transcarboxylase catalyzed carboxylation of 3-fluoropyruvate to form fluorooxaloacetate,[59] **98**. The ^{19}F NMR was used to determine the stereochemistry of the carboxylation. The *Z*-phosphoenolfluoropyruvate **99** was reduced with either Enzyme I from *Escherichia coli* or pyruvate kinase to form only the 3*R* (3,3 $^{1}H^{2}H$) fluoropyruvate, **100** or the 3*S* (3,3 $^{1}H^{2}H$) fluoropyruvate, **101**, respectively. In either case use of the fluoromethyl group greatly simplifies the stereochemical analysis relative to the classic $^{1}H^{2}H^{3}H$ approach. The transcarboxylation reaction of *P. shermanii* formed only the 2*R*,3*R* compound on reduction with malate dehydrogenase.



Scheme 7.

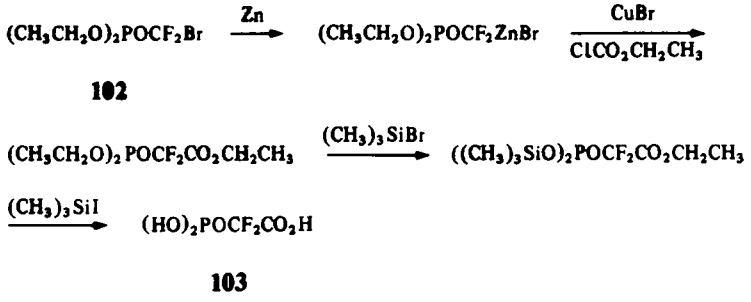




4.4. *Difluorophosphonoacetic acid*

Diethyl (bromofluoromethyl)phosphonate, **102**, readily prepared from triethyl phosphite and dibromofluoromethane, was allowed to react with zinc dust in the presence of cuprous bromide

followed by ethyl chloroformate.[60] Sequential treatment of the product with trimethylsilyl bromide followed by trimethylsilyl iodide, formed on hydrolysis, the title compound **103**. This effective synthetic strategy makes available quantities of an interesting phosphonoacetic analog with potential antiviral activity.



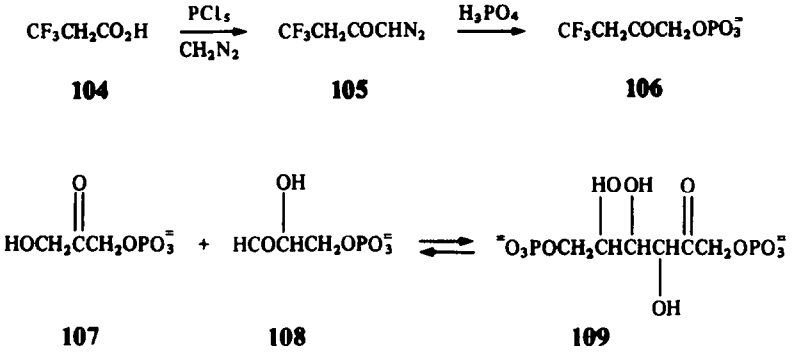
5. FLUORINATED KETONES

Fluorinated ketones have been successfully employed as suicide enzyme inhibitors. As described earlier, such an inhibitor forms a reversible complex with the target enzyme. While bound to the ezyme, the substrate is transformed in such a way as to activate the latent functionality present in the molecule. This initial transformation is often related to the process the enzyme promotes with the natural substrate. The activated suicide inhibitor now undergoes an irrversible reaction with a functional group on the enzyme, inactivating the enzyme.

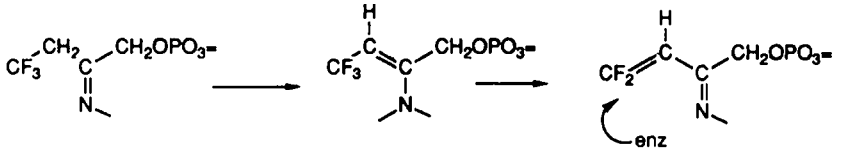
5.1. 1-*Hydroxy*-2-*keto*-4,4,4-*trifluorobutane phosphoric acid* (*HTFP*)

An inhibitor of aldolase, where an enolate intermediate is postulated, might contain a good leaving group which would readily be lost to form a Michael acceptor. If nucleophilic residue on the enzyme was located nearby, conjugate addition to the nearby substrate would tie up the enzyme.

1-Hydroxy-2-keto-4,4,4-trifluorobutane phosphoric acid (HTFP) was prepared to test this postulate.[61a] 3,3,3-Trifluoropropionic acid, **104**, was converted to the fluorinated diazobutanone **105** which was then treated with phosphoric acid to form the desired substrate **106**. Rabbit muscle aldolase promotes the reversible cleavage of fructose 1,6-diphosphate **109** into dihydroxyacetone phosphate, **107**, and D-glyceraldehyde-3-phosphate, **108**. Introduction of HTFP resulted in irreversible inhibition of the enzyme. Presumably the intermediate enamine, formed via the Schiff base, lost fluoride ion to form the Michael acceptor to which added a neighboring thiol to bind the enzyme to the activated substrate. (See Scheme 9.)



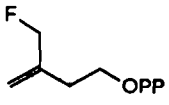
Scheme 8.



Scheme 9.

5.2. 3-(*Fluoromethyl*)-3-*buten*-1-*yl diphosphate*

3-(Fluoromethyl)-3-buten-1-yl diphosphate, **110**, and (*Z*)-4-fluoro-3-methyl-2-buten-1-yl diphosphate, **111** were both potent inhibitors of isopentyl diphosphate:dimethallyl diphosphate isomerase. It was postulated that the analogs were covalently bound to the enzyme by nucleophilic displacement of the allylic fluoride in an S_N2 or S_N2' process.[61b,c]



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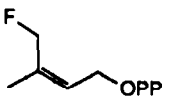
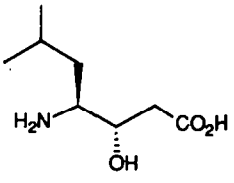


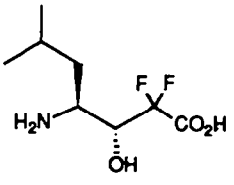
111

Fluoroketone enzyme inhibitors. Fluorinated ketones have been explored as inhibitors of hydrolytic enzymes[62] where the fluorines adjacent to the carbonyl stabilize the hemiketals formed by those carbonyls. These tetrahedral compounds resemble the tetrahedral intermediates postulated in the hydrolysis of a peptide linkage. A number of fluorinated ketones have been prepared and have been examined as inhibitors of acetylcholinesterase, carboxypeptidase A and angiotensin converting enzyme. As can be seen in Table 3, the fluorinated ketones show a very strong tendency to remain associated with the enzymes. The strong binding of the fluorinated ketones to angiotensin converting enzyme suggests the potential of fluorinated ketones as anti-hypertensives, as angiotensin is a potent vasoconstrictor.

Statine, **73**, has been suggested to be a transition state analog for aspartyl protease. A similar increase in association with the enzyme was found when fluorinated analogs were prepared.[63] The details of the synthesis have been described earlier.



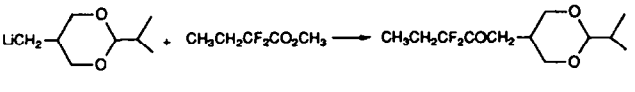
73



112

5.3. *Fluoroketone phospholipids*

Esterases, such as phospholipidase A_2 have also been successfully inhibited with fluorinated ketone analogs,[64] **113**. The hydrolysis of an ester has also been postulated to involve a tetrahedral intermediate. (See Scheme 10.)



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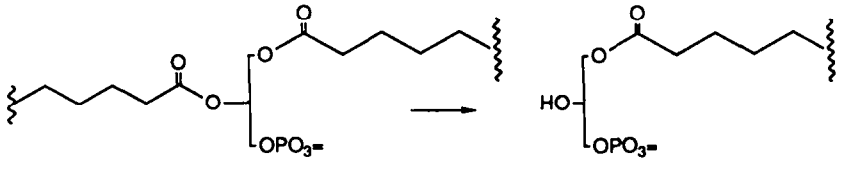
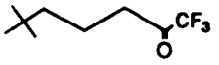
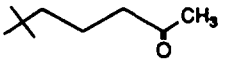
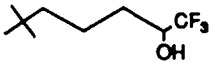
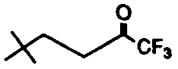
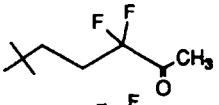
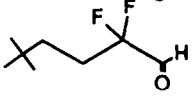
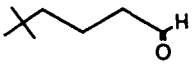
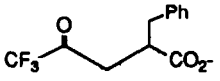
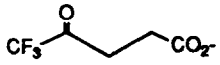
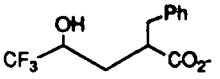
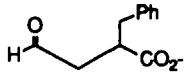
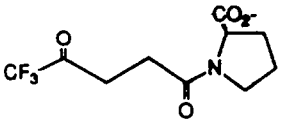
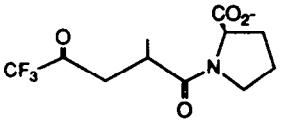
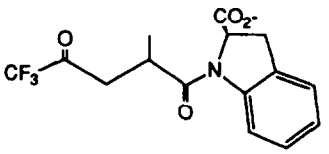
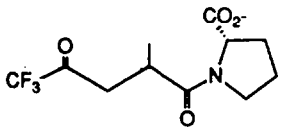
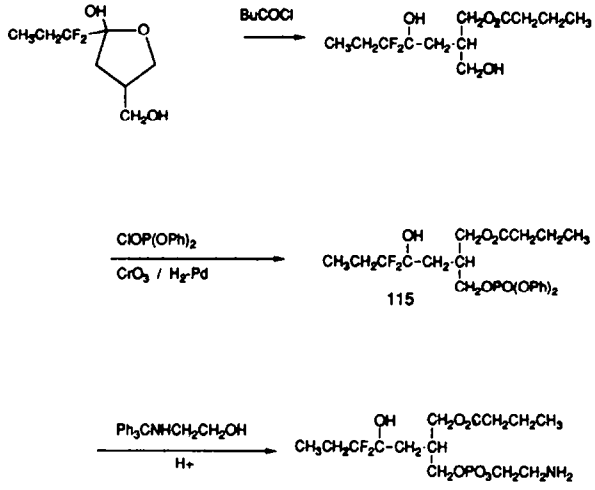


Scheme 10.

Table 3. Fluoroketone enzyme inhibitors

Enzyme	Compound	$K_{dissociation}$
A		16
A		310000
A		410000
A		8000
A		1.6
A		600
A		10^6
B		0.2
B		700
B		90
B		0.48
C		15
C		0.2
C		0.012
C		4500

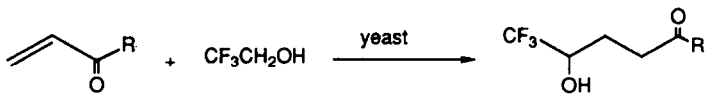
A = acetylcholinesterase; B = carboxypeptidase; C = angiotensin converting enzyme.



The required fluoroketone analog was prepared by addition of the protected organolithium reagent **114** to methyl 2,2-difluorobutyrate. Following protecting group manipulations and phosphorylation, the phosphotidic ester **115** was condensed with *N*-tritylethanolamine. Deprotection yielded the desired phosphotidyl ethanolamine analog which binds about 300× tighter than the corresponding non-fluorinated substrate, 1,2-dibutyryl-*sn*-glycero-3-phosphatidyl-ethanolamine.

5.4. *General preparative methods*

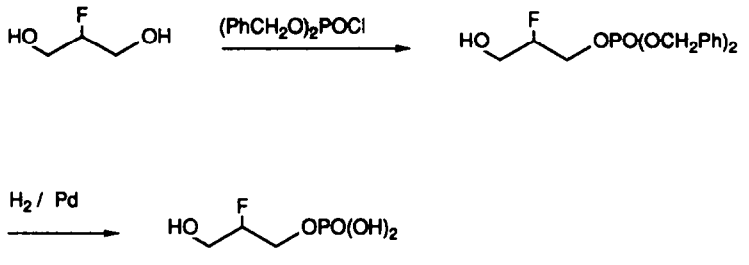
5.4.1. *Addition reactions.* Chiral fluorinated ketones have been prepared by yeast promoted additions of 2,2,2-trifluoroethanol to alpha, beta unsaturated ketones.[65] The reactions proceed in 38–50% yield with enantiomeric excesses as high as 93%. In contrast to the yeast promoted reductions of unsaturated esters and ketones, the trifluoroethanol addition was very fast.



6. FLUORINATED ALCOHOLS

6.1. *Fluoro-deoxy-glycerol phosphate*

1-Fluoro-1-deoxy-glycerol-3-phosphate, 2-fluoro-2-deoxy-glycerol phosphate and 3-deoxy-3-fluoro-glycerol-1-phosphate have been prepared as specific inhibitors of *sn*-glycerol-phosphate dehydrogenase isolated from the locust flight muscle.[66] The required fluoroglycerols were prepared by known methods[67] and were converted into the phosphate esters first by treatment with dibenzylphosphoryl chloride and then subsequent hydrogenolytic deprotection. The hydroxy groups made little contribution to enzyme substrate interactions. There was no evidence for enhanced binding of any isomer, suggesting that neither the polarity of the C–F bond or its ability to accept a hydrogen bond influenced the interaction of the fluorinated analogs.

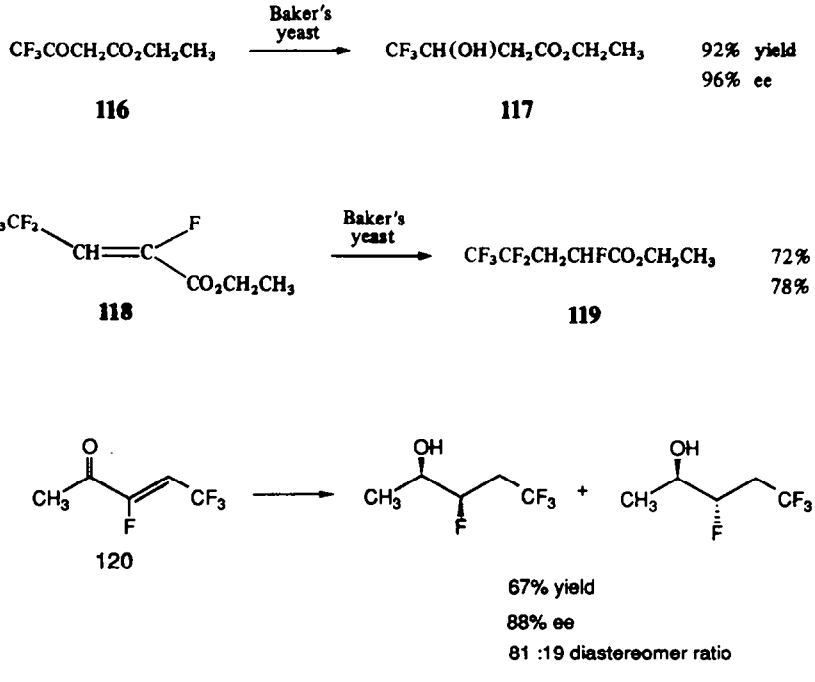


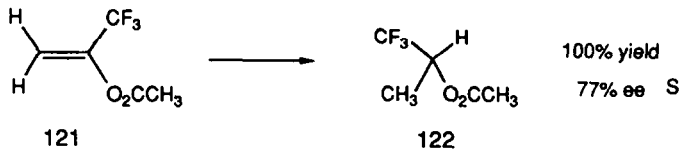
6.2. *Trifluoroethanol*

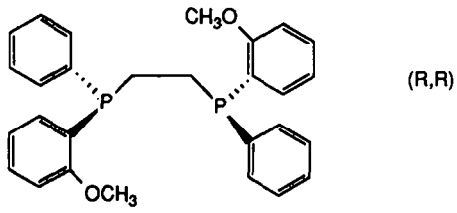
Fluorinated alcohols have been used as probes of enzymatic reactions, where inhibition of reaction was not as important as the ability to monitor binding by ^{19}F NMR. Trifluoroethanol was incubated with Horse liver alcohol dehydrogenase, while the ^{19}F NMR spectrum was monitored.[68] The sensitivity of the chemical shift to ionization made it possible to monitor the ionization of the alcohol as binding occurred. This NMR probe was sufficiently sensitive to allow the study of the effect of added NAD during the formation of a tertiary complex with the enzyme.

6.3. *General preparative methods*

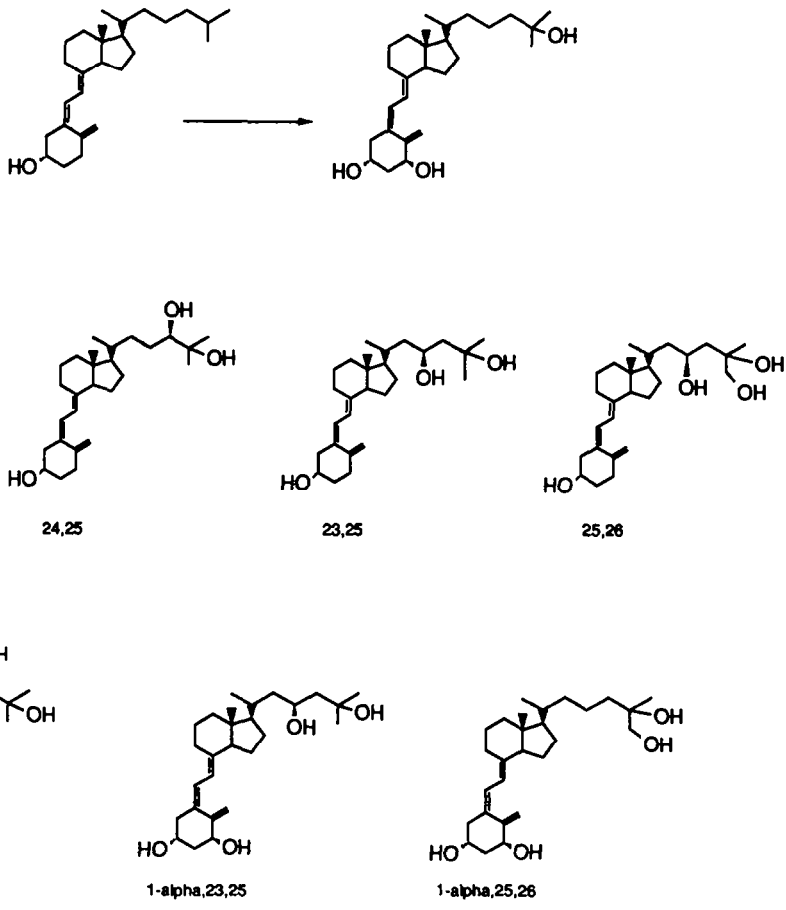
6.3.1. *Enzymatic reduction.* Chiral fluorinated alcohols may be prepared by enzymatic reduction of fluorinated olefins and ketones.[69] When fluorinated ketones such as ethyl 4,4,4-trifluoro-acetoacetate, **116**, was treated with baker's yeast, ethyl 4,4,4-trifluoro-3-hydroxy-butanoate, **117**, was formed in excellent yield and in greater than 96% enantiomeric excess(ee). Reduction of ethyl 2,4,4,5,5,5-hexafluoropent-2-enoate, **118**, with baker's yeast led to formation of ethyl 2,4,4,5,5,5-hexafluoropentanoate, **119**, in 72% yield and in 78% ee. When unsaturated ketones, such as 3,5,5,5-tetrafluoro-3-penten-2-one, **120**, were reduced with baker's yeast[70] it was found that the carbonyl group could be selectively reduced prior to reduction of the double bond. The reduction proceeded in 67% yield with 88% ee and a diastereoselectivity of 4 : 1.







6.3.2. *Catalytic reduction.* It is also possible to prepare chiral fluorinated alcohols by asymmetric catalytic reduction. Reduction of 1,1,1-trifluoro-2-(acetyloxy)-2-propene, **121**, with hydrogen in the presence of (1,5-cyclooctadiene)((*R*,*R*)-1,2-ethanediylbis(*o*-methoxyphenyl)phenylphosphine) ((*R*,*R*)-diPAMP) rhodium tetrafluoroborate, led to formation of (*S*)-1,1,1-trifluoro-2-propyl acetate, **122**, in quantitative yield and 77% ee.[70]



Scheme 11.

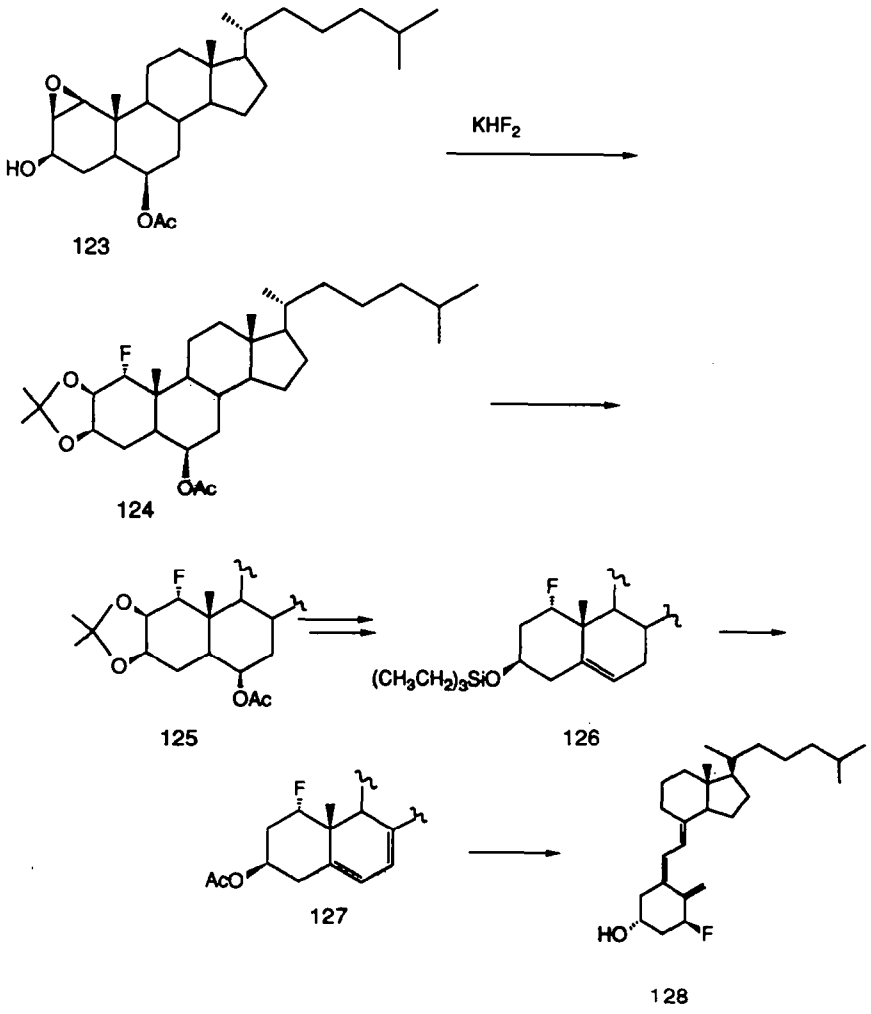
7. STEROIDS

Fluorination of steroids has been known to have profound effects on biological activity since the early work of Fried.[72] Fluorinated steroids have also been described in other reviews.[73] Recently, fluorination has proved especially useful in the preparation of analogs of vitamin D_3 and in preparation of estrogen or estrogen analogs for estrogen receptor labeling.

The preparation of fluorinated analogs of vitamin D_3 has been reviewed[74] but the most recent report is in Japanese.[75] Selective fluorination was employed to block hydroxylation or to modify the reactivity of neighboring hydroxyl groups and has been very successful, with the biological studies guiding synthesis.

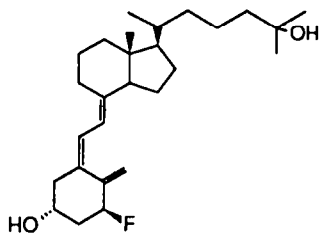
7.1. 1-*alpha-Fluoro-vitamin* D_3

1-alpha-Fluoro-vitamin D_3, **128**, has been prepared previously by direct fluorinative dehydroxylation of 1-alpha-hydroxy-vitamin D_3 by treatment with DAST,[76] but the stereochemistry of fluorination was not determined definitively. More recently a regio- and stereoselective synthesis based upon the KHF_2 opening of 6-beta-acetoxy-1-beta-2-beta-epoxy-5-alpha-cholesten-3-beta-ol, **123**, in 45% yield has been reported.[77] Work up with acetone and acid formed the acetonide. The acetate was saponified and the 6-hydroxy group dehydrated with phosphorous oxychloride **125**. Deprotection of the acetonide, followed by selective protection of the 3-beta hydroxyl with triethylsilylchloride facilitated conversion of the 2-beta hydroxyl to a xanthate ester. Reduction with tributyl tin hydride formed **126**. Allylic bromination, dehydrobromination formed the diene **127** which was photolyzed to yield the vitamin D_3 analog **128**. From this work it was determined that the earlier DAST reaction had formed the 1-beta-fluoro material.



7.2. 1-*alpha-Fluoro*-25-*hydroxy-vitamin* D_3

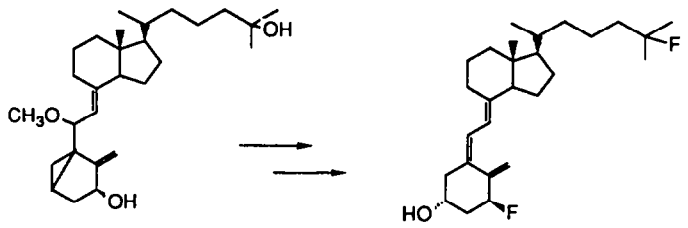
As was described in the introduction, hydroxylation at carbon-1 and carbon-25 produces the hormonally active form of vitamin D_3 which mediates calcium and phosphorous metabolism. The synthesis of the desired compound was modeled on the synthesis of 1-alpha-fluoro-vitamin D_3 employing cholenic acid to facilitate functionalization of carbon-24.[78] The synthetic material did not stimulate intestinal calcium transport or bone mobilization of calcium. However, the synthetic material was nearly 30 × more effective at binding than the 25-hydroxy-vitamin D_3.



129

7.3. 1,25-*Difluoro-vitamin* D_3

Treatment of a protected form of 1-alpha, 25-dihydroxy-vitamin D_3, **130**, with DAST yielded, what has been established on the basis of the previously discussed synthetic results, as 1-beta-25-difluoro-vitamin D_3,[78] **131**.



130 131

7.4. 2-*beta-Fluoro*-1-*alpha-hydroxy-vitamin* D_3

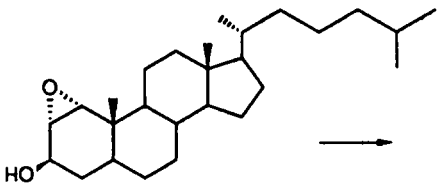
Introduction of fluorine at carbon-2 was predicted to affect the hydrogen bonding of the 1-alpha-hydroxy to the receptor.[80] Potassium bifluoride treatment of 6-beta-acetoxy-1-alpha-2-alpha-epoxy-5-alpha-cholesten-3-beta-ol, **132**, formed the 6-beta-acetoxy-2-beta-fluoro-cholesten-1-alpha-3-beta-diol, **133**. Conversion of the diol to the corresponding vitamin D_3 analog was carried out by the standard methods described above following acetylation of the alcohols. The biological activity of this material has not yet been reported.

7.5. 3-*beta-Fluoro-vitamin* D_3

Cholesta-5,7-diene-3-beta-ol was protected as the Diels–Alder adduct of 4-phenyl-1,2,4-triazoline-3,5-dione. Treatment of the free hydroxyl with DAST resulted in a 35% yield of the protected 3-beta fluoride **136**. On deprotection and photolysis, 3-beta-fluoro-vitamin D_3, **137**, was formed.[81] The 3-beta-fluoro-vitamin D_3 was less active than vitamin D_3 but more active than 3-dehydroxy-vitamin D_3.

7.6. 19,19-*Difluoroprevitamin* D_3

The thermal isomerization of previtamin D_3, **138**, to vitamin D_3, **139**, has been shown to be sensitive to substituent on the triene portion of the molecule. Treatment of 19-oxocholesterol acetate **140** with DAST yielded, after conventional manipulations, 19,19-difluorocholesta-5,7-dien-3-beta-ol, **141**. Irradiation formed 19,19-difluoroprevitamin D_3 in 20% yield, however, neither thermal or photochemical transformations led to the desired vitamin D_3 analog. Only 19, 19-difluorotachysterol



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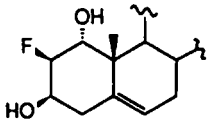

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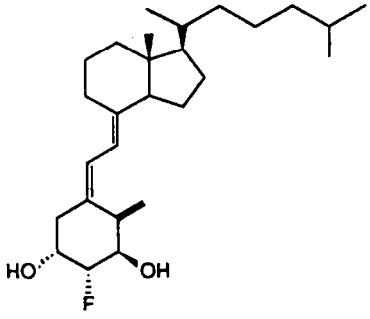

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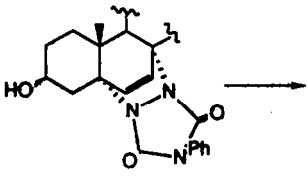

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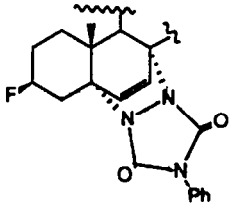

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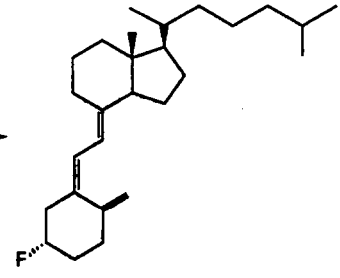

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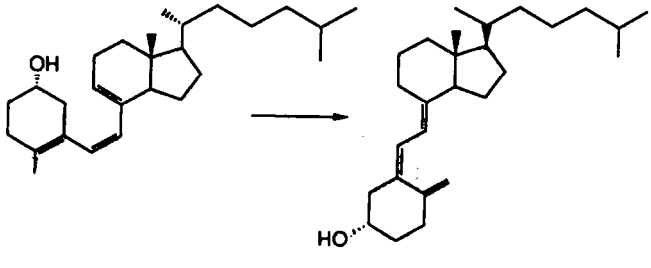
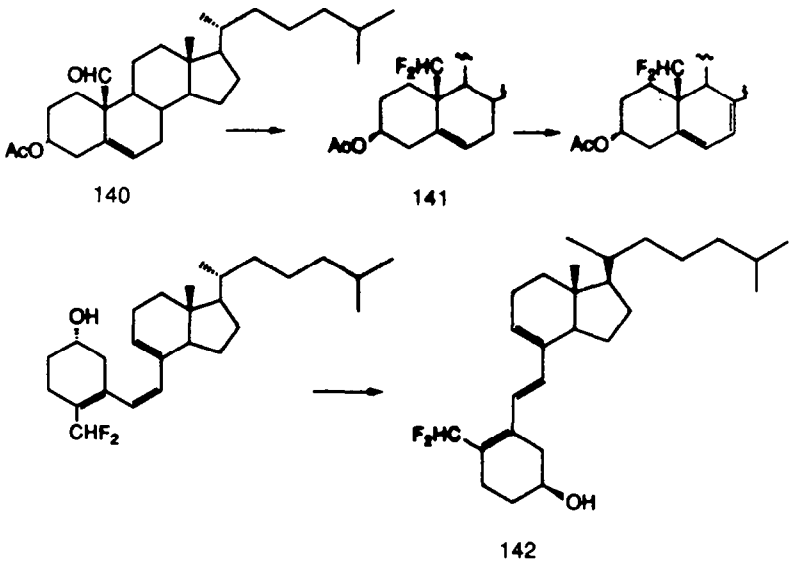


138 139

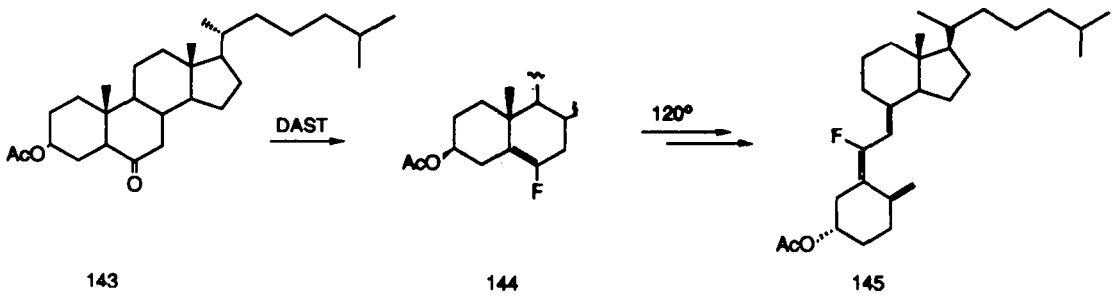
Scheme 11.

142 was isolated.[82] The thermally induced (1,7) hydrogen shift is no longer thermodynamically favored when carbon-19 is difluorinated.



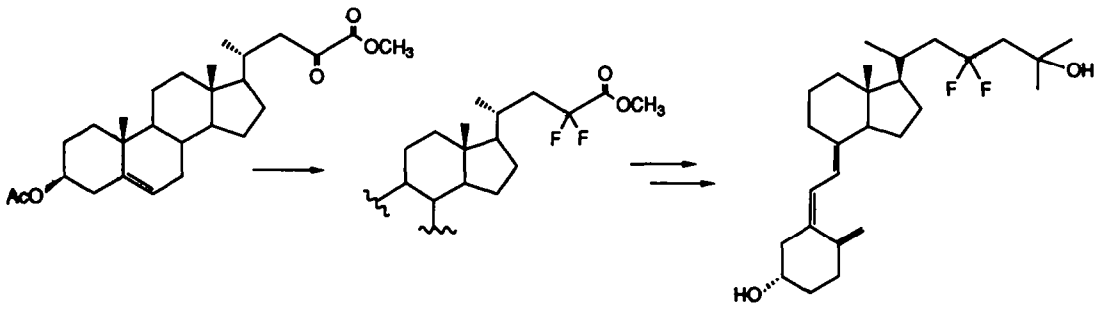
7.7. *6-Fluoro-vitamin D_3*

Substitution of the trienic portion of vitamin D_3 was successful at the 6-position. Treatment of 6-ketocholestanyl acetate, **143**, with DAST lead to formation of 6-fluorocholesteryl acetate, **144**, in 55% yield. Allylic bromination and dehydrohalogenation lead to 6-fluoro-7-dehydro-cholesterol in 48% yield. On irradiation, the previtamin D_3 analog was formed in 43% yield. Rearrangement to acetyl 6-fluoro-vitamin D_3, **145**, in 30% yield occurred on heating to 120°.[83] Fluorination of carbon-6 is having relatively little effect on the (1,7) hydrogen shift, therefore thermal conversion is successful. 6-Fluoro-vitamin D_3 bound to the receptor, but did not stimulate calcium absorption or mobilization.[84] It was the first vitamin D_3 analog reported to antagonize 1-alpha-25-dihydroxy-vitamin D_3.



7.8. 23,23-*Difluoro*-25-*hydroxy-vitamin* D_3

Hydroxylation of the side chain of vitamin D_3 has profound effects on the activity of the hormone and on the site specificity of the hormone. Fluorination at carbon-23 was proposed to prohibit the hydroxylation at that position known to occur during the course of vitamin D_3 metabolism. Fluorination of the ketoester, prepared in three steps from 6-beta-methoxy-3-alpha-5-cyclo-23,24-dinor-5-alpha-cholen-22-ol, **146**, with DAST yielded the difluoro ester **147** in 74% yield. Additional functional group manipulations led to formation of the desired previtamin. Conventional vitamin D_3 transformations followed by photolysis formed 23,23-difluoro-25-hydroxy-vitamin D_3,[85] **148**. Although the biological activity of the analog was somewhat reduced, apparently the binding was diminished,[86] 1-hydroxylation did occur.

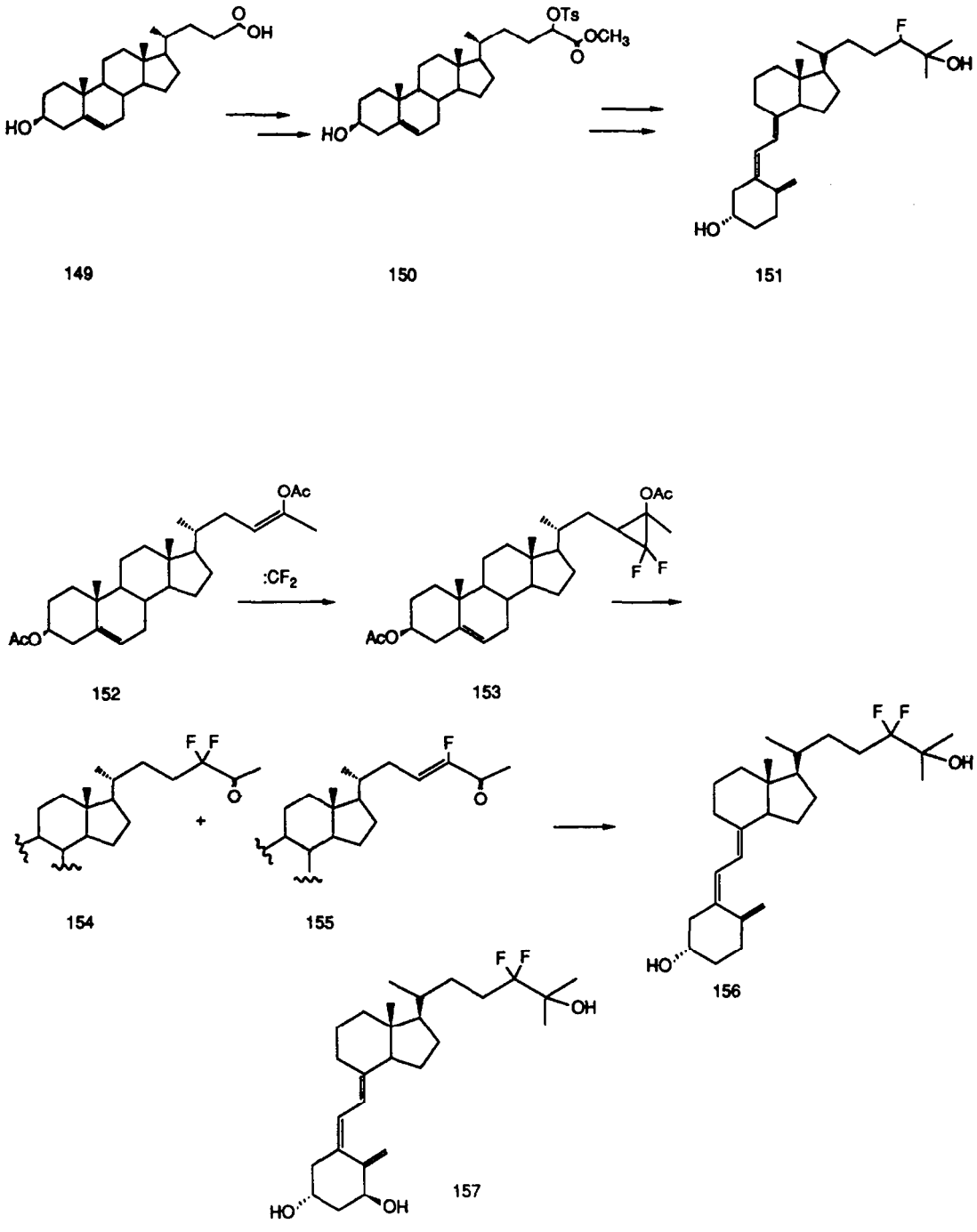


146 147 148

7.9. 24,24-*Difluoro*-25-*hydroxy-vitamin* D_3 *and* 24-*eta-fluoro*-25-*hydroxy-vitamin* D_3

24-eta-Fluoro-25 hydroxy-vitamin D_3 was prepared in 73% yield by potassium fluoride treatment of the 24-tosylate, **149**. The required tosylate was prepared in several steps from cholenic acid.[87] Addition of methyl magnesium iodide formed the 25-hydroxy compound which was then subjected to the usual manipulations and photolysis to form 24-eta-fluoro-25 hydroxy-vitamin D_3, **151**, as a one to one mixture of epimers.

24,24-difluoro-25-hydroxy-vitamin D_3 was prepared by conversion of cholenic acid into the enol acetate **152** which was then treated with difluorocarbene, generated by thermolysis sodium chlorodifluoroacetate. The difluorocyclopropane **153** was formed in 34% yield. Ring opening followed treatment with lithium hydroxide forming both the difluoroketone **154**, 9% and the fluoroenone **155**, in 61% yield. Following the addition of methyl magnesium iodide to the difluoroketone, the usual operations formed 24,24-difluoro-25-hydroxy-vitamin D_3, **156**. These compounds were equal or slightly more active than the unfluorinated materials.[88]

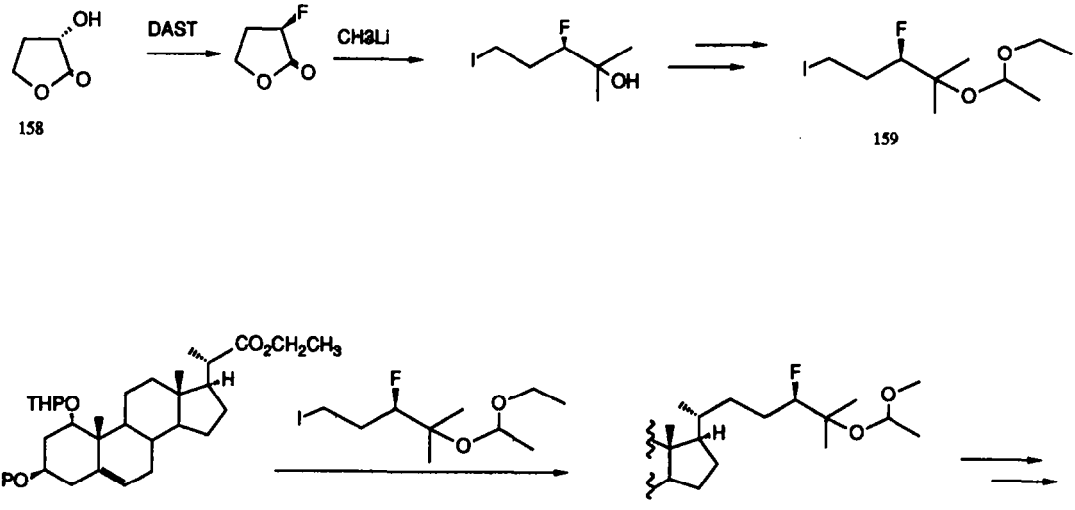


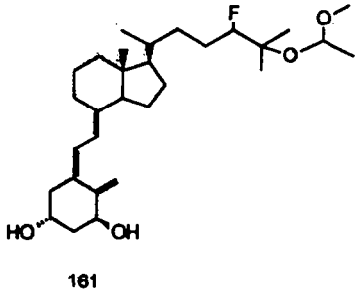
7.10. 1-*alpha*-,25-*Dihydroxy*-24,24-*difluoro-vitamin* D_3

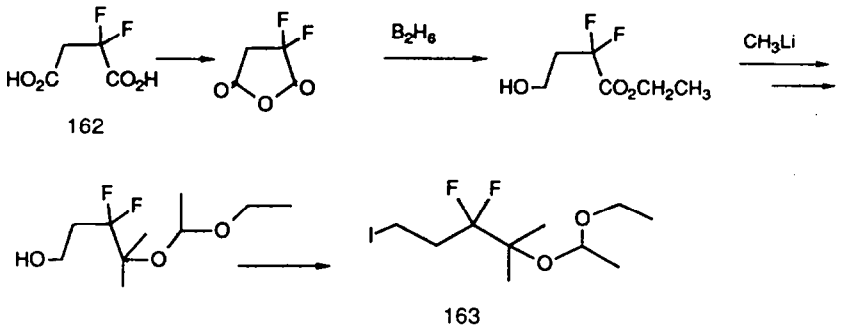
With supplies of 24,24-difluoro-25-hydroxy-vitamin D_3, **156**, in hand it was possible to introduce the 1-alpha-hydroxyl enzymatically.[89] 1-alpha-,25-Dihydroxy-24,24-difluoro-vitamin D_3, **157**, was found to be 5–10 times more active than 1-alpha-,25-dihydroxy-vitamin D_3 *in vivo*. Although this increased activity was notable, the very high activity associated with 1-alpha-,25-dihydroxy-vitamin D_3 makes it less significant than the prolonged lifetime of the analog *in vivo*.[90] The compound also demonstrated potential anti-cancer activity.

7.11. 24(R)-*Fluoro*-1-*alpha*-,25-*dihydroxy-vitamin* D_3

The evidence that 1-alpha-,25-dihydroxy-vitamin D_3 was metabolized by a stereospecific hydroxylation at carbon-24 to form 1-alpha-,24(*R*),25-trihydroxy-vitamin D_3, suggested that a single enantiomer of 24-monofluorinated 1-alpha-,25-dihydroxy-vitamin D_3 might be extremely potent. To test this hypothesis 24(*R*)-fluoro-1-alpha-,25-dihydroxy-vitamin D_3 was prepared by condensation of (*R*)3-fluoro-5-iodo-2-methyl-2-pentanol, **159**, with the lithium enolate of functionalized, commercially available dehydroepiandrosterone, **160**. The alkylating agent was prepared stereospecifically by DAST fluorination of 2-hydroxy-butyrolactone prepared from l-malic acid,[91] **158**. Reduction, tosylation, hydrogenolysis, deprotection and acetylation formed the acylated 24(*R*)-fluoro-1-alpha-,25-dihydroxycholesterol. Conversion into the 5,7-dienes and photolysis was effected under standard conditions to form 24(*R*)-fluoro-1-alpha-,25-dihydroxy-vitamin D_3, **161**. This synthetic scheme was easily adapted to the preparation of 24,24-difluoro analogs. 2,2-Difluorosuccinic acid, **162**, was converted to iodide **163** required for enolate alkylation by standard techniques. Alkylation and elaboration was as described for the monofluorinated material. These compounds inhibited tumor cell proliferation and differentiation and had good antirachitogenic activity in concert with prolonged half-lives relative to non-fluorinated materials.

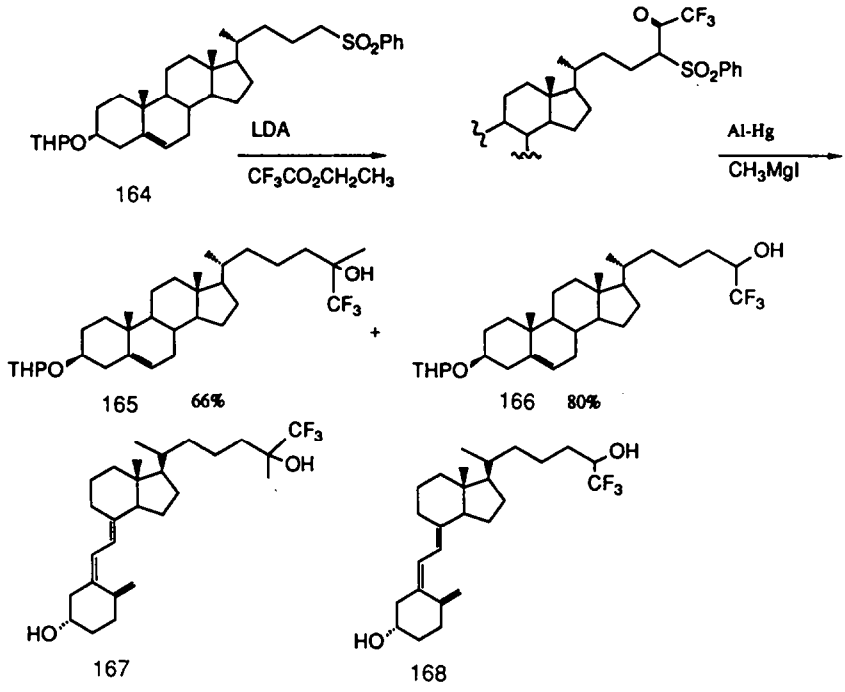






7.12. 25-*Hydroxy*-26,26,26-*trifluoro-vitamin* D_3, **167** *and* 25-*Hydroxy*-26,26,26-*trifluoro*-27-*nor-vitamin* D_3, **168**

24-Phenylsulfonyl-25,26,27-trinorcholest-5-en-3-beta-yl tetrahydropyranyl ether, **164**, was deprotonated with LDA and condensed with ethyl trifluoroacetate. The sulfone was removed with aluminum amalgam followed by treatment of the ketone with methyl magnesium iodide forming the 25-hydroxy-26,26,26-trifluoro compound **165** in 66% yield. Desulfonylation followed by sodium borohydride reduction rather than Grignard addition lead to the 25-hydroxy-26,26,26-trifluoro-27-nor compound **166** in 80% yield. Both materials were elaborated to the vitamin D_3 analogs following previously described procedures.[92]

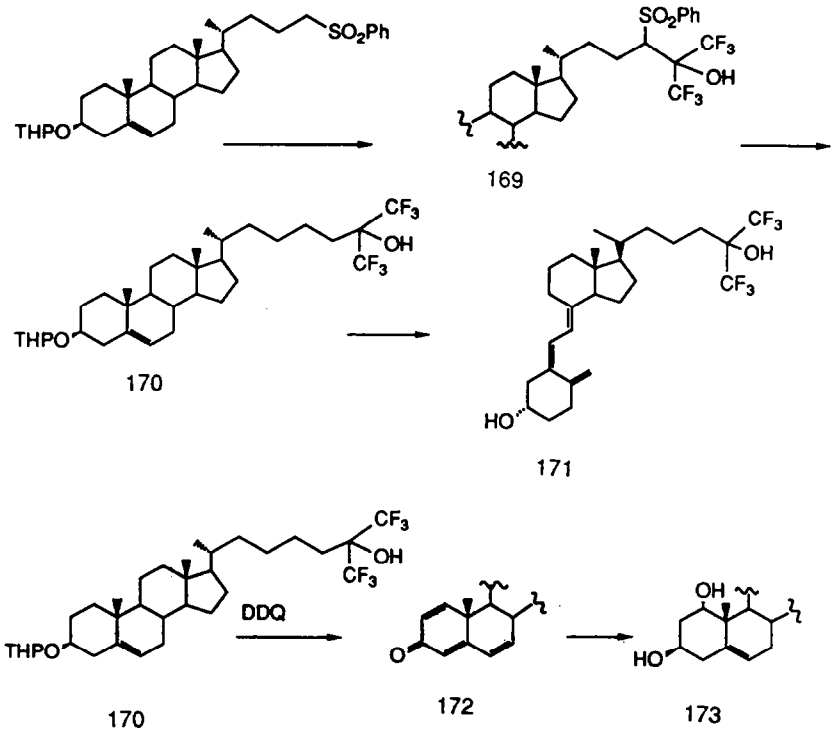


7.13. 25-*Hydroxy*-26,26,26,27,27,27-*hexafluoro-vitamin* D_3

When deprotonated **164** was condensed with hexafluoroacetone in 84% yield, the resultant sulfone **169** could be desulfonylated in 64% yield with sodium amalgam.[93] This material was converted uneventfully to 25-hydroxy-26,26,26,27,27,27-hexafluoro-vitamin D_3, **171**.

7.14. 1-*alpha*-,25-*Dihydroxy*-26,26,26,27,27,27-*hexafluoro-vitamin* D_3

The intermediate **170** was deprotected and oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to form the 1,4,6-triene-3-one **172** in 55% yield. Epoxidation with alkaline hydrogen peroxide followed by lithium/ammonia reduction yielded the 1-alpha-hydroxy compound **173** in 63% yield.[94] The product was converted to the vitamin D_3 analog in the usual manner.



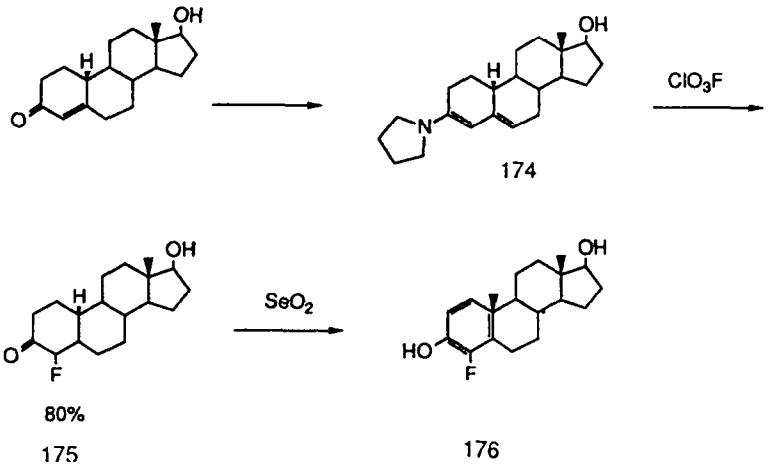
It was found that although 1-alpha-,25-dihydroxy-26,26,26,27,27,27-hexafluoro-vitamin D_3 is more active than 1-alpha-,25-dihydroxy-vitamin D_3, this analog exhibited diminished binding to the receptor.[95] The increase in activity has been attributed to the resistance to metabolism exhibited by the analog. 25-Hydroxy-26,26,26,27,27,27-hexafluoro-vitamin D_3 was approximately 20 times more active than the 25-hydroxy-vitamin D_3 itself. The trifluoro analogs 25-hydroxy-26,26,26-trifluoro-27-nor-vitamin D_3 and 25-hydroxy-26,26,26-trifluoro-vitamin D_3 were slightly less active and 8 times more active than 25-hydroxy-vitamin D_3, respectively.

From these studies of variously fluorinated vitamin D_3 compounds it becomes apparent that with the 1-alpha-,25-dihydroxy-vitamin D_3 affinity for the receptor is apparently optimized. In the case of 24,24-difluoro-1-alpha,25-dihydroxy-vitamin D_3 as well as 1-alpha-,25-dihydroxy-26,26,26,27,27,27-hexafluoro-vitamin D_3 the activity observed has been suggested to be a result of the slower metabolism of the fluorinated analogs.

Estrogen receptor binding agents. Fluorination has also been very effectively employed as a method for preparing modified estrogen receptor binding agents. These compounds are examined for their binding affinity then are frequently prepared bearing an ^{18}F. ^{18}F is an especially useful isotope as it decays via positron emission. When incorporated in a biologically active substance such as an estrogen analog, the distribution of the radiolabeled material may be followed by positron emission tomography. Since ^{18}F has a half-life of 110 minutes, there are severe limitations on the techniques which can be used for its introduction. Additionally the ^{18}F must be incorporated late in the synthesis, so that the analog retains enough activity for radiolabeling purposes upon completion of the synthetic scheme. And, if it is to be used as an *in vivo* receptor ligand, material with high specific activity (*ca* 1000 Ci/mmol) must be produced.

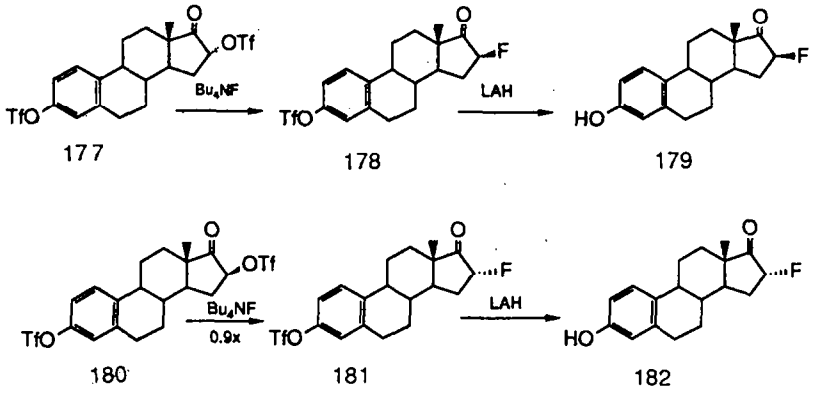
7.15. 4-*Fluoro-estradiol*

The pyrrolidine enamine of 19-nortestosterone **174** was treated with perchloryl fluoride to form 4-fluoro-nortestosterone, **175**, in 80% yield. Oxidation of the A ring with selenium dioxide yielded the desired 4-fluoro-estradiol,[96] **176**. The 4-fluoro-17-beta-estradiol was an active antitumor agent against rat mammary adrenocarcinoma.[97]



7.16. 16-*Fluoro-estradiol*

The 16-alpha-trifluoromethanesulfonate ester **177**, prepared in four steps from estrone, was treated wih tetra-*n*-butylammonium fluoride in tetrahydrofuran to afford the 16-beta-fluoroestrone 3-trifluoromethanesulfonate, **178** in 82% yield.[98] The reaction does not proceed with clean inversion of configuration if excess tetra-*n*-butylammonium fluoride is used. The excess tetra-*n*-butylammonium fluoride epimerizes the newly created 16-fluoride. Reduction with lithium aluminum hydride yielded 16-beta-fluoro-17-beta-estradiol, **179**, in 78%, presumably as a result of the accessibility of the beta face of the carbonyl. The 16-alpha-fluoro compound, **181**, was prepared in 62% yield by tetra-*n*-butyl ammonium fluoride displacement of the 16-beta-trifluoromethanesulfonate **180**. The reduction with lithium aluminum hydride was somewhat less selective, affording the 16-alpha-fluoro-17-beta-estradiol, **182**, in 65% yield, reflecting a 4 : 1 selectivity of reduction from the beta-face.

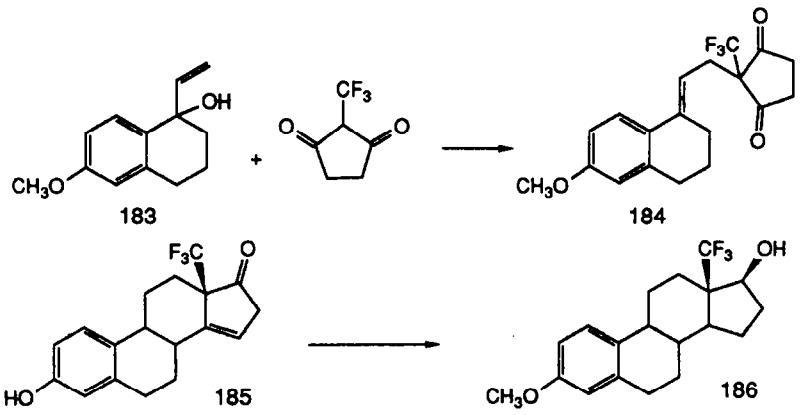


7.17. 13-*Trifluoromethyl estrogen*

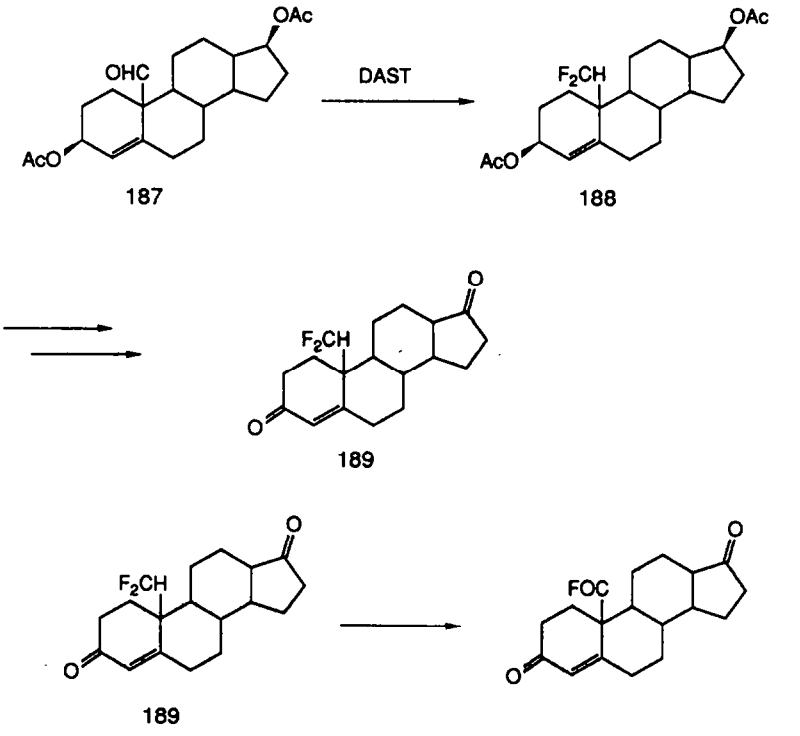
18,18,18-Trifluoro-17β-estradiol was prepared by a Torgov-type reaction.[98b,c] 2-Trifluoromethylcyclopentan-1,3-dione was condensed with allyl alcohol **183** to yield **184** in 44% yield. The diketone was cyclized to **185** in 84% yield. Further elaboration yielded the trifluoro-estradiol **186** in 40% yield over four steps. The deprotected compound manifested antiestrogenic activity and only 1% of the estrogenic activity of estradiol in mice.

7.18. 19,19-*Difluoroandrost-4-ene-3,17-diene*

Estrogen synthetase is a key enzyme in conversion of androgens to estrogen. This enzyme is effectively deactivated by 19,19-difluoroandrost-4-ene-3,17-dione,[101] **189**. 19-Oxoandros-5-ene-3β,17β-diol diacetate, **187**, was fluorinated with DAST to form the 19,19-difluoro material **188** in less than 35% yield. The difluoro compound **189** was postulated to be metabolized to the 19-acyl



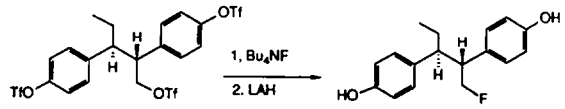
fluoride, which covalently bonded to the enzyme deactivating it. These compounds exhibited a very high affinity for estrogen receptors.[99] The 16-alpha-fluoro-17-beta-estradiol, the best compound, was subsequently prepared in radiolabeled form.



7.19. *Fluoronorhexestrol*

Non-steroidal estrogen receptor binding agents have also been prepared.[100] (2*R*,3*S*)-1-Fluoro-2,3-bis(4-hydroxyphenyl)pentane, **191**, was prepared by tetra-*n*-butylammonium fluoride ion displacement of the (2*R*,3*S*)-1-trifluoromethanesulfonate-2,3-bis(4-phenyl trifluoromethanesulfonate)pentane, **190**. The (2*R*,3*S*)-1-fluoro-2,3-bis(4-phenyl trifluoromethanesulfonate)pentane was not isolated but the phenolic trifluoromethanesulfonates were reduced directly with lithium aluminum hydride to form the desired compound in 57% yield. The non-steroidal material also had a very high affinity for estrogen receptors. As a consequence, the radiolabeled material was also prepared.

Corticosteroids. As mentioned in the introduction, one of the earliest reports of the effectiveness of fluorination in biological systems was the fluorination of corticosteroids. Not surprisingly interest in this area is still undiminished.

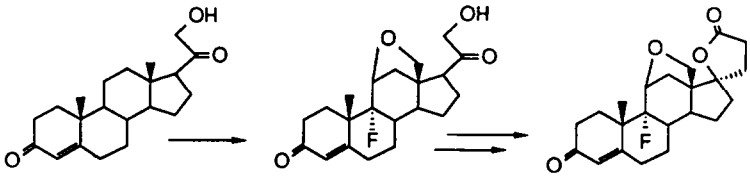


57%

190 191

7.20. *9-alpha-Fluoro-corticosteroids*

9-alpha-Fluoro-corticosterone, **192**, was oxidized with the resting mycelium of *Corynespora cassiicola* to afford the 9-alpha-fluoro-18-hydroxycorticosterone 18,20-hemiacetal which on acetic acid treatment yielded 9-alpha-fluoro-18-deoxy-aldosterone, **193**, in 17% yield. Through a multistep sequence of transformations this compound was converted to 3-(9-alpha-fluoro-17-beta-hydroxy-11-beta, 18-epoxy-3-oxo-androst-4-en-17-alpha-yl) propanoic acid gamma lactone,[102] **194**. **193** seemed to have no antialdosterone activity but was approximately as potent as aldosterone. However, **194** was a more effective antialdosterone agent than spironolactone when compared at the same dose. Particularly notable, is the lack of or very weak binding affinity for androgen, progestin estrogen and glucocorticoid receptors.



192 17% 193 194

The influence of the 9-alpha-fluorine on steroid activity has been the subject of speculation for some time. In the solid state, single crystal X-ray diffraction studies have shown that the A ring of 9-alpha-fluorinated steroids is deformed down below the plane of the steroid relative to non-fluorinated compounds.[103] Recently it has been established by ^{19}F-proton coupling constants that the conformation of ring A is also deformed in solution.[104]

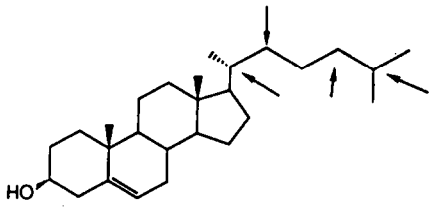
7.21. *General preparative methods*

Advances have been made in understanding the nature of the regioselectivity possible in the direct fluorination of bile acids.[105] Fluorine is generally an unselective reagent, yet at low temperature fluorination of methyl 3-alpha-acetoxy-5-beta-cholanate can be limited to replacement of accessible tertiary hydrogens and is affected by protecting groups.

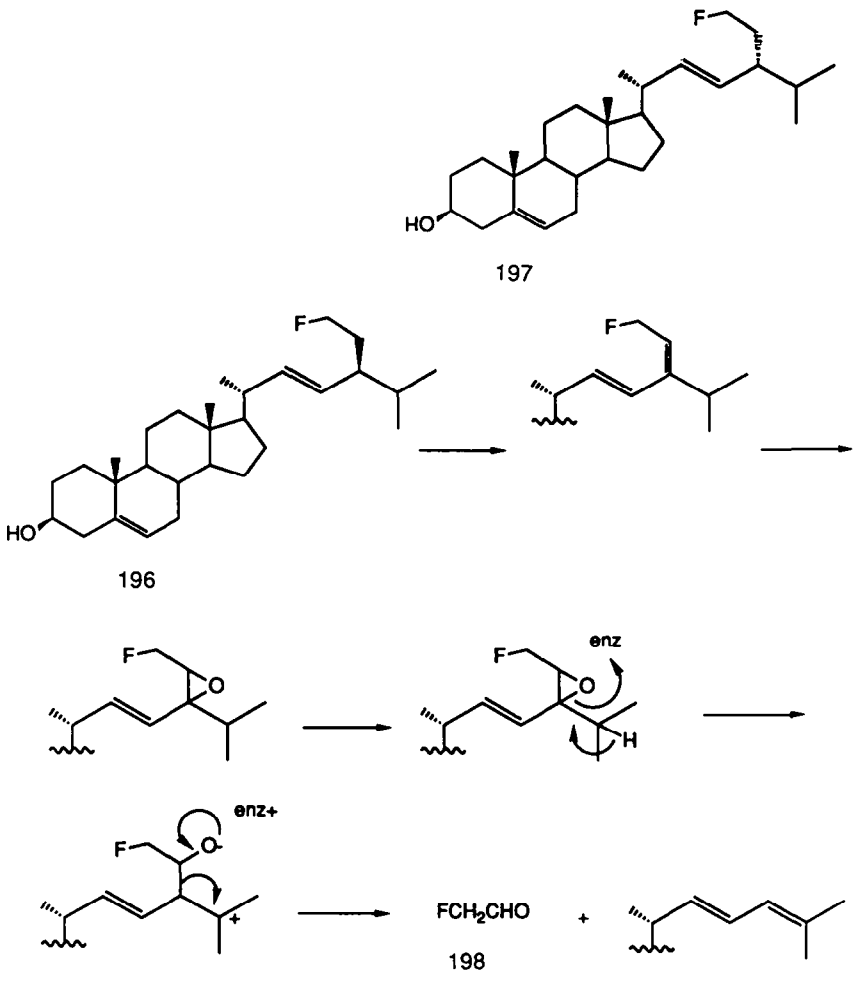
Fluorinated sterols. Inhibition of insect development via the metabolism of selectively fluorinated sterols was approached from two different pathways; the first required the preparation of a fluorinated steroid which would inhibit an essential enzymatic hydrolysis. The second approach was based upon the lethal synthesis of fluorocitrate by the insect on dealkylation of a suitably fluorinated sterol. It was this approach which has proved most successful.[106]

7.22. *Fluoro-cholesterol*

Attempts to employ C-20, C-22, C-24 or C-25 monofluorinated cholesterols **195** to block ecdysone biogenesis by inhibiting enzymatic processes were unsuccessful.



195



Scheme 12.

7.23. *29-Fluoro-phytosterol*

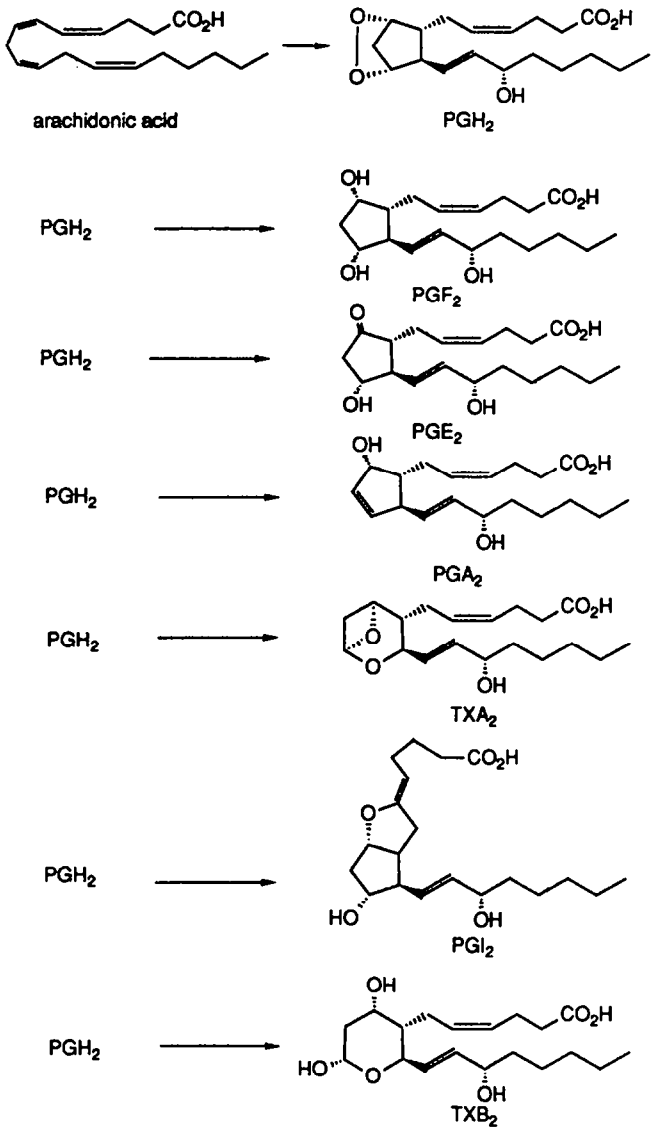
However, 29-fluoro-phytosterol were readily metabolized by *Manduca sexta*, the tobacco hornworm, to release toxic 2-fluorocitrate. Both 29-fluoro-stigmasterol, **196** and its C-24 epimer **197**, were very potent inhibitors of insect development. Severely poisoned larvae had trouble shedding their skins and developed fifth stadium heads on bodies of third instar size.

8. PROSTAGLANDINS, PROSTACYCLINS AND THROMBOXANES

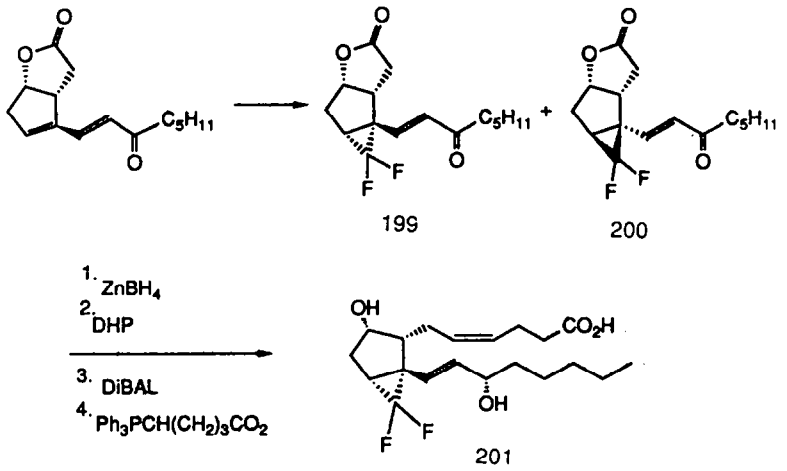
Fluorination of prostaglandins, prostacyclins and thromboxanes has led to exciting and useful modifications of activity, much as fluorination so effectively modified the activity of steroids. The biosynthetic pathway of these compounds begins with arachidonic acid. The three classes of compounds to be discussed here can all be derived from the prostaglandin endoperoxide, PGH_2. The chemistry and biology of fluorinated prostaglandins, prostacyclins and thromboxanes through 1981 has been reviewed,[107] but is summarized here for completeness.

8.1. *Difluoromethylene prostaglandins*

An early report of the introduction of fluorine into prostaglandins was based on the addition of difluorocarbene, generated by the pyrolysis of the sodium salt of chlorodifluoroacetic acid, to the unsaturated lactone to form a mixture of the alpha **199**, 26% and beta **200**, 38%, difluoromethylene compounds,[108] which were elaborated to desired difluoromethylene prostaglandin analog **201**.

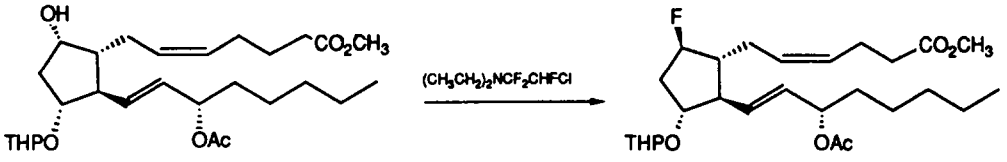

arachidonic acid
PGH2
PGF2
PGE2
PGA2
TXA2
PGI2
TXB2

Scheme 13.


199
200
1. ZnBH4
2. DHP
3. DiBAL
4. Ph3PCH(CH2)3CO2
201

8.2. *9-Fluoro, 11-fluoro- and 9,11-difluoro PGF_2*

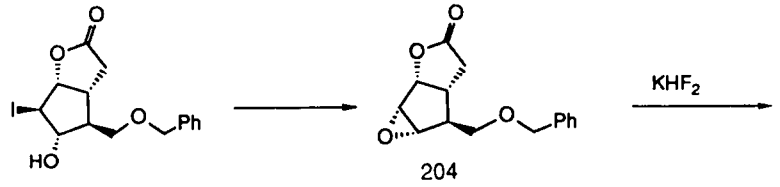
The 9-alpha-fluoro, 9-beta-fluoro, 11-alpha-fluoro, and 11-beta-fluoro PGF_2 analogs were prepared by dehydroxylative fluorination of the appropriate prostaglandin.[109] Diethyl(2-chloro-1,1,2-trifluoroethyl) amine was used to effect the fluorination with inversion of configuration. In a typical example, the 11,15-bis-tetrahydropyranyl ether of PGF_{2alpha} was treated with diethyl(2-chloro-1,1,2-trifluoroethyl) amine to form the 9-beta-fluoro compound **203** in 30–40% yield. The 9-beta-fluoro-11-alpha-hydroxy compound was particularly interesting in that it was 3–4 times more effective than PGE_2. The other compounds 9-alpha-fluoro, 11-alpha-fluoro, and 11-beta-fluoro PGF_2 analogs were less active.



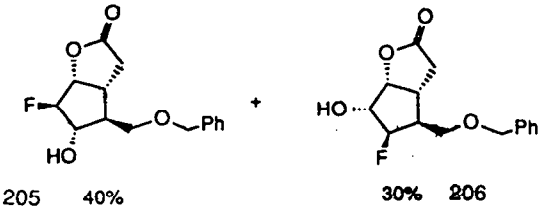
202 203

8.3. *10-Fluoro PGF_{2alpha}*

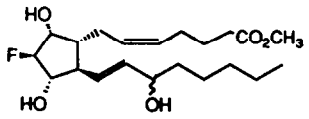
The 10-beta-fluoro analog was prepared by potassium bifluoride opening of the epoxide lactone **204**. The ring opening yielded 40% of the desired regioisomer **205** but also 30% of the undesired 11-beta-fluoro compound[110] **206**. The 10-beta-fluoro compound was very sensitive and thus susceptible to side reactions during attempts to elaborate the prostaglandin structure. However, careful reduction and oxidation did in fact permit preparation of 10-beta-fluoro-PGF_{2alpha} **207**. It was additionally found that if opening of the epoxide was postponed, that the desired 10-beta-fluoro compound could be prepared in 25% yield. Opening of the beta epoxide **208** with potassium bifluoride did not form the desired fluoride **209**. Only the lactone formed by initial saponification of the ester and lactonization was isolated.[109] The 10-alpha-fluoro compound was successfully prepared by displacement of the 10-beta-trifluoromethanesulfonate **210**. Tetra-*n*-butylammonium fluoride in tetrahydrofuran formed **209** in 55% yield. Upon successful fluorination the remaining elaborations were conventional.



204



205 40% 30% 206



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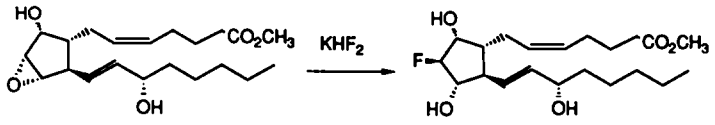
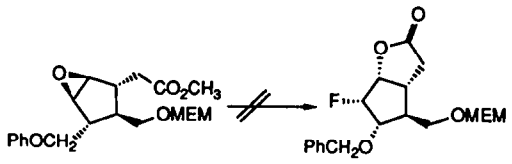
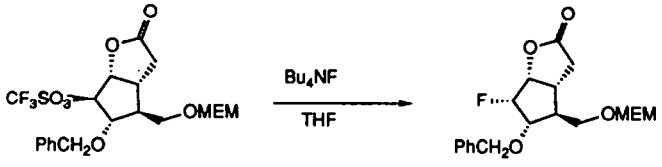


25%



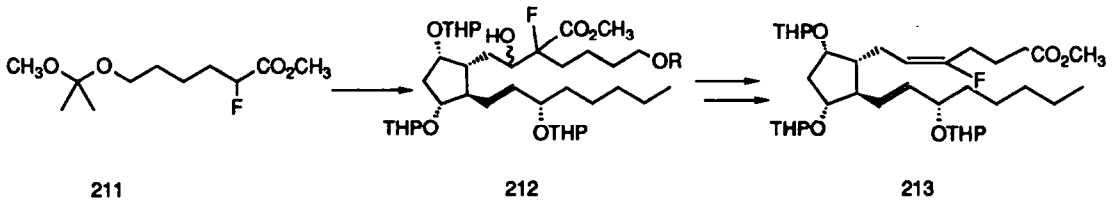
208 209



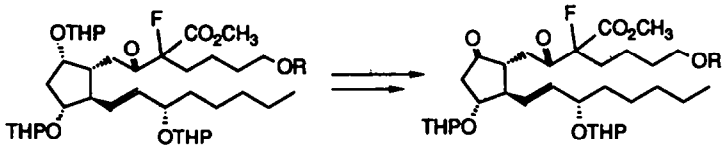
210 209

8.4. *5-Fluoro PGF_{2alpha}*

Both the *E* and the *Z* isomers of 5-fluoro PGF_{2alpha} were accessible from the aldol condensation of a functionalized methyl ester of 2-fluorohexanoate,[112] **211**. The lithium enolate was prepared by deprotonation and condensed with the required aldehyde to afford a 70% yield of a mixture of diastereomers **212**. Decarboxylative elimination formed a mixture of the *E* and *Z* isomers **213** which was separated on esterification. Decarboxylation of **212** with aqueous DMSO to form the oxidized and protected aldol adduct **214** leads to preparation of the 5-fluoro-6-keto-PGE_1 methyl ester, **215**. 5-Fluoro-6-keto-PGE_1 was 10 times more potent than PGE_1 in inhibition of stress ulcers in rats and 10 times more potent in uterine contractile activity.



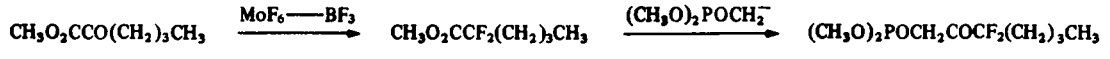
211 212 213



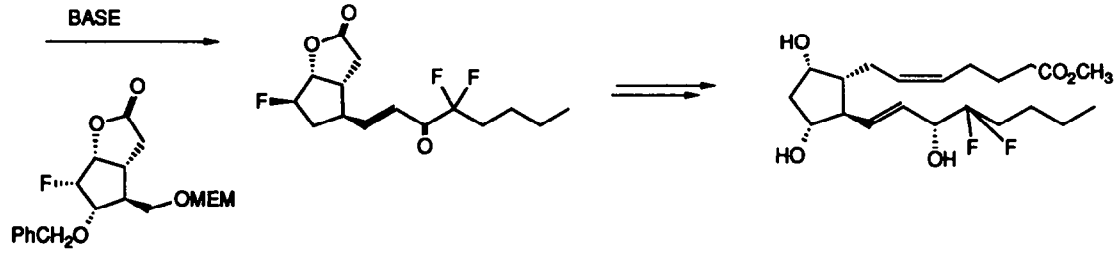
214 215

8.5. 16-*Difluoro PGF*$_{2alpha}$

The difluoro compound was prepared by condensation of the difluoroketo phosphonate **217** with the appropriate aldehyde.[113] The difluorophosphonate **217** was prepared by fluorination of **216** with molybdenum hexafluoride in the presence of boron trifluoride.[114] Dimethyl methylphosphonate was deprotonated and condensed with methyl 2,2-difluorohexanoate. This compound had very good antifertility activity with diminished smooth muscle activity.

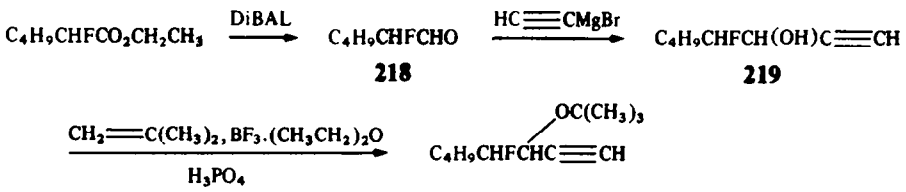


216 **217**

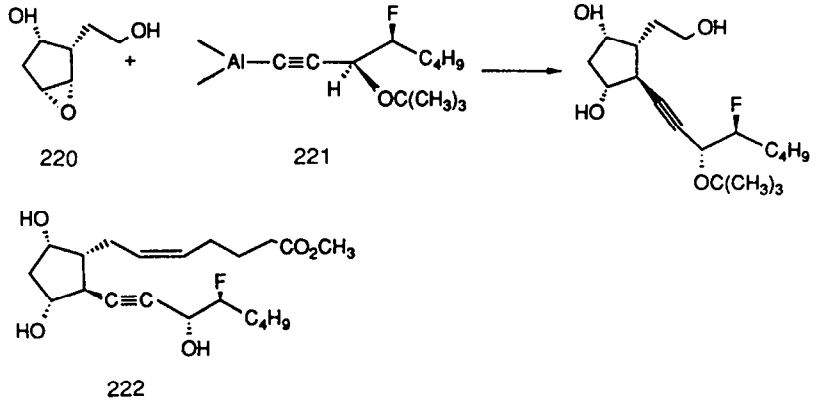


8.6. 16-*Fluoro*-13-*dehydro PGF*$_{2alpha}$

Following reduction of ethyl 2-fluorohexanoate with diisobutylaluminum hydride, 2-fluorohexanal, **218**, was condensed with acetylene magnesium bromide. The *erythro* and *threo* diastereomers, formed in a 7:3 ratio were separated by chromatography. Following protection of the alcohol as a *t*-butyl ether, the acetylene was converted into the alane reagent **221**. Addition of **221**

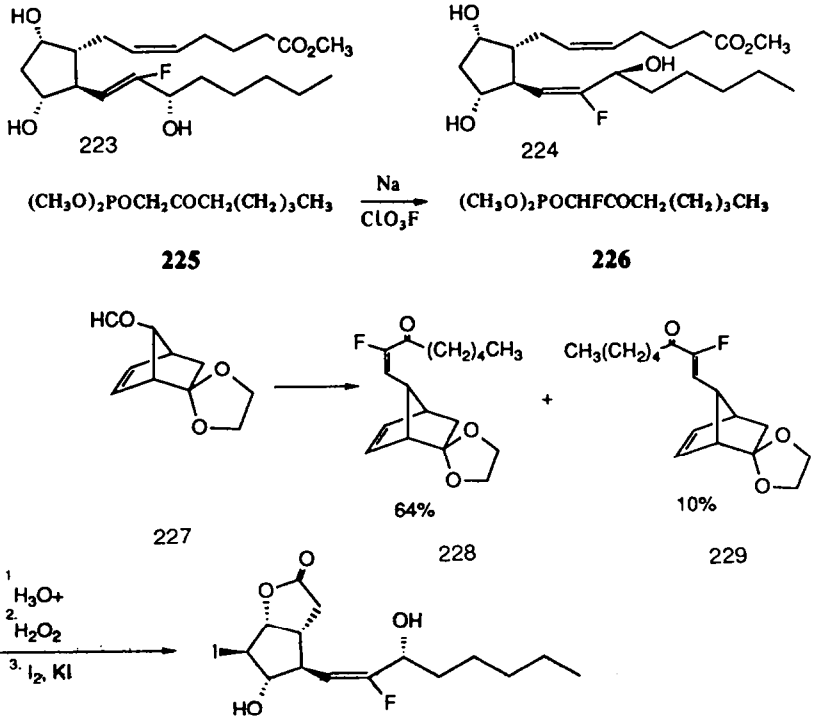


to **220** formed the triol *t*-butyl ether with the correct stereochemical relationships. Following conversion to the lactol, Wittig olefination and deprotection formed the target compound[115] **222**. These compounds possessed potent antifertility activity, but one-fifth lower smooth muscle activity than the non-fluorinated parent dehydro compound.



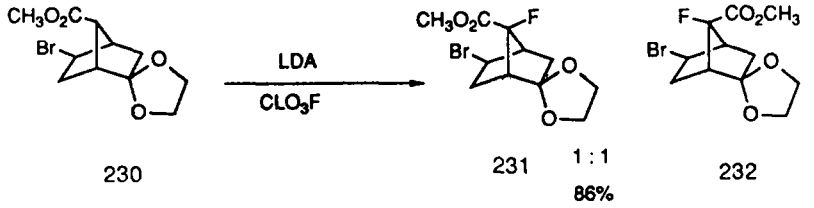
8.7. 14-*Fluoro* PGF_{2alpha}

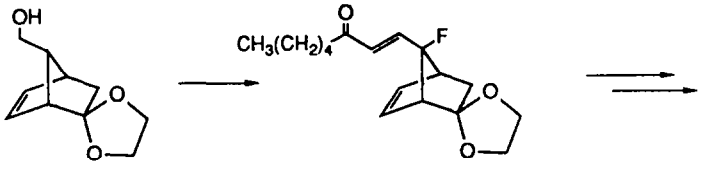
Both the 13(*E*)- and 13(*Z*)-14-fluoro-PGF_{2alpha} **223** and **224** were prepared via a fluorinated Horner–Emmons reagent. Dimethyl 2-ketoheptyl phosphonate **225** was deprotonated and then was treated with perchloryl fluoride to form a 29% yield of dimethyl 2-fluoroheptyl phosphonate[116] **226**. Treatment of **226** with sodium hydride generated the reactive ylide which was added to the aldehyde **227** to form a 64% yield of the undesired *E* stereoisomer **228** and 9% of the desired **229**. Both materials were elaborated by conventional manipulations to desired 14-fluoro PGF_{2alpha} compounds. These compounds retained antifertility activity but exhibited diminished smooth muscle activity.

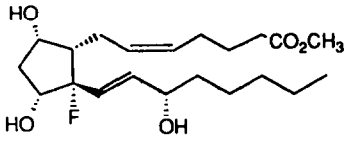


8.8. 12-*Fluoro* PGF_{2alpha}

Fluorine was introduced into the target molecule again by the successful fluorination of an enolate. The methyl bicyclo-carboxylate **230** was deprotonated with LDA and was fluorinated with perchloryl fluoride to form a one to one mixture of **231** and **232** in 86% yield.[117] Following chromatographic separation of the diastereomers, conventional manipulation led to the prostaglandins. The compounds were 25 times more potent than the parent materials in antifertility assays but with diminished smooth muscle activity.



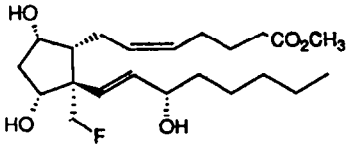




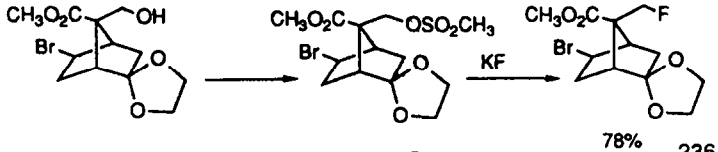
233

8.9. 12-*Fluoromethyl* PGF_{2alpha}

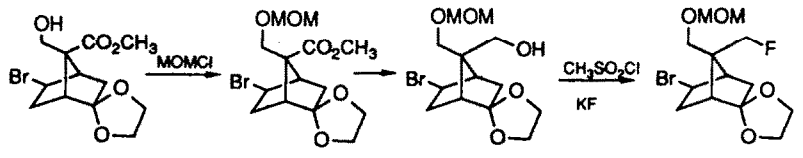
Introduction of fluorine into a 12-methyl substituent as in **234** illustrated the difficulty which frequently accompanies fluorination of multifunctional molecules. Although fluoride ion displacement of the primary methanesulfonate **235** provided a 78% yield of the desired fluoride **236**, all attempts to reduce the carbomethoxy group resulted in loss of fluorine.[118] Reduction of the carbomethoxy group and protection prior to formation of the methanesulfonate and displacement by potassium fluoride in ethylene glycol, avoided this difficulty. However, the protected alcohol **237** inhibited the displacement reaction. The recovery of fluoride **238** was only 43% as well as 21% of the starting methanesulfonate. Variation in the displacement conditions offered no improvement. Elaboration to the prostaglandin proceeded uneventfully. Unfortunately the compounds did not affect fertility or possess smooth muscle activity.



234



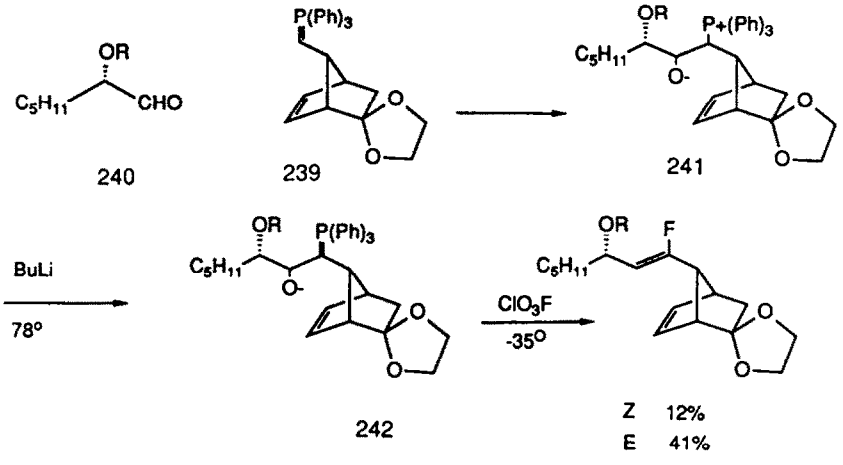
235 236

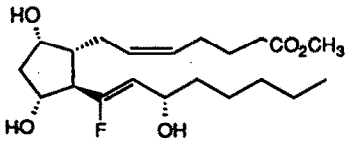


237 238

8.10. 13-*Fluoro* PGF_{2alpha}

Preparation of the 13-fluoro compound again employed fluorination of an anion but in a novel setting.[119] Following addition of the bicyclic Wittig reagent **239** to **240** at low temperature, prior to collapse of the betaine **241**, a second equivalent of butyl lithium was added to form the deprotonated betaine **242**. Perchloryl fluoride was passed into the solution, which on warming formed a 12% yield of the *Z* olefin and a 41% yield of the *E* olefin. The 13-fluoroprostaglandin **243** prepared from this material possessed slightly improved antifertility activity but undiminished smooth muscle response.

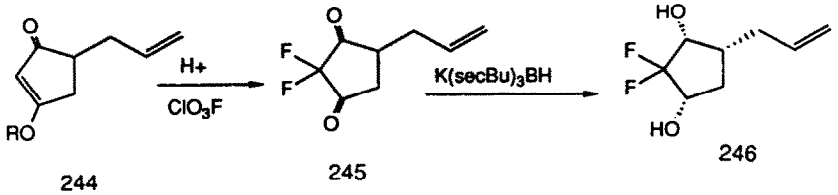




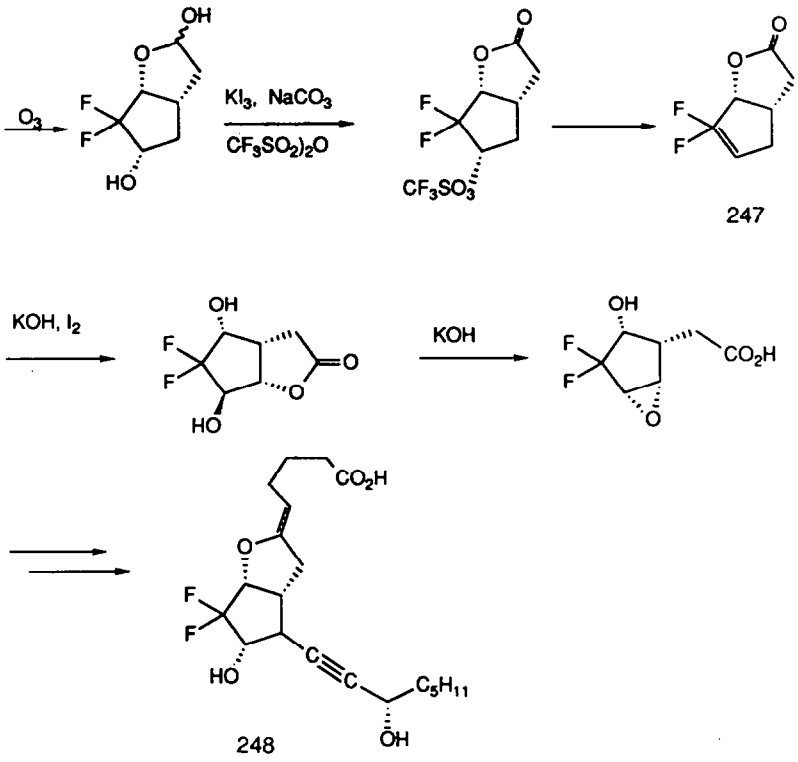
243

8.11. 10,10-*Difluoro*-13-*dehydro-prostacyclin*

The natural prostacyclins contain an unusually acid-labile enol ether grouping which makes the study of these materials difficult. It was proposed that fluorinated analogs would exhibit increased acid stability. 4-Allyl-1,3-pentanedione, **244**, was treated with perchloryl fluoride to form the difluoroketone, **245**, which was reduced with potassium sec-butyl borohydride to the cis diol **246** in 36% yield after purification.[120] Ozonolysis, periodate oxidation and dehydration via the triflate formed **247**. Epoxidation was effected via saponification and iodolactonization, as the allylically fluorinated olefin was unreactive toward direct epoxidation. Following conversion to the prostacyclin, biological evaluation showed **248** mimicked PGI_2 yet had 150 times greater half-life under the same conditions.

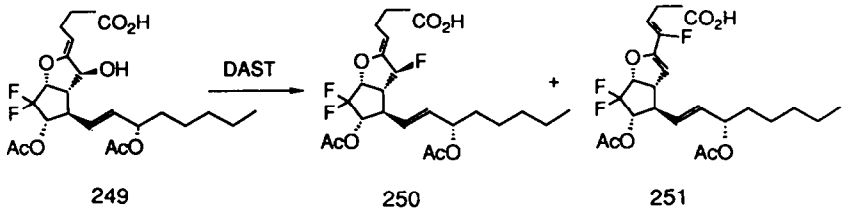


244 245 246



8.12. *7-Fluoro PGI_2*

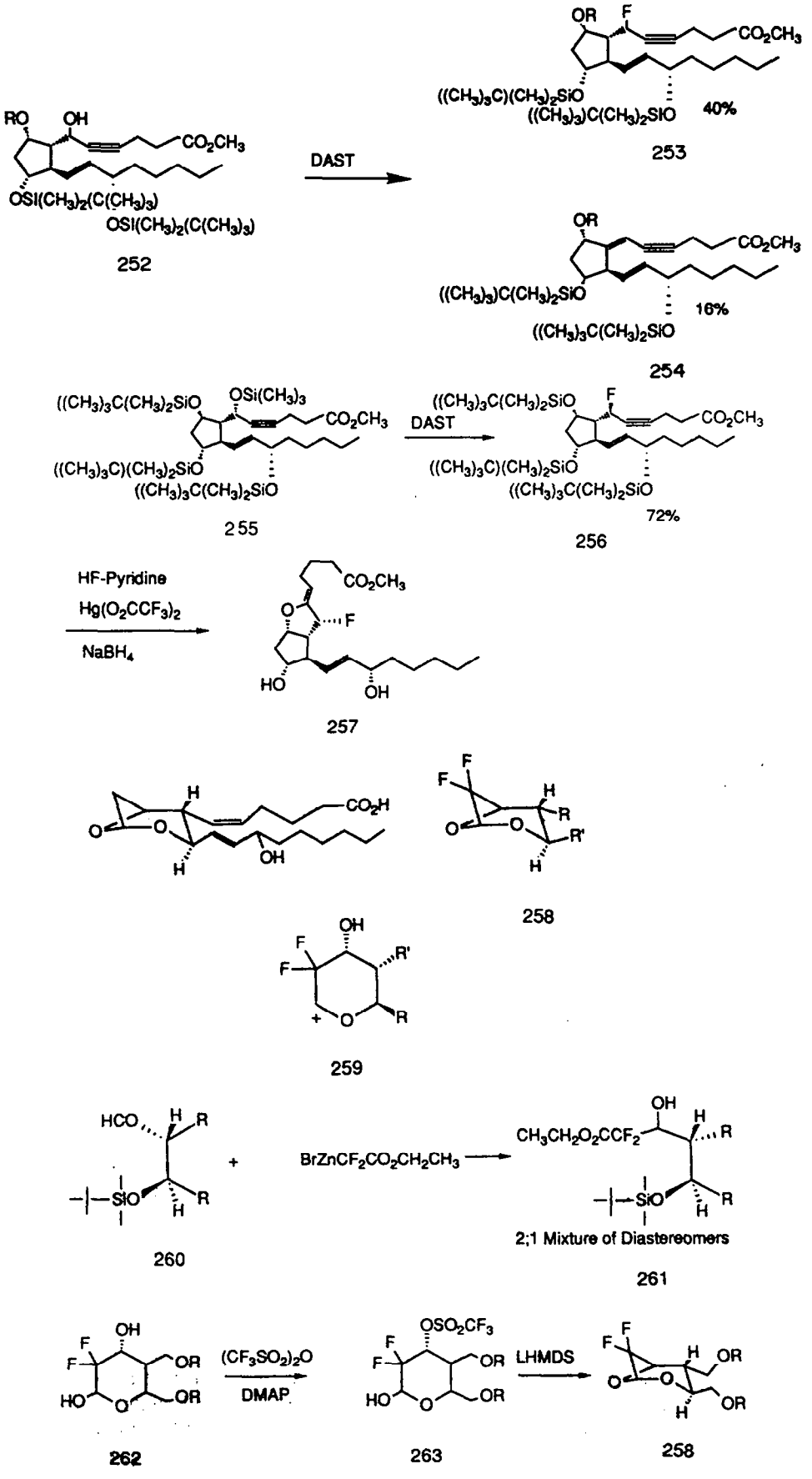
Direct fluorinative dehydroxylation of diacetyl (7*S*) 7-hydroxy-PGI_2 methyl ester, **249**, with DAST formed the diacetyl (7*S*) 7-fluoro-PGI_2 methyl ester, **250**, in 27% yield as well as diacetyl 5-fluoro-delta^6-PGI_2 methyl ester, **251**, in 32% yield.[121] Apparently an allylic cation intermediate was formed which when trapped by fluoride at the 7-position reacted to form the beta fluoride because of the steric hindrance of the alpha face. Fluorination at carbon-7 clearly reduced the nucleophilicity of the 5-double bond, stabilizing the enol. The half life of the (7*S*) 7-fluoro-PGI_2 was greater than one month under conditions where the half life of PGI_2 was ten minutes.



The precursor to (7*R*) 7-fluoro-PGI_2 **241** was prepared by DAST fluorination of the alcohol **252** in 40% yield accompanied by a 16% yield of the elimination product[122] **254**. It was reported that the fluorination of the 7-trimethylsilyl ether **255** with DAST formed **256** in 72% yield by inversion of configuration. Stereochemical control was suggested to arise from the 9-triethylsilyloxy substituent. The (7*R*) 7-fluoro PGI_2, **257**, prepared from these materials was reported to have activity toward platelet aggregation similar to that of PGI_2 itself.

8.13. *Thromboxane A_2, TXA_2*

Thromboxanes pose an even greater challenge to the synthetic chemist as with a half-life of 32 s under physiological conditions, they are extremely difficult to manipulate. Application of the principles of fluorination to induce stability has led to the preparation of 7,7-difluoro derivatives of 2,6-dioxo(3.1.1)bicycloheptanes **258** as model compounds where the beta cation formed on ring


RO
OH
CO2CH3
OSi(CH3)2(C(CH3)3)
OSi(CH3)2(C(CH3)3)
252
DAST
OR
F
CO2CH3
((CH3)3C)(CH3)2SiO
((CH3)3C)(CH3)2SiO
40%
253
OR
CO2CH3
((CH3)3C)(CH3)2SiO
16%
((CH3)3C(CH3)2SiO
254
((CH3)3C(CH3)2SiO
OSi(CH3)3
CO2CH3
((CH3)3C)(CH3)2SiO
((CH3)3C(CH3)2SiO
255
DAST
((CH3)3C(CH3)2SiO
F
CO2CH3
((CH3)3C)(CH3)2SiO
((CH3)3C(CH3)2SiO
72%
256
HF-Pyridine
Hg(O2CCF3)2
NaBH4
CO2CH3
F
HO
OH
257
CO2H
H
O
OH
258
F
H
R
R'
259
OH
F
R'
R
HCO
H
R
SiO
BrZnCF2CO2CH2CH3
CH3CH2O2CCF2
2;1 Mixture of Diastereomers
260
261
OH
OR
HO
(CF3SO2)2O
DMAP
OSO2CF3
LHMDS
H
OR
262
263
258

cleavage is destabilized by the adjacent fluorines[123] **259**. Reformatsky reaction of ethyl bromodifluoroacetate and **260** led to a 2:1 mixture of diasteromers **261**. The 3-beta-trifluoromethanesulfonate **263**, prepared after reduction to the lactol **262**, was deprotonated with lithium hexamethyldisilazide to form the target oxetane. The half life of **258** was 86 minutes.

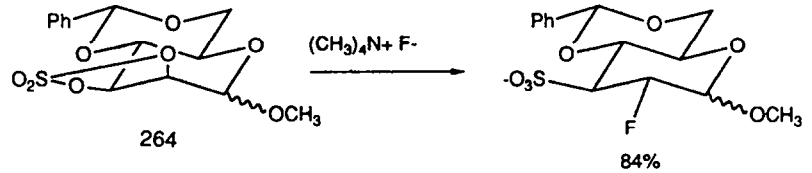
9. CARBOHYDRATES

Fluorinated carbohydrates, useful for probing biochemical mechanisms or for modifying the activity of glycosides, have been the subject of intensive research efforts.[124] More recently ^{18}F labeled sugars have found utility as *in vivo* imaging agents for carbohydrate metabolism. As before we will describe the methods employed in fluorination and limitations of those techniques for the preparations.

9.1. *2-Deoxy-2-fluoro-glucose*

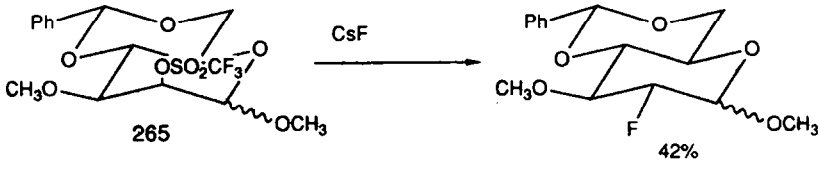
2-Deoxy-2-fluoro-glucose-(^{18}F) has been established as a useful radiopharmaceutical for studying glucose metabolism in both normal and diseased tissue.[125] Efficient syntheses are required because of the short half-life of ^{18}F, 110 minutes. Because of the difficulty associated with preparing the radionuclide, syntheses which utilize as much of the available ^{18}F as possible are required.

9.1.1. *Cyclic sulfate displacements.* Fluoride ion displacement reactions are particularly attractive synthetic processes. Both the 2,3-cyclic-sulfates and sulfites of methyl 4,6-*O*-benzylidene-alpha- and beta-D-mannopyranosides were prepared by reaction of the 2,3-diols with sulfuryl chloride and thionyl chloride respectively.[126] The sulfates and the sulfites were treated with anhydrous tetramethylammonium fluoride, prepared by azeotropic drying with acetonitrile. The reaction of the sulfites was very slow. However, **264** reacted very cleanly with tetramethylammonium fluoride to form methyl 2-deoxy-2-fluoro-beta-D-glucopyranoside triacetate on hydrolysis and acylation in 84% yield. The procedure also worked well with tetraethylammonium fluoride-18.[127]



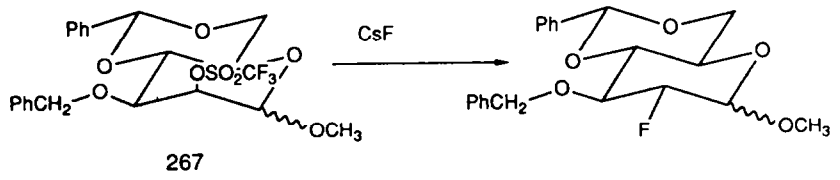
264 84%

9.1.2. *Trifluoromethanesulfonate ester displacements.* Although the 4,6-*O*-benzylidine-2-*O*-methanesulfonyl-3-*O*-methyl-alpha-D-mannopyranoside reacts sluggishly in displacement reactions, the beta anomer is much more reactive. It was found that in 4,6-*O*-benzylidine-3-*O*-methyl-2-*O*-trifluoromethanesulfonyl-alpha-D-mannopyranoside, **265**, the trifluoromethanesulfonate ester was easily displaced by cesium fluoride in dimethylformamide to form the 2-fluoro-glucopyranose, **266**, in 42% yield.[128] This reaction also was adapted to work with cesium fluoride-18.[129] Other workers have found the removal of the methyl ether to be very difficult. When the protecting groups were varied, the most effective protection was the 3-*O*-benzyl-4,6-*O*-benzylidene combination as in **267**. The yields were consistently good and protection facile.[130] By employing the 1,6-anhydro-3,4-di-*O*-benzyl-2-*O*-trifluoromethylsulfonyl-beta-D-mannopyranose, **268**, as the substrate for the displacement reaction, the tendency of the substrate to eliminate was suppressed.[131] The 1,6-anhydro bridge locks the carbohydrate into a conformation where the leaving group is trans-diequatorial to the neighboring hydrogen. Displacement with tetramethylammonium fluoride resulted in 91% yield of the desired fluoride. Cleavage and deprotection proceeded in 70% yield for 64% overall yield of the desired sugar **269**.

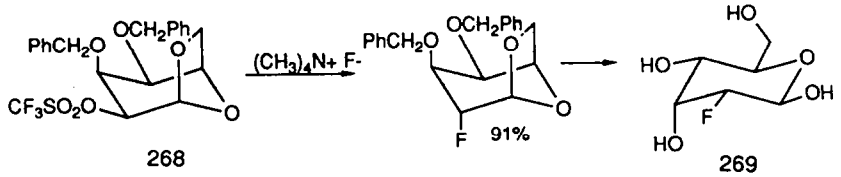


265 42%

266

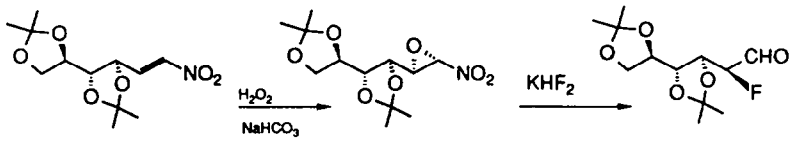


267



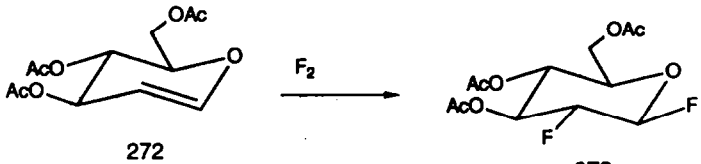
268 269

9.1.3. *Epoxide opening.* 2-Deoxy-2-fluoro-D-glucose was also prepared by an epoxide opening reaction. 1,2-Anhydro-3,4: 5,6-di-*O*-isopropylidene-1-*C*-nitro-D-mannitol, **271**, was prepared by epoxidation of 1-deoxy-3,4: 5,6-di-*O*-isopropylidene-*C*-nitro-D-*manno*hexitol, **270**. Following ring opening with potassium bifluoride in 79% yield, deprotection was effected in 85% yield.[132] Radiolabeled potassium bifluoride was successfully employed in the synthesis as well.[133]



270 271

9.1.4. *Glucal fluorination.* 2-Deoxy-2-fluoro-glucose has historically been prepared by direct fluorination of tri-*O*-acetyl-glucals **272**. The fluorination reactions have employed acetyl hypofluorite,[134] dilute fluorine[135] or xenon difluoride.[136] The yields range between 24% to 84% while the stereochemical selectivity may be very good.

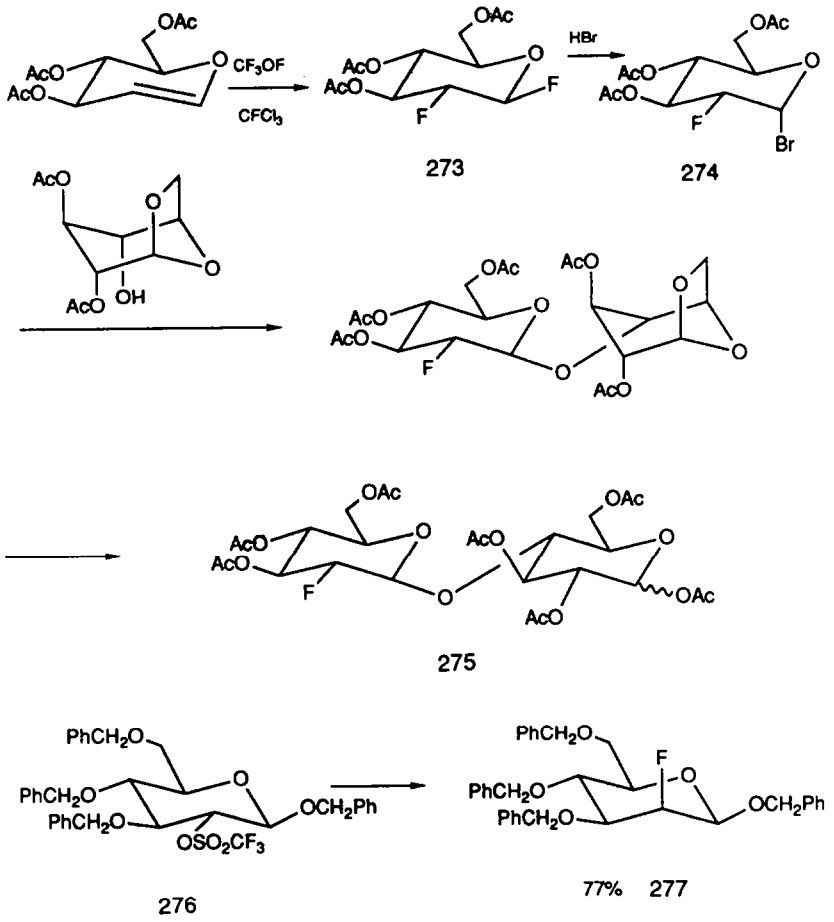


272 273

9.1.5. *Dissacharides. 4'-Fluoromaltose.* The 2-deoxy-2-fluoro-glucopyranoses have also been utilized in the synthesis of dissaccharide analogs. 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-alpha-D-glucopyranosyl bromide, **274**, prepared by trifluoromethylhypofluorite fluorination of **272**, was condensed with 2,3-di-*O*-acetyl-1,6-anhydro-beta-D-glucose in the presence of silver carbonate to form protected 4'-fluoromaltose, 4-*O*(2-deoxy-2-fluoro-alpha-D-glucopyranosyl)-D-glucopyranose,[137] **275**. Although the anomeric specificity of the coupling reaction has been attributed to the electrophile, the fluorine may also be influencing the stereoselectivity by destabilizing the developing cation required for acid catalyzed mutorotation. 4'-Fluoromaltose was prepared as a substrate to study glycosidases where this same destabilization of developing carbonium ion character would inhibit hydrolysis.

9.2. 2-*Fluoromannose*

In positron emission tomography using radiolabeled fluorinated carbohydrates, it was found that 2-deoxy-2-fluoromannose is also an effective agent for imaging subcutaneous AH109A tumors in rabbits.[138] Protected 2-deoxy-2-fluoro-D-mannose, **277**, was readily prepared by tetra-*n*-butylammonium fluoride treatment of benzyl 3,4,6-tri-*O*-benzyl-2-*O*-trifluoromethane-sulfonyl-mannopyranoside, **276**, in 77% yield.[139]

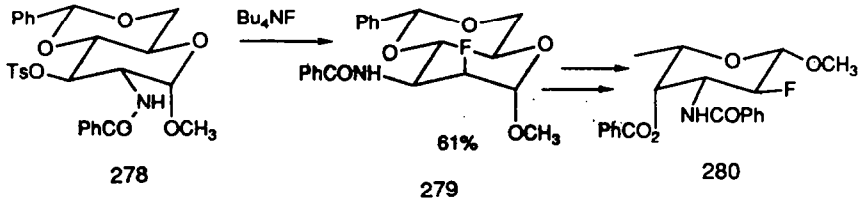


As was described for the preparation of 2-deoxy-2-fluoro glucoses the choice of protecting group at carbon-3 effects the yield and selectivity of the displacement reaction.[140] However in the mannose configuration, either the 3-*O*-acetyl- or 3-*O*-benzyl- give very comparable yields of 66% and 65%, respectively.

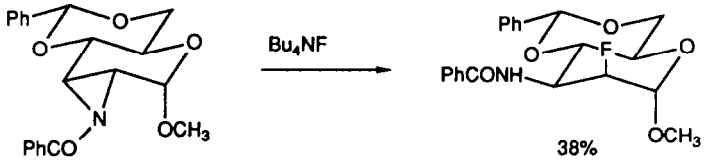
9.3. 2-*Fluorodaunosamine*

Although the anthracycline antibiotics are effective, clinically useful anti-tumor agents, the significant side-effects which accompany their administration have stimulated research into more specific analogs. In particular, syntheses of 2-fluorodaunosamine have been developed by several groups.

Methyl 2-benzamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-toluenesulfonyl-alpha-D-glucopyranoside, **278**, was treated with tetra-*n*-butylammonium fluoride to form methyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-alpha-D-altro-pyranoside, **279** in 61% yield[141] via an unisolated intermediate aziridine. Conventional manipulations including bromination, dehydrobromination and reduction formed the desired L sugar, **280**.

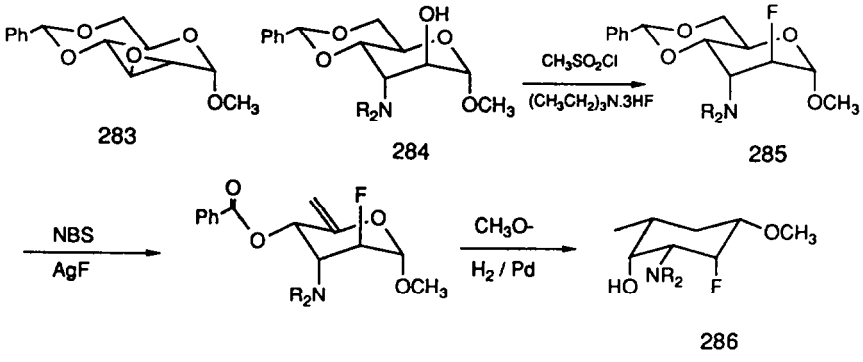


On a larger scale, other workers have treated the isolated aziridine, benzyl 4,6-*O*-benzylidene-2,3-benzoylepimino-2,3-dideoxy-alpha-D-allopyranoside, **281**, with tetra-*n*-butylammonium fluoride in hexamethylphosphoramide to form benzyl 3-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-alpha-D-altropyranoside, **282**, in 38% yield while recovering 40% of the unreacted epimine.[142]



281 282

Alternatively the *altro* compound has been prepared from methyl 2,3-anhydro-4,6-*O*-benzylidene-alpha-D-mannopyranoside,[143] **283**. The alcohol **284**, formed on opening of the epoxide with diallyl amine, was converted to a methane-sulfonate ester. Treatment with triethylamine-hydrogen fluoride yielded the 2-fluoro compound **285** via the intermediacy of an aziridinium ion. Bromination, dehydrohalogenation, saponification and reduction formed the 2-fluoro-*galacto* analog of daunosamine **286**.

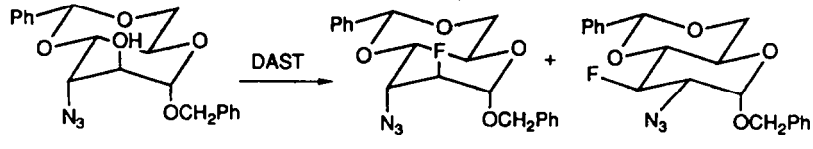


283 284 285

286

Fluorinative dehydroxylation of benzyl 3-azido-4,6-*O*-benzylidene-3-deoxy-alpha-D-altropyranoside, **287**, with diethylaminosulfur trifluoride formed benzyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-2-fluoro-alpha-D-altropyranoside, **288**, in 40% yield. Also isolated from the reaction mixture in 40% yield was 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-fluoro-alpha-D-glucopyranoside, **289**. Inversion of configuration at C-2 would have been extremely unlikely in view of the axially substituents at C-1 and C-3. S_Ni reaction has been suggested to account for the formation of the 2-azido material.

On conversion to the anthracyclinone glycoside, the fluorinated material was as active as daunomycin, but over a wider range of doses.[144]



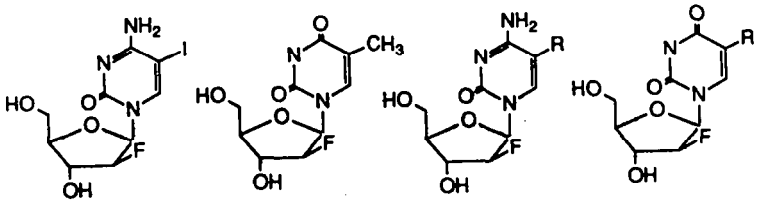
287 40% 40%

288 289

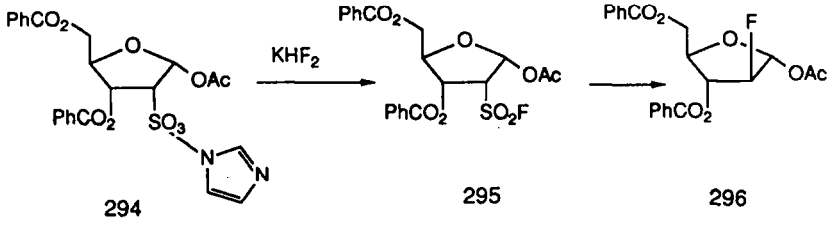
9.4. 2-*Deoxy*-2-*fluoro-arabinose*

2-Deoxy-2-fluoro-arabinose syntheses have been pursued with enhanced urgency with the development of anti-viral and anti-cancer nucleosides, such as 1-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)-5-iodocytosine, **290**, and 1-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)-5-methyluracil,[145] **291**. The 2-fluoro-arabinose containing nucleosides 1-(2-deoxy-fluoro-beta-D-arabinofuranosyl)-5-alkenylcytosine,[146] **292**, and 1-(2-deoxy-2-fluoro-beta-D-arabinofuranosyl)-5-alkyl-

uracil,[147] **293**, also have good antiviral activity as well as having much improved therapeutic indices (ID_{50}/ED_{90}). As was discussed earlier, displacement reactions at carbon-2 of pyranoses can be difficult and have seldom been employed with furanoses. The attempted displacement of 1-*O*-acetyl-3,5-*O*-dibenzoyl-2-*O*-methanesulfonyl-alpha-ribofuranoside or 1-*O*-acetyl-3,5-*O*-dibenzoyl-2-*O*-trifluoromethanesulfonyl-alpha-ribofuranoside with either tetra-*n*-butylammonium fluoride or potassium bifluoride in a variety of solvents was led to eliminations or no reaction. The attempted dehydroxylative fluorination of 1-*O*-acetyl-3,5-*O*-dibenzoyl-alpha-ribofuranoside with DAST was also unsuccessful. However treatment of 1-*O*-acetyl-3,5-*O*-dibenzoyl-2-*O*-imidazolesulfonyl-alpha-ribofuranoside,[148] **294**, with potassium bifluoride and four equivalents of 50% aqueous hydrogen fluoride did yield 1-*O*-acetyl-3,5-*O*-dibenzoyl-2-fluoro-alpha-arabinofuranoside,[149] **296**. It was suggested that the reactive intermediate in the displacement reaction is the fluorosulfate **295**.



290 291 292 293



294 295 296

9.5. *Fluorosucrose*

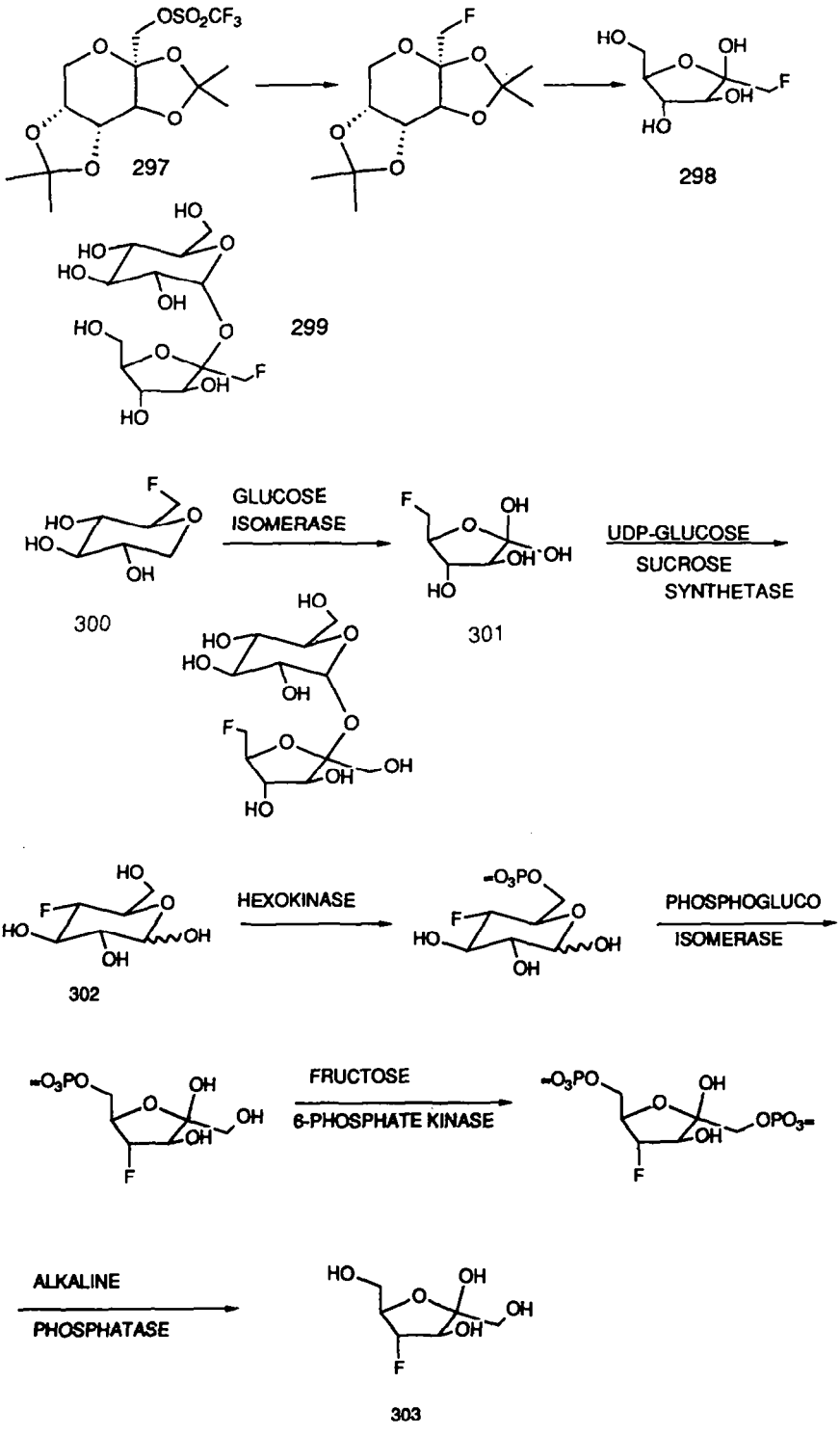
The importance of sucrose to plant metabolism is well established. However to facilitate the study of the sucrose carrier proteins, fluorinated sucrose analogs were prepared which exhibited binding properties but also were stable toward extracellular invertase.

Protected 1-deoxy-1-fluoro-fructose, **298**, was prepared in 80% yield by nucleophilic displacement on 2,3 : 4,5-diisopropylidene-1-*O*-trifluoromethanesulfonyl-D-fructopyranose, **297**, with tris (dimethylamino)sulfonium difluorotrimethylsilicate in tetrahydrofuran. Following hydrolysis of the ketals with an acidic ion exchange resin, incubation with uridine-5′-diphospho-glucose(UDP-glucose) and sucrose synthetase yielded 1-deoxy-1-fluoro-sucrose, **299**, in as high as 83% yield.[150]

Sucrose synthetase was also used to combine 6-deoxy-6-fluoro-glucose, **299**, with UDP-glucose in the presence of glucose isomerase. The isomerase converted 6-deoxy-6-fluoro-glucose to 6-deoxy-6-fluoro-fructose, **301**, which was then condensed by the synthetase with UDP-glucose in 73% isolated yield.[151]

This approach failed with 4-deoxy-4-fluoro-glucose, **302**, which was not a substrate for glucose isomerase. However, in another series of enzymatically linked steps, treatment with hexokinase to introduce the 6-phosphate, by reaction with phosphoglucoisomerase was followed by epimerization of the 3-position by fructose 6-phosphate kinase. The product 4-fluoro-fructose, **303**, was a substrate for sucrose synthetase.

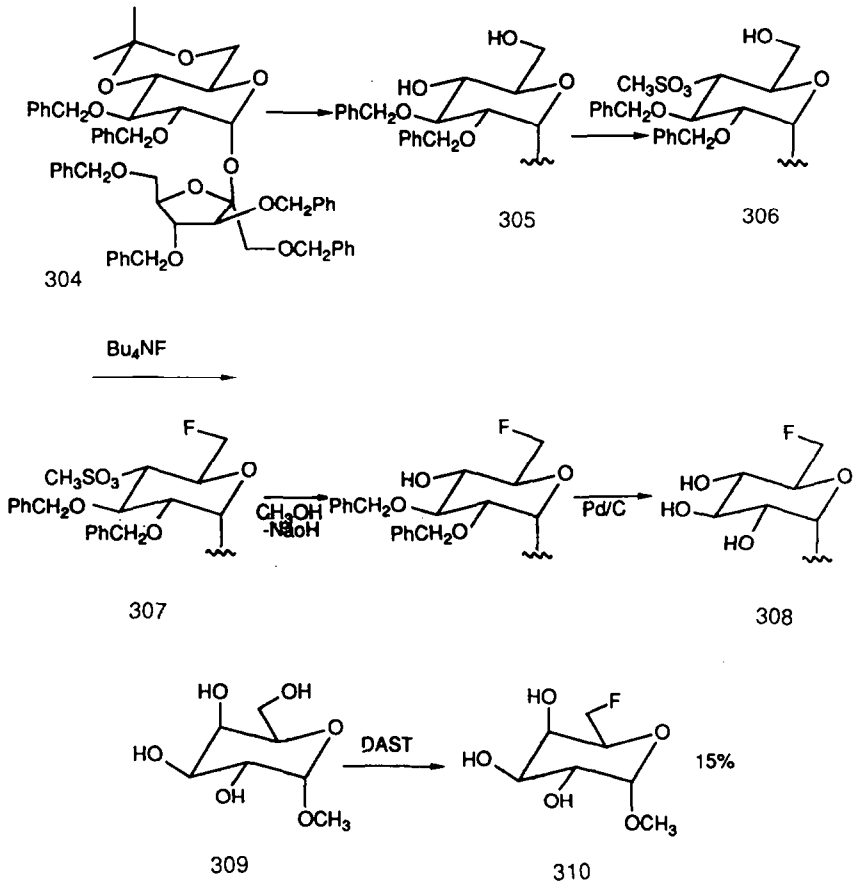
Preparation of fluorinated analogs of the glucopyranose portion of sucrose followed more conventional techniques on intact sucrose. 4,6-*O*-isopropylidenesucrose hexabenzoate, **304**, on treatment with acid formed the 4,6-diol **305** which was converted in turn to the 4,6-di-methanesulfonate,



306. Treatment of this material with tetra-*n*-butylammonium fluoride in acetonitrile yielded the 6-fluoro compound **307** in 80% yield.[152] Deprotection yielded 6-deoxy-6-fluorosucrose, **308**.

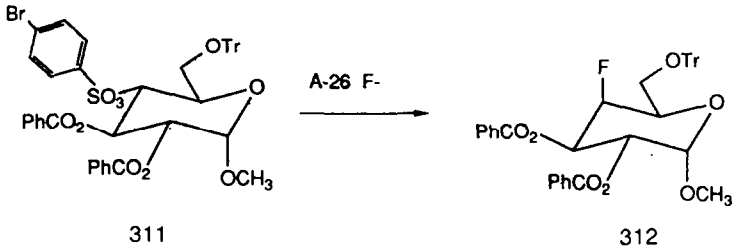
9.6. *Fluorogalactose*

In the investigation of the importance of galactose as a constituent of polysaccharides thought to be important in binding to immunoglobulins, the preparation of fluorogalactose analogs was undertaken to help define the role of electrostatic, hydrophobic and hydrophilic forces on this binding.



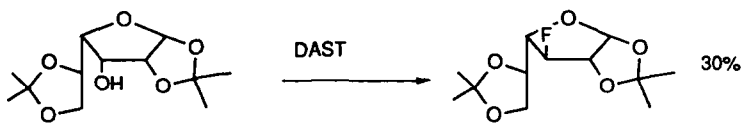
9.6.1. 6-*Deoxy*-6-*fluoro-galactose*, **310**. This was easily prepared in 15% yield by treatment of the beta-methyl glycoside **309** with DAST.[153]

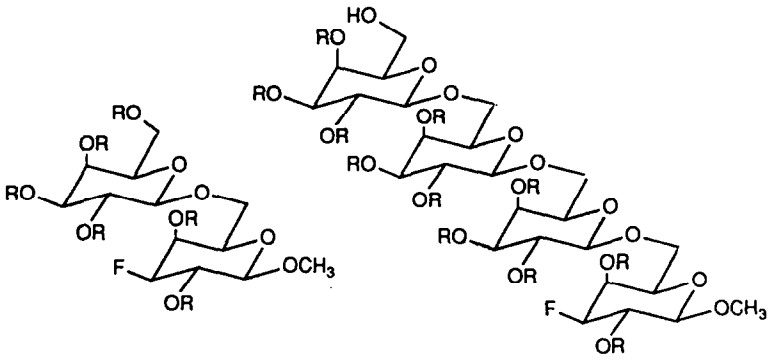
9.6.2. 4-*Deoxy*-4-*fluoro-galactose*. Treatment of methyl 2,3-di-*O*-benzyl-4-*O*-(*p*-bromobenzenesulfonyl)-6-*O*-trityl-beta-D-glucopyranoside, **311**, with Amberlyst A-26 in the fluoride form produced methyl 2,3-di-*O*-benzyl-4-fluoro-6-*O*-trityl-beta-D-glucopyranoside, **312**, in 75% yield.



9.6.3. 3-*Deoxy*-3-*fluoro-galactose*. 3-Deoxy-3-fluoro-galactose was prepared by either direct treatment with DAST or displacement of the appropriately functionalized sulfonate ester.[154]

Fluorinated galactose has been incorporated in galactobiose, -triose and tetraose[155] as well as other polysaccharides to determine conformation and to probe binding to immunoglobins.[156]

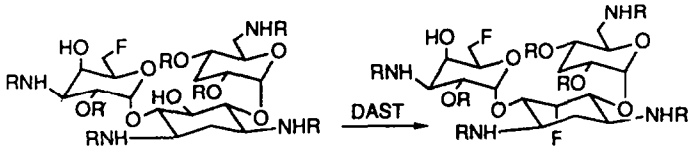




9.7. *Fluorokanamycin*

Fluorinated sugars have also been incorporated in analogs of aminoglycoside antibiotics. Fluorination beta to an amino group of Kanamycin A was proposed to decrease the basicity of amino residue and thereby modify the binding of the analog. After careful manipulation of protecting groups, functionalization of Kanamycin by introduction of a trifluoromethanesulfonate at the desired 6″ position was possible. Displacement of the leaving group by tetra-*n*-butylammonium fluoride yielded the desired fluoride in 76% yield.

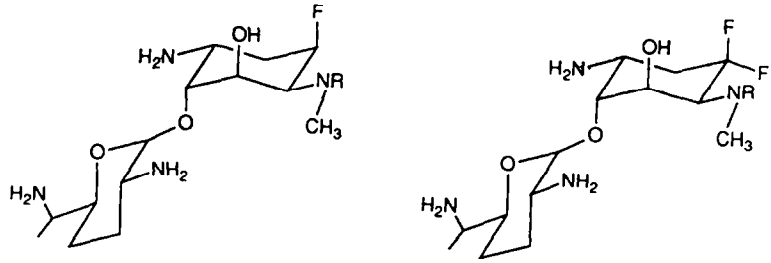
Direct dehydroxylative fluorination of the free 6″-hydroxyl **313** with DAST formed the 5,6″-difluoride **314** in 79% yield.[157] Variation of the protection facilitated the preparation of number of selectively fluorinated Kanamycin A analogs by treatment with DAST. Screening of these analogs demonstrated that in comparison with Kanamycin the analogs showed generally improved activity.



313 314

9.8. *Fluorosporaricin*

Sporaricin was protected and converted into the 3-methanesulfonate ester. Attempted fluorination with tetra-*n*-butylammonium fluoride by displacement of the sulfonate ester failed.[158] Direct dehydroxylative fluorination with DAST yielded the 3-epi-fluoro **315** in 59%. Oxidation of the 3-hydroxyl was effected with pyridinium chlorochromate to the 3-oxo compound was followed by treatment with DAST to form the 3,3-difluoro compound **316** in 72%. It was possible to prepare the 3-fluoro compound via fluorination of the 3-epi-hydroxyl, prepared by sodium borohydride reduction of the 3-oxo compound, in 68% yield.

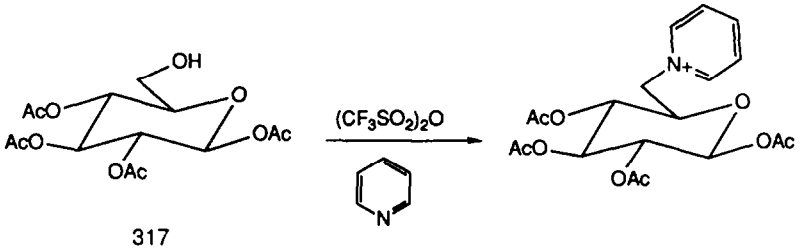


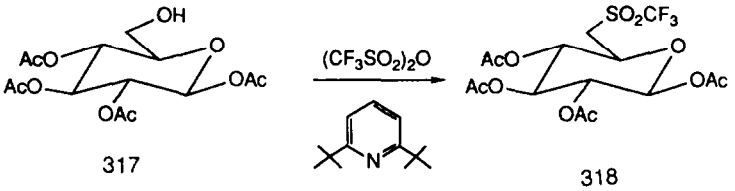
315 316

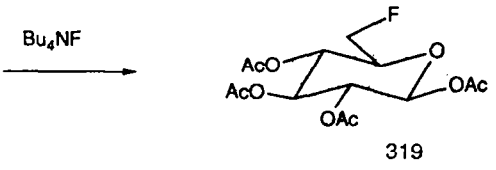
9.9. *General synthetic methods*

In this section are summarized general methods which have utility in preparing a variety of fluorinated carbohydrates. Some of these methods have been employed earlier, but these reports described the application of the methods in general manner rather than optimization of a specific case.

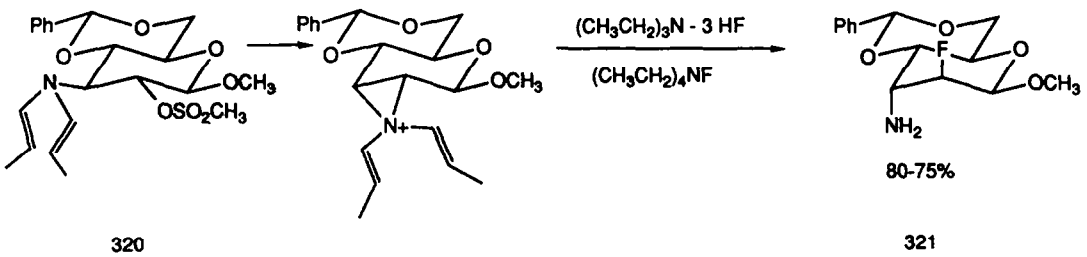
9.9.1. *Trifluoromethanesulfonate ester displacements.* The displacement reactions of 1,2,3,4-tetra-*O*-acetyl-6-*O*-trifluoromethyl-sulfonyl-glucopyranose, **318**, has been studied in depth.[159] The use of a hindered base, such as 2,6-di-*t*-butyl-4-methyl-pyridine, was reported to give the highest yields of the desired ester, suppressing displacement of the ester by the base. Conversion of the 6-trifluoromethylsulfonates **318**, prepared in this way, to the fluoride **319** with tetra-*n*-butylammonium fluoride proceeded in 27% yield.



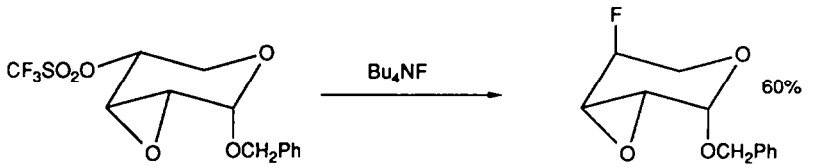




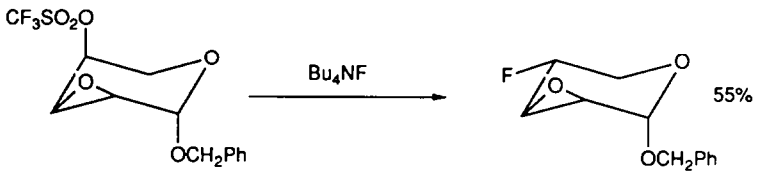
9.9.2. *Methanesulfonate displacements. Diallyl amine neighboring group participation.* Methyl 3-deoxy-3-diallylamino-4,6-*O*-benzylidene-2-*O*-methanesulfonate-altropyranoside, **320**, when heated with tetra-ethylammonium fluoride or triethylamine tris(hydrogen fluoride) reagent formed methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-diallylamino-2-fluoro-altropyranoside, **321**, in 86% yield.[160] The propensity of the beta diallylamino group to participate in the displacement reaction was general. The regiochemistry of the reaction was controlled by the steric effects of the remaining carbohydrate substituents.



9.9.3. *Trifluoromethanesulfonate displacements. Epoxide neighboring group participation.* Neighboring group participation by diallylamino substituents has been shown earlier to enhance the efficiency of methanesulfonate displacement reactions. In related work, epoxides have been shown to anchimerically assist the displacement of neighboring trifluoromethanesulfate esters by tetra-*n*-butyl ammonium fluoride.[161] In a typical reaction **322** formed benzyl 2,3-anhydro-4-deoxy-4-fluoro-beta-L-lyxopyranoside, **323**, in 60% yield and **324** formed benzyl 2,3-anhydro-4-deoxy-4-fluoro-alpha-D-lyxopyranoside, **325**, in 55% yield.



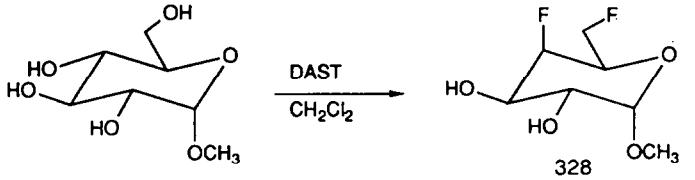
322 323



324 325

9.9.4. *Diethylaminosulfur trifluoride (DAST).* DAST has become one of the most generally useful reagents for the fluorination of carbohydrates. In addition to the numerous examples where DAST was used to fluorinate protected carbohydrates, unprotected carbohydrates may demonstrate selectivity in their fluorination reactions. Methyl alpha-D-glucopyranoside, **326**, when treated with DAST at $-30°$ in dichloromethane selectively forms 6-deoxy-6-fluoro-alpha-D-glucopyranoside, **327**, in 70–88% yield.[162] However neat DAST will form methyl 4,6-dideoxy-4,6-difluoro-alpha-D-galacto pyranoside, **328**, in 60% yield.[163] As a general rule it has been found that neat DAST will replace the 6-hydroxyl as well as the equatorial hydroxyls at positions 3 and 4 of methyl glycosides.[164] The reaction of equatorial hydroxyls is effected by the anomeric configuration. Reaction at the 3-position can be suppressed by short reaction times.

326 327



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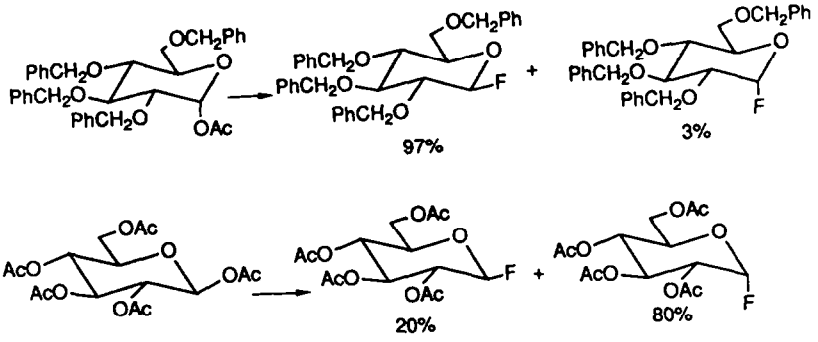
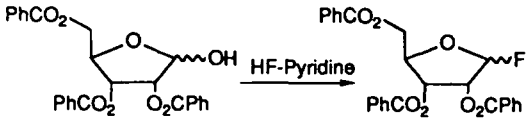


Scheme 14.

9.9.5. *Glycosyl fluorides.* Recent investigations by several groups have shown that glycosyl fluorides are synthetically useful in controlling stereochemistry at the anomeric carbon in glycosidation reactions.[165] The anomeric hydroxyl of protected carbohydrates has been converted to glycosyl fluorides in 60–80% yields by treatment with the hydrogen fluoride pyridine reagent.[166] 1-Acetyl carbohydrates form the glycosyl fluorides in good yields, 70–90%, but also with good anomeric selectivity.[167] DAST treatment of protected 1-hydroxy carbohydrates will form the desired fluorides in excellent yields, 84–99%.[168] Control of stereochemistry is strongly effected by the choice of protecting groups.

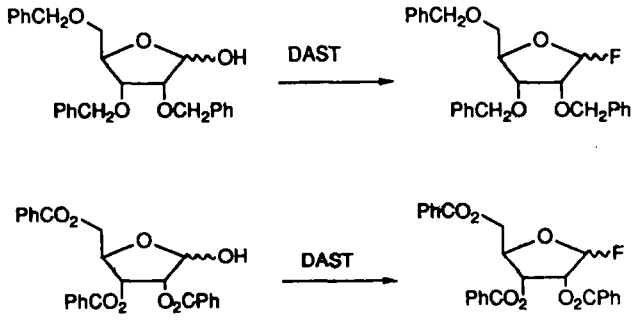


10. PURINES AND PYRIMIDINES

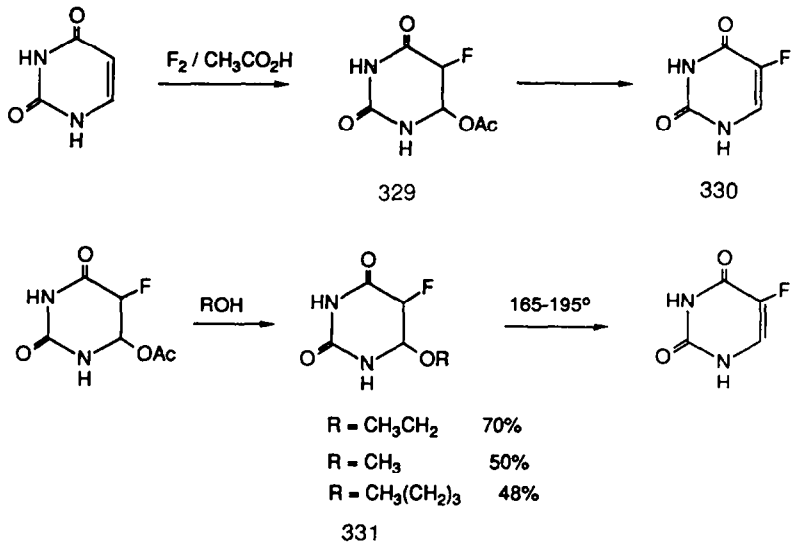
The utility of fluorinated pyrimidines such as the well known and clinically useful 5-fluorouracil has established the importance of fluorinated purines and pyrimidines as potential anticancer agents. However, the search continues for analogs which have improved properties, especially derivatives which may be administered orally. The significance of these compounds has driven investigators to continue to develop new and better syntheses of the fluorinated heterocycles.[169]

10.1. 6-*Alkoxy*-5-*fluoro*-5,6-*dihydrouracil*

The synthesis of 5-fluorouracil, **330**, by direct fluorination of uracil in acetic acid is well known.[170] By direct treatment of **329** with alcohol, the 6-alkoxy-5-fluoro-5,6-dihydrouracils **331** can be prepared in 48–70% yield.[171] Thermolysis of these compounds leads to formation of the 6-alkoxy-5-fluorouracils themselves.

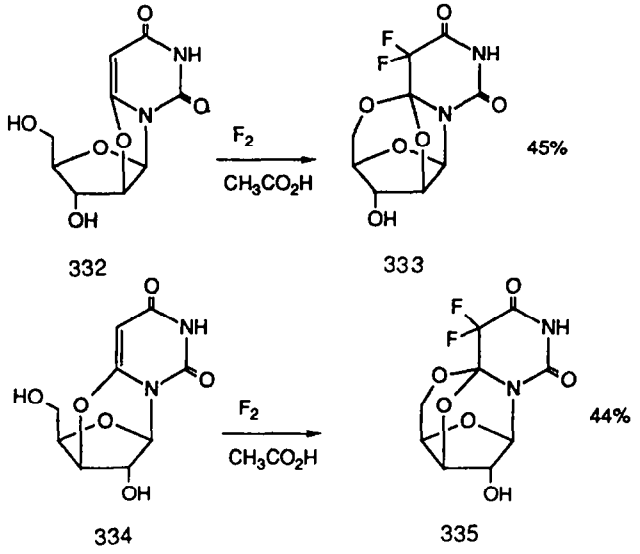


Scheme 15.



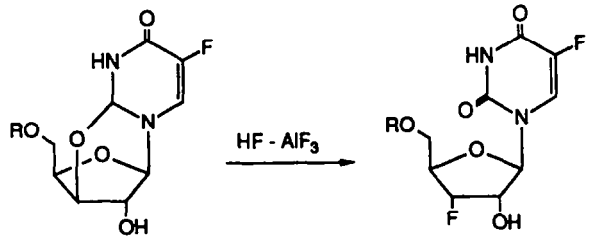
10.2. 6-O-*dicyclo*-5,5-*difluoro*-5,6-*dihydrouracil*

When 6:2′-cyclo-uracil arabinoside, **332**, and 6:3′-cyclo-uracil arabinoside, **334**, were treated with fluorine in acetic acid at 40°,[172] careful control of the temperature was crucial to the success of the reaction. Fluorination of **332** formed 6:2′, 6:5′-dianhydro-5,5-fluoro-6,6-dihydroxy-5,6-dihydrouracil arabinoside, **333**, in 45% yield and 6:3′, 6:5′-dianhydro-5,5-fluoro-6,6-dihydroxy-5,6-dihydrouracil xyloside, **335**, in 44% yield from the **334**.



10.3. 5-*Fluoro*-2′,3′-*dideoxy*-3′-*fluorouridine*

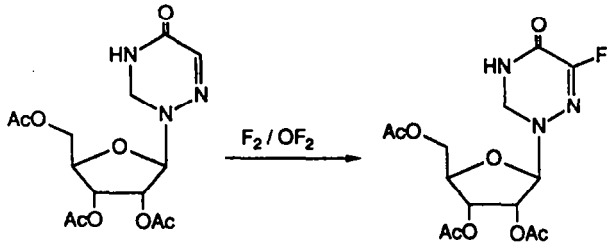
5-Fluoro-2′-deoxy-uridine is a potent cytotoxic agent in cell culture, however, *in vivo* it is substantially degraded to the free pyrimidine base, 5-fluorouracil, already described as cytotoxic itself, but substantially less so than 5-fluoro-2′-deoxy-uridine. Additionally 5-fluoro-2′-deoxy-uridine is very specific for DNA where 5-fluorouracil is often incorporated into RNA. 5-Fluoro-2′-deoxy-uridine was converted into 2′,3′-anhydro-1-(2′-deoxy-beta-D-lyxofuranosyl)-5-fluorouracil, **336**, by known methods.[171] The anhydro compound was opened with anhydrous hydrogen fluoride in the presence of aluminum trifluoride to form 5-fluoro-2′,3′-dideoxy-3′-fluorouridine, **337**, in 30% yield after deprotection.[174] The overall activity of the compound was diminished by 3-fluorination but the stability of the nucleosidic linkage was improved toward cleavage.



336 337

10.4. *6-Aza-5-fluorouracil*

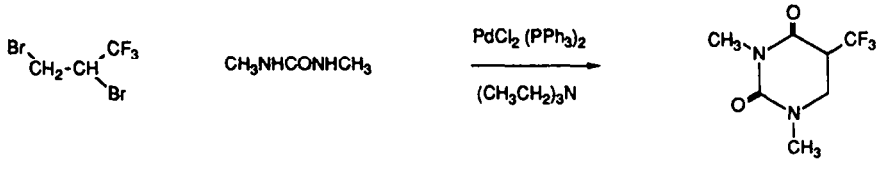
As described several times previously, selective fluorination with molecular fluorine is highly dependent upon the reaction conditions. When 1-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)-6-azauracil, **338**, was treated with F_2 directly only an 0.3% yield of the desired 6-aza-5-fluoro-nucleoside **339** could be isolated.[175] However, when 6-azauracil was treated with fluorine in the presence of oxygen difluoride, the 6-aza-5-fluorouracil was formed in 55% yield.[176] **338** formed the 5-fluoro nucleoside **339** in 20% isolated yield when reacted under similar conditions.



338 339

10.5. *5-Trifluoromethyluracil and 5,6-dihydrouracil*

5-Trifluoromethyluridine has been demonstrated to have anti-viral and anti-cancer activity (7g) but better methods for the synthesis of 5-trifluoromethyluracil are still under investigation. When 2-bromo-3,3,3-trifluoropropene, bis(triphenylphosphine) palladium(II) chloride, urea, triethylamine and dimethylformamide are heated together at 100° for 10 hours under 40 atmospheres of carbon monoxide, 5-trifluoromethyl-5,6-dihydrouracil is formed[177] in 26% yield. 1,3-Dimethyl-5-trifluoromethyl-5,6-dihydrouracil, **340**, is formed by reaction of *N,N'*-dimethylurea in 70% yield. The reaction proceeds nicely with 2,3-dibromo-1,1,1-trifluoropropane as well. 5-Trifluoromethyluracil is prepared by bromination and dehydrobromination.



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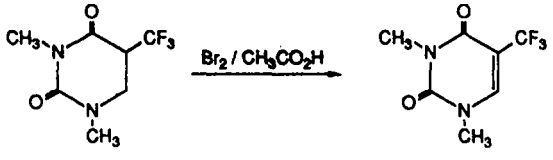

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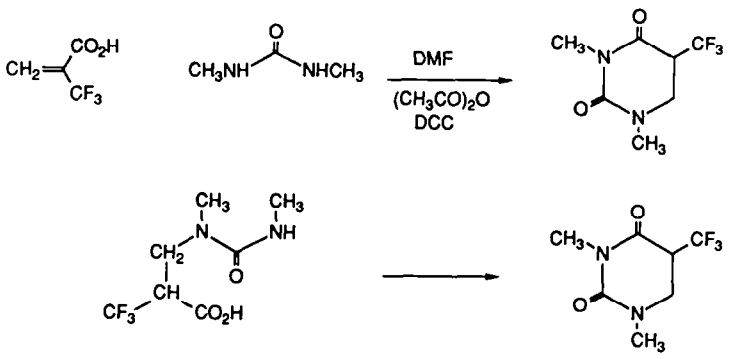


Scheme 15.

The yields with urea have been improved by using trifluoromethylacrylic acid, prepared by the reaction of carbon monoxide with 2-bromo-3,3,3-trifluoropropene catalyzed by bis(triphenylphosphine) palladium(II) chloride, heated with urea in the presence of acetic anhydride.[178] The reaction tends to stop after the first addition so acetic anhydride was added to improve the yield of the ring closure step. The yields are as high as 67% by this method. Both **329** and *N*-methyl-5-trifluoromethyluracil have good activity against ascitic mastocarcinoma MM2 of mice.

10.6. 5-*Trifluoromethyluridine*

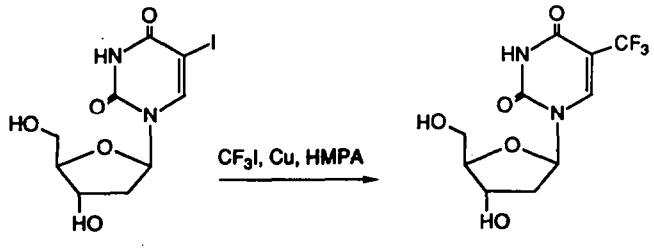
The reaction of 5-iodouridine with trifluoromethyl iodide in the presence of copper powder in hexamethylphosphoramide to form 5-trifluoromethyluridines in 37–54% yield[179] has been extremely useful in preparing both protected and unprotected uridines.[180] This technique was extended to the preparation of 5-pentafluoroethyl uridine and also 1-beta-D-arabinofuranosyl-5-(trifluoromethyl)uracil. The *arabino* compound displayed good anti-viral activity but the pentafluoro compound was inactive.

10.7. (E)-5-(3,3,3-*Trifluoro*-1-*propenyl*)-2′-*deoxyuridine*

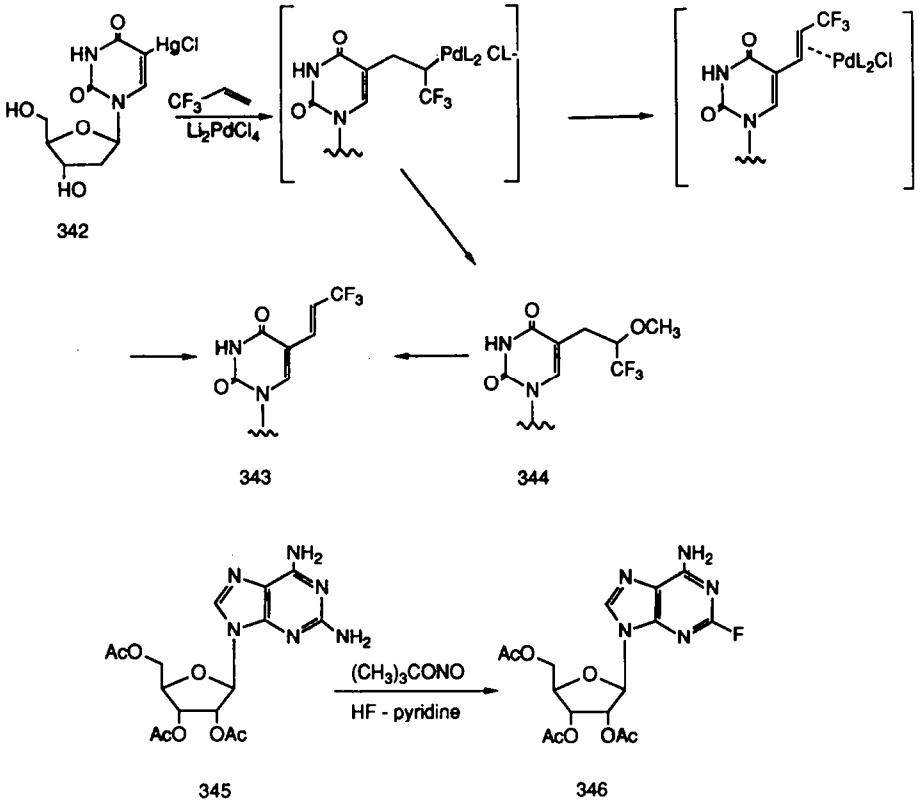
2-Choromercuri-2′-deoxyuridine, **342**, was allowed to react with 3,3,3-trifluoropropene in the presence of lithium tetrachloropalladate.[181] The desired (*E*)-5-(3,3,3-trifluoro-1-propenyl)-2′-deoxyuridine, **343**, was formed in 26% yield along with 5-(3,3,3-trifluoro-1-methoxyprop-1-yl)-2′-deoxyuridine, **344**, in 59% yield. The methoxy compound could be converted to the desired trifluoropropene in 65% by treatment with trifluoroacetic anhydride. (*E*)-5-(3,3,3-trifluoro-1-propenyl)-2′-deoxyuridine was very effective against herpes simplex virus I but was not at all active against herpes simplex virus II.

10.8. 2-*Fluoroadenine*

2-Fluoroadenine nucleosides are resistant to deamination by the catabolic enzyme deaminase. Thus it is possible to improve the lifetime of adenosine *in vivo*.[182] The non-aqueous diazotization of



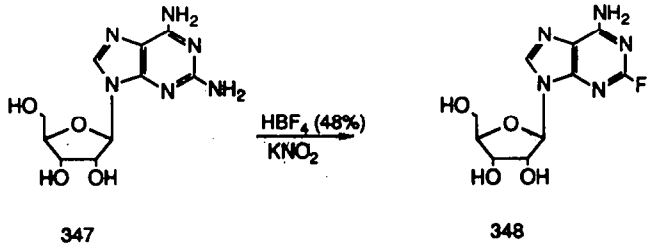
Scheme 16.



2,6-diamino-9-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)purine, **345**, with *t*-butylnitrite in hydrogen fluoride pyridine solution afforded a 48% yield of 2-fluoroadenosine triacetate,[183] **346**. The reaction was general and yielded 6-chloro-2-fluoro-9-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)purine in 85% and 2,6-difluoro-9-(2,3,5-tri-*O*-acetyl-beta-D-ribofuranosyl)purine in 66%. The transformation was very sensitive to the concentration of hydrogen fluoride, e.g. 70% hydrogen fluoride in pyridine was ineffective, whereas a concentration between 45–65% worked well.

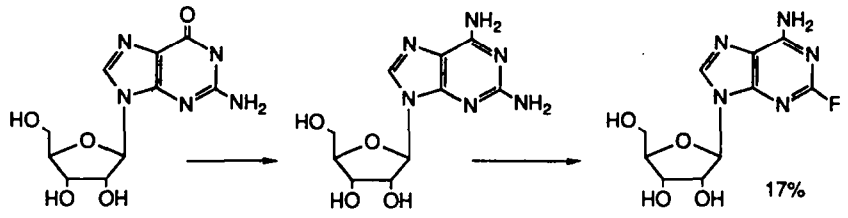
10.9. *2-Fluoro-8-aza-adenosine*

Fluorination of 8-aza-adenosine was undertaken to suppress deamination as described above. 2-Amino-8-aza-adenosine, **347**, prepared from the 2-thiomethyl compound, was diazotized with potassium nitrite in fluoboric acid. *In situ* dediazoniation formed the desired 2-fluoro-8-aza-adenosine, **348**, in 21% yield.[184] The compounds showed good activity against P388 leukemia in mice.



10.10. *2-Fluoroformycin*

Formycin has some *in vivo* anticancer activity but is subject to deamination by adenosine deaminase whereupon the *in vivo* cytotoxicity is greatly reduced. 5,7-Diamino-3-(beta-D-ribofuranosyl)pyrazolo(4,3-d)pyrimidine, **349**, was dissolved in hydrogen fluoride-pyridine (60% hydrogen fluoride) and was treated with *t*-butyl nitrite. The desired 2-fluoro compound **350** was isolated in 17% yield.[185] Fluorination diminished the activity ten-fold, relative to the parent formycin,

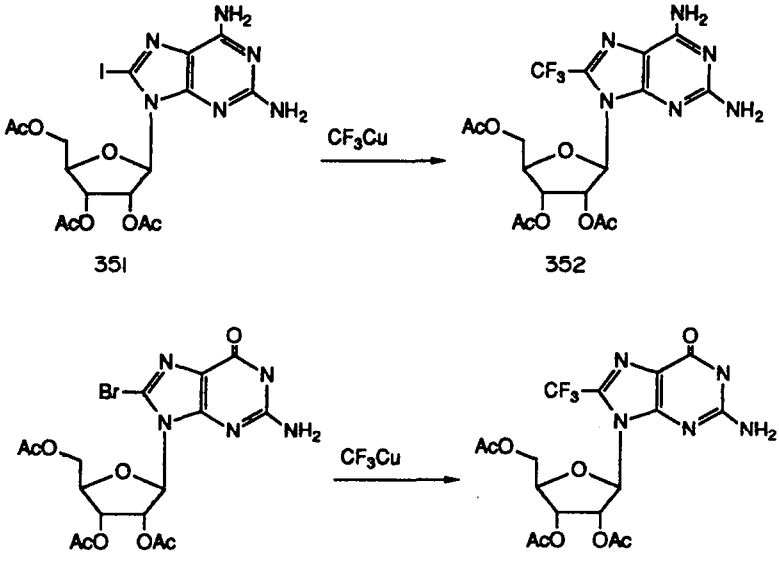


349 350

against L1210 cells. Apparently the loss of potency is related to the failure of di- and triphosphate of 2-fluoroformycin to form.

10.11. *8-Trifluoromethyl adenosine and 8-trifluoromethyl inosine*

The 2′,3′,5′-tri-*O*-acetyl-8-iodoadenosine, **351**, was subjected to trifluoromethylation with trifluoromethyliodide and copper as was described for the pyrimidines earlier. The principal product was reduction of the iodide. Removal of unreacted copper powder by filtration, demonstrating the solubility of the trifluoromethylating reagent, suppressed the reduction reaction[186] and yielded the **352** in 64%. The procedure was general, yielding 8-trifluoromethyl inosine from 2′,3′,5′-tri-*O*-acetyl-8-bromo-inosine in 42%. The compounds had only modest anticancer activity.



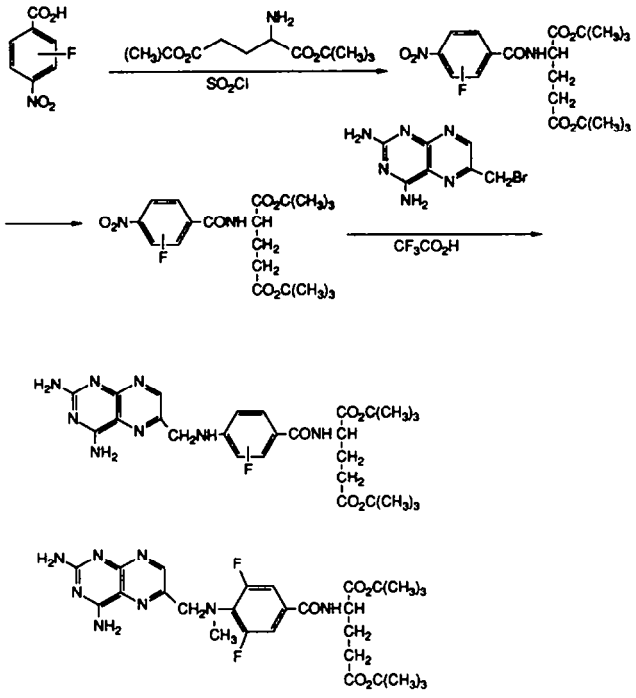
351 352

11. AROMATIC FLUORIDES

The synthesis of aromatic fluorides efficiently and in high yields is very difficult. Aryl fluorides appear in a broad variety of molecules, some of which have activity as antibiotics,[49] anti-folates,[187] sedatives[188] and estrogen receptor imaging agents.[189] The common problem associated with the synthesis of these diverse materials is substitution of fluorine into the aromatic unit.

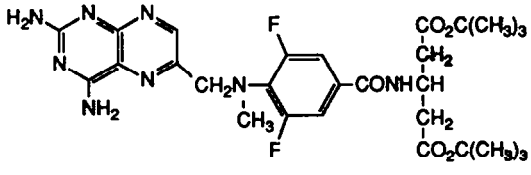
11.1. *2′ and 3′-Fluoroaminopterin*

The respective fluoro-nitro-benzoic acids were coupled to the t-butyl esters of L-glutamic acid and were then reduced to the p-amino-fluoro- benzamides. The amino compounds were condensed with 6-(bromomethyl)-2,4-pteridine diamine to form on deprotection a 40% yield of the fluoroaminopterins.[187a] Both the 2′-fluoro and 3′-aminopterins were more active than methotrexate against L1210 cells or human stomach cancer HuTu80 cells.



11.2. 3′,5′-*Difluoromethotrexate*

Fluorination of methotrexate has also been employed as a tool for studying the binding of the material to dihydrofolate reductase.[187b] When bound to the enzyme, each of the fluorines in **341** is in a different chemical environment. It was possible to observe the effect of added NADH or NADPH to the bound methotrexate analog.



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11.3. *Fluorotamoxifen*

Fluorotamoxifen was found to be a good estrogen receptor binding agent. As such, radiolabeled with fluorine-18, fluorotamoxifen might be useful for studying the distribution of the estrogen binding sites. Since preparation of radiolabeled material required a brief efficient synthesis, two approaches were developed.[189a]

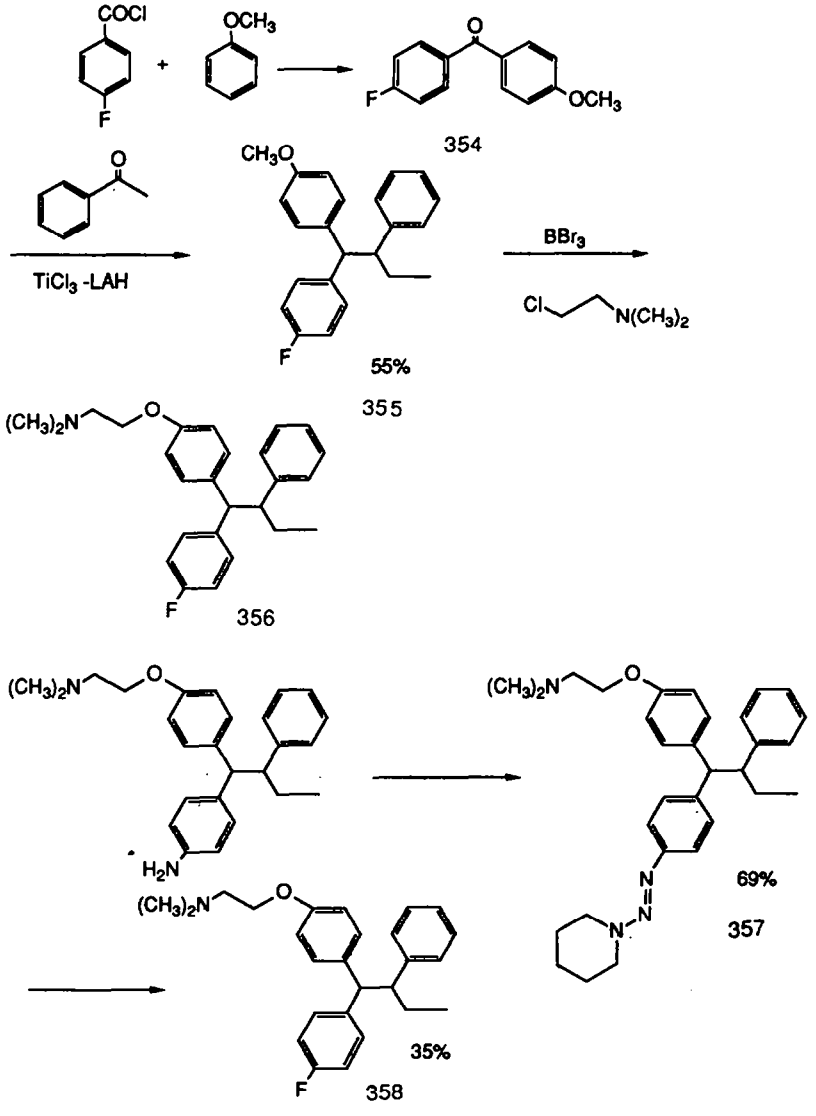
Anisole was acylated with 4-fluoro-benzoyl chloride, to form the unsymmetric benzophenone **354** in 75% yield. McMurry coupling of propiophenone in 55% formed the desired triphenylethylene derivative **355**. The 2-(dimethylamino)ethyl ether **356** was prepared in 36% yield. Where this synthesis was useful for preparing unlabeled material it was not appropriate for labeling studies.

Conversion of aminotamoxifen into 1-(4-(piperidinoazo)phenyl)-1-(4-(2-(*N*,*N*-dimethylamino)ethoxy)phenyl) 2-phenyl-1-butene followed by treatment with aqueous hydrogen fluoride or pyridine hydrogen fluoride yielded fluorotamoxifen in 35% and 28% yield, respectively.

Table 4. Aryl triazene decomposition to aryl fluorides

Triazene	Reaction conditions[a]	Yield (%)
4-CH_3	anhydrous HF/THF	15
	HF-pyridine	15
	48% aqueous HF	27
4-$CH_3(CH_2)_3$	48% aqueous HF	16
2-$(CH_3)_2CH$	HF-pyridine/benzene	22
3-CH_3O	HF-pyridine/benzene	19
	48% aqueous HF	17
	anhydrous HF/benzene	18
	anhydrous HF/CH_2Cl_2	trace
2-CH_3O-5-phenyl	48% aqueous HF	0
	HF-pyridine/benzene	0
2-CH_3SO_3	48% aqueous HF	0
2-CH_3O	48% aqueous HF	0
2-CH_3O-5-CH_3	48% aqueous HF	0

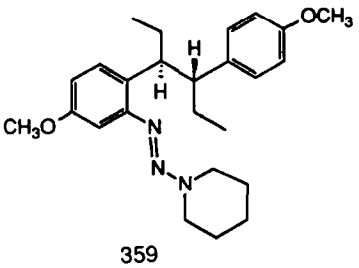
[a] Room temperature, 30 minutes.



11.4. *2′-Fluorohexestrol*

In closely related work, 2′-fluorohexestrol was prepared for use as an estrogen receptor binding agent. A very thorough investigation of the conditions for the introduction of fluorine was made assuming that with radiolabeled fluoride ion, fluoride should be utilized efficiently.[189b] In model studies it was determined that ortho substituents markedly reduce the yield of fluoride where *meta* and *para* substituents are tolerated well. As can be seen in the table the substituents strongly affect the outcome of the fluorination reaction.

Decomposition of the triazene prepared from 2′-aminohexestrol, **359**, formed the 2′-fluorohexestrol, **360**, in 25–43% yield but the reaction was accompanied by formation of a considerable amount, 46–50%, of a ring closed product, **361**, from intramolecular alkylation.



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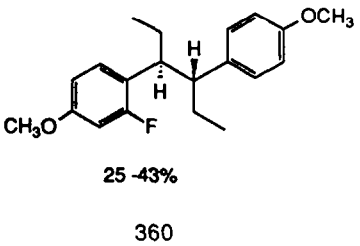
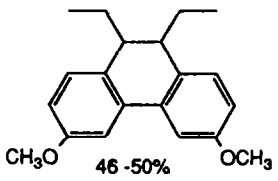


25 -43%

360

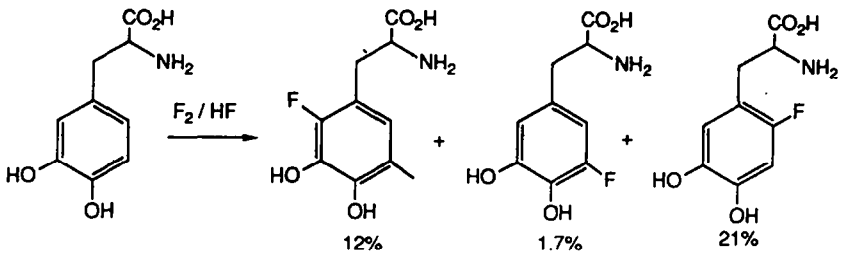


46 -50%

361

11.5. *6-Fluorodopamine*

For imaging of dopamine receptors in normal and diseased tissues, 6-fluorodopamine was prepared by the direct fluorination of dopamine with fluorine-18 gas in hydrogen fluoride.[190] Although the 6-fluoro compound was formed in 21% yield along with the 2-fluoro material in 12%, and with a small amount, 1.7%, of the 5-fluorodopamine, the reaction did not demonstrate strict electrophilic substitution character. Earlier studies had suggested that fluorine could behave as an electrophile but was generally unselective.[191]



12. TRIFLUOROMETHYL RETINALS

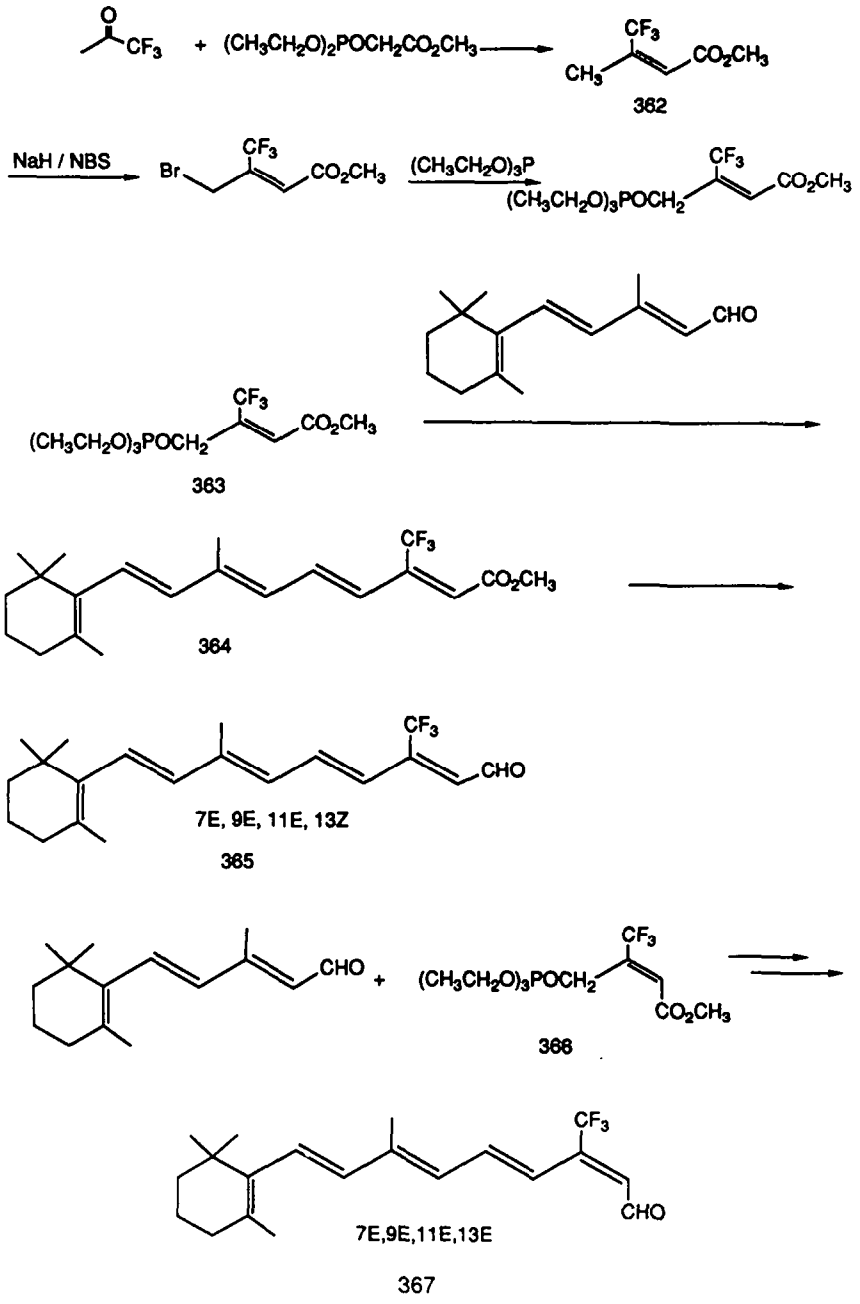
Combination of *cis*-retinal with a protein opsin, forms the light-sensitive compound rhodopsin important to the chemistry of vision. Binding of retinal to the protein causes a red shift in the absorption spectra of retinal from 440 nm to 570 nm. Substitution of retinal has been suggested to shift the absorption spectra in a manner which would mimic this effect.

12.1. 20,20,20-*Trifluororetinal*

Several groups have attempted the preparation of the all *trans*, (7*E*,9*E*,11*E*,13*Z*-)20,20,20-trifluororetinal with contradictory results. In early work, the Wittig–Horner olefination of 1,1,1-trifluoroacetone with methyl (diethylphosphonato) acetate was reported to form the methyl *Z* 3-(trifluoromethyl) crotonate, **362**. Allylic halogenation followed by Arbuzov reaction with triethyl phosphate formed a new Wittig–Horner reagent **363**. Olefination of beta-ionylideneacetaldehyde provided **364** which was easily reduced to the aldehyde,[192] **365**. Other workers have reported the condensation of 1,1,1-trifluoroacetone with methyl (diethylphosphonato) acetate formed the methyl *E* 3-(trifluoromethyl) crotonate, **366**. Condensation of the *E* Wittig–Horner reagent would form the 13-*cis* compound, methyl 7*E*,9*E*,11*E*,13*E*-20,20,20-trifluororetinoate,[193] **367**. The spectral properties of the material so prepared were in agreement with those reported for the compound prepared independently.[194] An alternative approach to the preparation of the *trans* compound began with chain elongation of beta-ionylidene, **368**, by treatment with carbon tetrabromide and triphenylphosphine. Treatment of the dibromoolefin **369** with butyl lithium followed by ethyl trifluoroacetate yielded the trifluoromethyl ketone **370** in 65%. The triple bond was reduced to the required *trans* olefin **371** with sodium bis-methoxyethoxy-aluminum hydride. After reoxidation to the ketone, Peterson olefination formed a 1 : 1 mixture of 13-*E*, **372**, and 13-*Z*, **373**, esters which were separated. Reduction formed the pure aldehyde isomers.[195] *Trans* **374** was very susceptible to isomerization to the *cis* olefin.

12.2 19,19,19-*Trifluororetinal*

The lithium acetylide of 1-ethynyl-2,2,6-trimethylcyclohexanol, **375**, was condensed with ethyl trifluoroacetate. Wittig olefination, protection, reduction to the *trans* olefin and reoxidation to the aldehyde formed the 9-*cis* compound, (7*E*, 9*E*). The 9*Z*-olefin **377** was prepared in 34% yield by photolysis. Wittig–Horner olefination gave a one to one mixture of the 7*E*,9*Z*,11*E*,13*E*- and 7*E*,9*Z*,11*E*.13*Z* esters.[196]



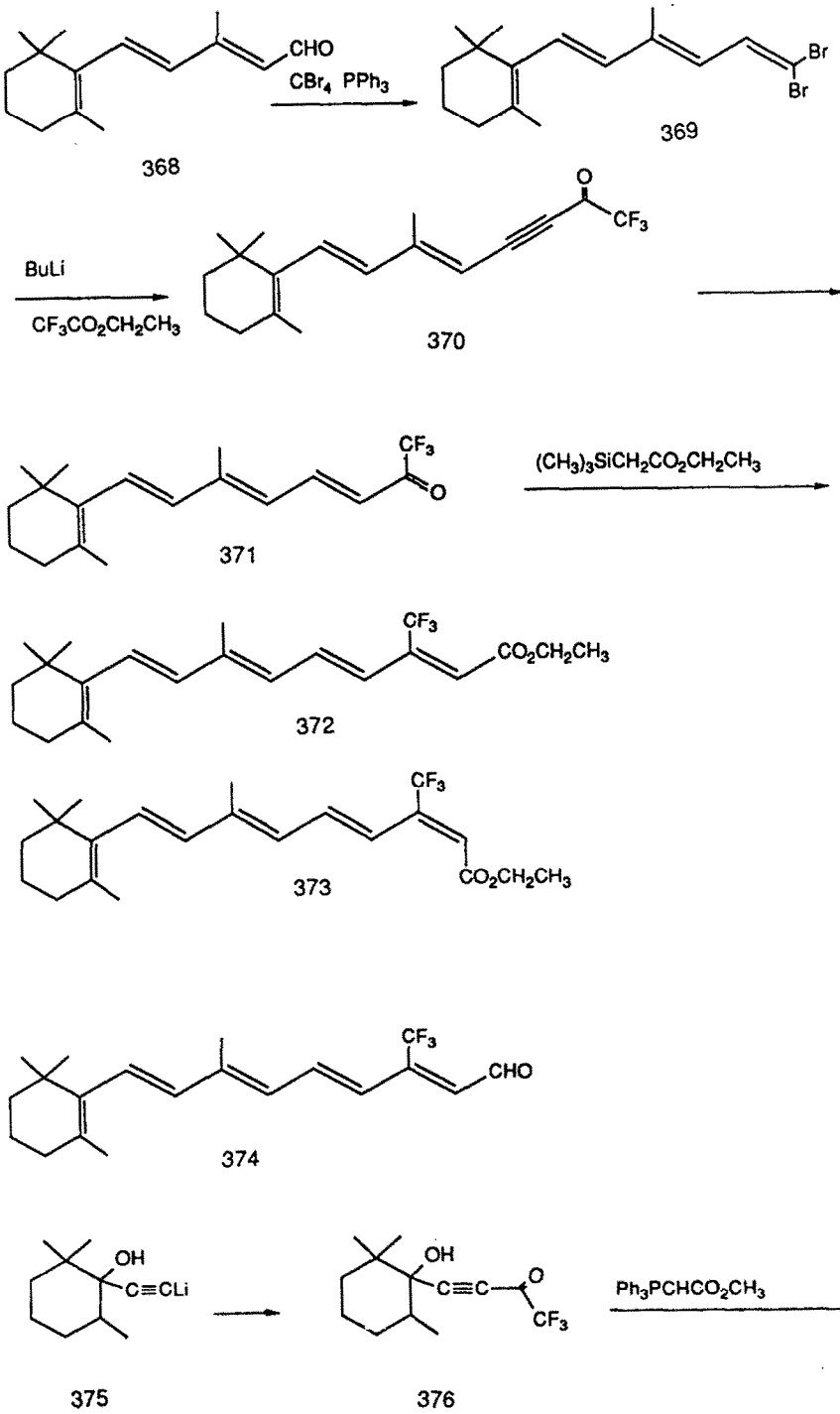
13. MISCELLANEOUS

13.1. *Fluoroerythronolides*

3-*O*-Mycarosyl-8,9-anhydroerythronolide B 6,9-hemiketal **378** prepared from 3-*O*-mycarosyl erythronolide B was treated directly with trifluoromethyl hypofluorite to form a 1 : 9 mixture of 3-*O*-mycarosyl-(8*S*)-8-fluoro-erythronolide B, **379**, and 3-*O*-mycarosyl-(8*S*)-8-fluoro-erythronolide B 6,9 : 9,11-spiroketal,[197] **380**. No biological activity data for the compound was presented.

13.2 *Fluoro-benzodiazepin* N-*oxide*

Deprotonation of 7-chloro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2-one N^4-oxide, **381**, with potassium hydride followed by treatment with *N*-fluoro-*N*-(*exo*-2-norbornyl)-*p*-toluenesulfonamide formed 7-chloro-3-fluoro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-2-one N^4-oxide, **382**, in 52% yield.[198] *N*-fluoro-*N*-alkyl sulfonamides were found to be general efficient and selective fluorinating reagents for reaction with anions.



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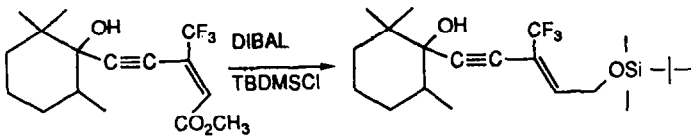

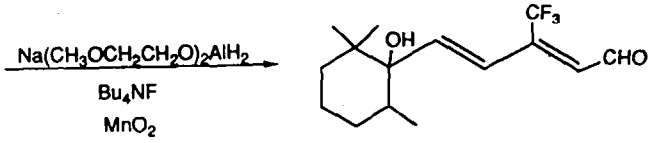

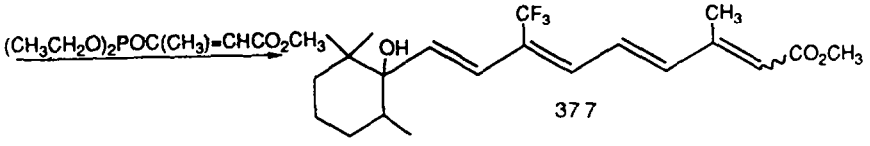

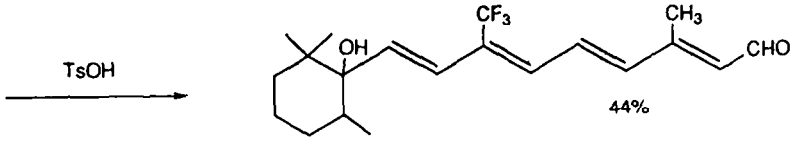

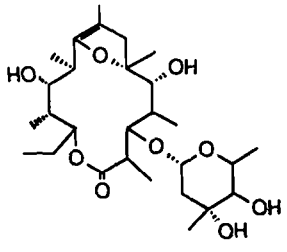

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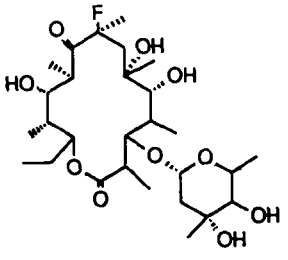

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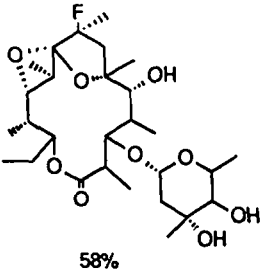

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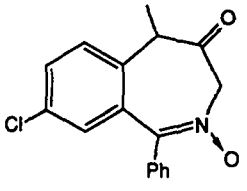

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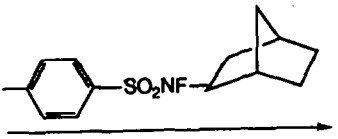

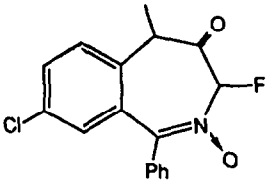

52%

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