Chem. Soc. Rev., 1987, **16**, 381—436

Modern Methods for the Introduction of Fluorine into Organic Molecules: An Approach to Compounds with Altered Chemical and Biological Activities

By John Mann
CHEMISTRY DEPARTMENT, READING UNIVERSITY, WHITEKNIGHTS, READING RG6 2AD

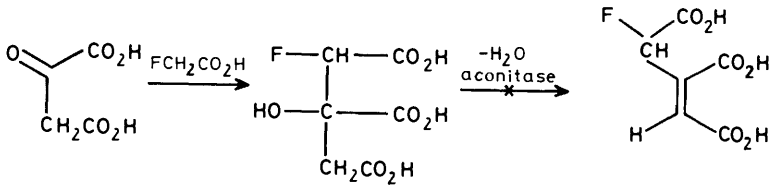
1 Introduction

It is almost one hundred years since the Belgian chemist Swarts described (in 1896) the synthesis of methyl fluoroacetate by heating methyl iodoacetate with silver fluoride [1]—and although French chemists had prepared fluoromethane as early as 1835, Swarts' synthesis heralded the beginnings of modern fluoro-organic chemistry. He also prepared trifluoroacetic acid in 1922, and laid the foundations for all subsequent organofluorine chemistry. In the 1930s Midgley and Henne synthesized a range of fluorocarbons,[2] and pioneered their use as thermally and chemically stable refrigerants and lubricants. This latter property was to prove invaluable in the Manhattan Project since the gaskets used in the gaseous diffusion plant for the enrichment of ^{235}U using the highly corrosive UF_6 were fluorocarbon polymers.

Other polyfluoro compounds have been introduced in more recent times as aerosol propellants (presently under a cloud due to fears about depletion of the ozone layer), *e.g.* CCl_2F_2 and $CF_2ClCFCl_2$: fire extinguishing agents, *e.g.* CF_3Br and CF_2ClBr; anaesthetics, *e.g.* halothane $CF_3CHClBr$; polymers, *e.g.* polytetrafluoroethylene; and rather exotically as blood substitutes, *e.g.* perfluorodecalins and polyfluorocyclohexanes. In this last role the fluorocarbons act as efficient transporters of both oxygen and carbon dioxide, and can substitute for blood when haemorrhage has occurred where blood is not readily to hand, as in a battlefield situation.

The biological affects of introducing fluorine into organic molecules were first studied during World War II by Saunders and co-workers at Cambridge, and by Schrader in Germany; [3] but it was the demonstration by Marais in 1943,[4] that the toxicity of the South African plant *Dichapetalum cymosum* was due to monofluoroacetate, which provided the impetus for studies on the toxicology and pharmacology of organofluorine compounds. Extensive biochemical investigations

[1] F. Swarts, *Bull. Soc. Chem. Belg.*, 1896, **15**, 1134.
[2] 'Organofluorine Chemicals and their Industrial Applications', ed. R. E. Banks, Ellis Horwood, Chichester, 1979.
[3] B. C. Saunders, 'Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine', Cambridge University Press, Cambridge, 1957.
[4] J. S. C. Marais, *Onderstepoort J. Vet. Sci. Anim. Ind.*, 1943, **18**, 203.



Scheme 1

by Peters and Martius [5,6] resulted in the identification of the aberrant biochemistry underlying the toxicity of monofluoroacetate. The enzymes of the tricarboxylic acid cycle (citric acid cycle) utilize fluoroacetate in place of acetate, and catalyse the formation of 2-fluorocitrate (Scheme 1). This then binds irreversibly to the enzyme aconitase, and the strong $-I$ effect of the fluorine atom ensures that dehydration to form fluoroaconitate is repressed. The cycle is thus completely disrupted by the 'lethal synthesis' of an 'anti-metabolite', and the implications for the rational design of enzyme inhibitors for use in chemotherapy were immediately apparent.

But why does fluorine change the properties of organic compounds so dramatically? Three main reasons are usually cited:

(a) The van der Waals radius of fluorine (*ca.* 1.35 Å) is very similar to that of hydrogen (*ca.* 1.10 Å), and the C–F bond length (1.26—1.41 Å) is not much greater than the C–H bond length (1.08—1.11 Å). This means that substitution of fluorine for hydrogen in a molecule will not dramatically alter the steric bulk of the molecule.

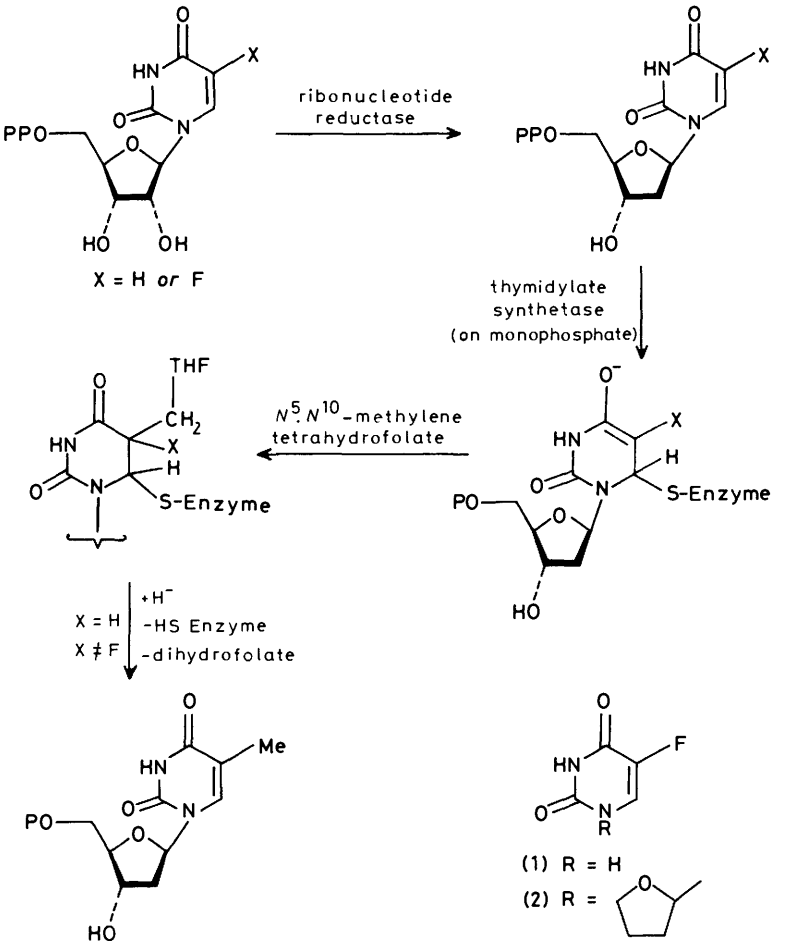
(b) On the electronegativity scale, fluorine (4.0) greatly exceeds hydrogen (2.1), and a large electronic effect on reactions at neighbouring carbon centres may thus be anticipated. It may also function as an H-bond acceptor, and replacement of hydroxyl by fluorine often has interesting results. In addition it is a moderately good leaving group, and may be displaced by nucleophiles at or near to the active-sites of enzymes, with resultant covalent attachment of an organic moiety to the enzyme.

(c) C–F bonds substantially increase the lipophilicity of molecules, and the CF_3 group is one of the most lipophilic groups known. This will obviously increase the fat-solubility of organofluorine compounds, and this feature is of considerable importance in drug design.

All of these features, either individually or in combination, will influence the outcome of a reaction (whether enzyme-catalysed or not) in which a fluoro analogue of the natural substrate is employed, and it is instructive to consider some compounds which exemplify this principle. One frequently cited example of an anti-metabolite is 5-fluorouracil (1). This is an inhibitor of the enzyme thymidylate synthetase which catalyses the process shown in Scheme 2 whereby deoxyuridylate is methylated to produce deoxythymidylate.[7]

The conversion is believed to proceed *via* a Michael addition of a thiol group of

[5] R. A. Peters, *Proc. R. Soc. London B.*, 1951, **139**, 143.
[6] C. Martius, *Justus Liebigs Ann. Chem.*, 1949, **561**, 227.
[7] A. L. Pogolotti, K. M. Ivanetich, H. Sommer, and D. V. Santi, *Biochim. Biophys. Res. Commun.*, 1976, **70**, 972.



Scheme 2

the enzyme to the uracil moiety, followed by electrophilic addition of N^5,N^{10}-methylene tetrahydrofolate. The process is completed by elimination. Clearly if 5-fluorouracil has been incorporated into the deoxyuridylate, this final step requires abstraction of F^+ which is unlikely. Since formation of deoxythymidylate is essential for DNA biosynthesis 5-fluorouracil is an effective cytotoxic agent, and is much used in cancer chemotherapy. The corresponding tetrahydrofuranyl analogue (2) is often even more effective since it is slowly metabolized to 5-fluorouracil, and thus acts as a slow-release form of the drug.

The efficacy of both drugs obviously depends upon their acceptability as enzyme

substrates, at least in terms of their steric bulk. They are incorporated into 5-fluorouridylate (and thence into RNA), and with the intervention of ribonucleotide reductase they yield 5-fluorodeoxyuridylate. This clearly has chemical characteristics markedly different from those of the natural compound by virtue of a change from a C–H to a C–F bond.

A second classical example is provided by the fluorocorticosteroids. The parent compound, cortisol (3, R = H), is one of the glucocorticoids (these enhance the synthesis and deposition of glycogen in the liver but are actually produced in the adrenal cortex) and has potent anti-inflammatory activity. The 9-α-fluoro analogue (4, R = Ac) was prepared by addition of anhydrous HF to the epoxide (5), and had eleven times greater glucocorticoid activity than cortisol acetate (3, R = Ac).[8] This has been ascribed to the increased acidity of the 11-β-hydroxyl due to the neighbouring fluorine atom, with resultant enhanced binding to an hydrogen bond acceptor of the steroid receptor in liver cells. In addition, oxidation to the corresponding cortisone analogue (4, R = Ac, 11-keto), which is probably inactive, is also disfavoured due to the difficulty of removal of the hydrogen at C-11. Numerous cortisol analogues have been prepared, many with a 9-α-fluoro substituent, *e.g.* (6), and although the inhibition of inflammatory processes is effected in many ways, high affinity for the glucocorticoid receptor is a prerequisite for selectivity and potency.[9]

As an increasing number of enzymes have been characterized in terms of three-dimensional structure, and as the mechanisms by which reactions occur at their active sites have been probed, so it has become possible to design mechanism-based inhibitors, or 'suicide substrates'. Several of these will be discussed in the subsequent sections, but one well-documented example will suffice at this point. The β-fluoro and α-difluoromethyl amino acids are of particular interest, and act by inactivation of enzymes that utilize pyridoxal phosphate as a co-factor.[10] The mode of action of α-difluoromethyl ornithine (7) is exemplary (Scheme 3).[11] Decarboxylation and fluoride loss generates an electrophilic species that is then attacked by a nucleophile at or near to the active-site of the enzyme, with resultant irreversible binding and inactivation. Other decarboxylases are similarly inhibited by the corresponding fluoro amino acids.

The enzyme ornithine decarboxylase is responsible for the conversion of ornithine into putrescine, and this is the first stage of polyamine biosynthesis. Modifications of this pathway appear to be important in the aetiology of certain malignancies, psoriasis, and in various parasitic infections. In recent *in vivo* investigations, compound (7) was in fact curative for rats infected with a trypanosome closely related to the one responsible for sleeping sickness in humans.[12] Its efficacy as an anticancer agent is, however, limited.

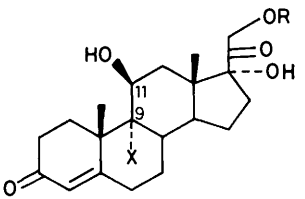
[8] J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, 1954, **76**, 1455.

[9] J. Elks and G. H. Phillipps, 'Medicinal Chemistry: the Role of the Organic Chemist in Drug Research', ed. S. M. Roberts and B. J. Price, Academic Press. London. 1985.

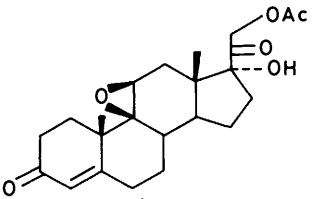
[10] C. Walsh, *Tetrahedron*, 1982, **38**, 871; *Ann. Rev. Biochem.*, 1984, **53**, 493.

[11] B. W. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara, and J. P. Vevert, *J. Am. Chem. Soc.*, 1978, **100**, 2551.

[12] C. J. Bacchi, H. C. Nathan, S. H. Hutner, P. P. McCann, and A. Sjoerdsma, *Science*, 1980, **210**, 332.



(3) X = H
(4) X = F



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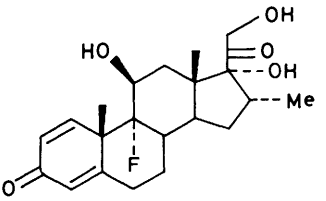


(6)

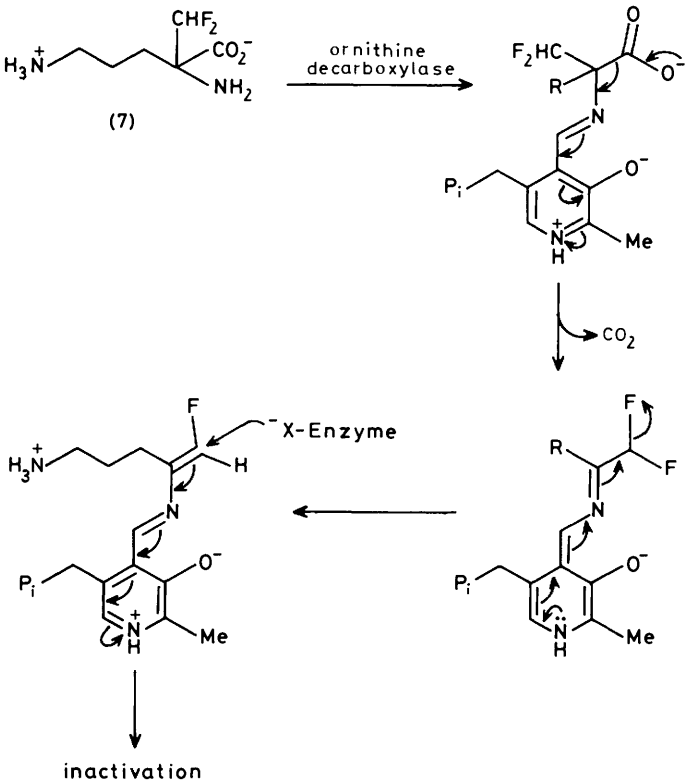
Clearly introduction of fluorine into a compound can have a marked effect upon its biological activity profile, and two recent reviews highlight this aspect.[13,14] The remainder of this review is concerned primarily with the methodology of fluorine insertion.

2 Methodology of Fluorine Insertion

Given the interest in fluoro-organic compounds, it is hardly surprising that numerous methods for fluorine insertion have been developed, especially during the past ten years. A number of excellent reviews have been published recently, and these include ones on the use of elemental fluorine,[15] the use of sulphur tetrafluoride,[16,17] and on general methodology.[18–20] In consequence, in this review an attempt will be made to provide a realistic assessment of the utility of the various methods, and many of the examples have been taken from the very recent literature (1984—1987).

Other reviews have classified reagents into groups according to their supposed mode of action, *i.e.* nucleophilic, electrophilic, or free-radical fluorine transfer; but here the most useful reagents will be dealt with individually.

[13] R. Filler and Y. Kobayashi, 'Biomedical Aspects of Fluorine Chemistry', Elsevier, Amsterdam, 1982.
[14] J. T. Welch, *Tetrahedron*, 1987, **43**, 3123.
[15] S. T. Purrington, B. S. Kagen, and T. B. Patrick, *Chem. Rev.*, 1986, **86**, 997.
[16] C.-L. J. Wang, *Org. React. (N.Y.)*, 1985, **34**, 319.
[17] W. Dmowski, *J. Fluorine Chem.*, 1986, **32**, 255.
[18] A. Haas and M. Lieb, *Chimia*, 1985, **39**, 134.
[19] S. Rozen and R. Filler, *Tetrahedron*, 1985, **41**, 1111.
[20] M. R. C. Gerstenberger and A. Haas, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 647.



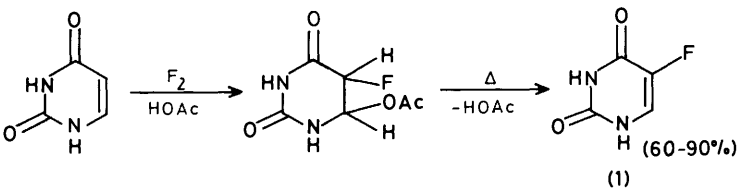
Scheme 3

A. Fluorine.—During 1986 there were numerous celebrations to mark the centenary of Moissan's discovery (on Saturday June 26th, 1886) of fluorine gas. As well as the review already cited,[15] a special edition of the *Journal of Fluorine Chemistry* was also published.[21]

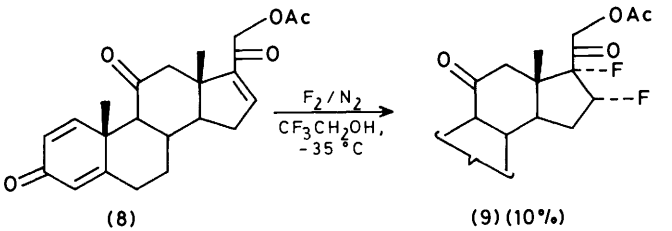
Elemental fluorine is a dangerous oxidizing agent, and it is only during the past 25 years that the gas has been widely used for the fluorination of organic compounds, usually diluted with nitrogen or argon. In this way it is possible to fluorinate alkenes selectively in the presence of other functional groups, and the synthesis of 5-fluorouracil (1) shown in Scheme 4 is exemplary.[22]

It was originally proposed that the reaction involved *syn* addition of fluorine, with subsequent solvent-assisted elimination of fluoride, though more recent work would suggest the involvement of acetyl hypofluorite ($MeCO_2F$) (*vide infra*).

[21] R. E. Banks, D. W. A. Sharp, and J. C. Tatlow, 'Fluorine—The First Hundred Years', *J. Fluorine Chem.*, 1986, **33**, 1—399.
[22] D. Cech and A. Holy, *Collect. Czech Chem. Commun.*, 1976, **41**, 3335.



Scheme 4



Scheme 5

The problem with using fluorine in less polar solvents is its tendency to cleave homolytically (the F–F bond is relatively weak), and free-radical reactions probably account for the low yields obtained in many reactions, *e.g.* the conversion of the steroid (8) into the prednisone analogue (9) (Scheme 5[23]). Rozen discovered that by adding a proton donor, for example ethanol, to the usual solvent mixture ($CHCl_3$ and $CFCl_3$), and by working at low temperatures with very dilute stream of fluorine in nitrogen, fluorine-radical formation could be suppressed and polar processes enhanced.[24] This publication probably best represents the current state of the art, and gives examples of *syn* additions to alkenes and to enones. One example is shown in Scheme 6, and the stereospecificity is ascribed to rapid collapse of an initially formed ion pair involving an α-fluorocarbocation.

An interesting application of this kind of process is shown in Scheme 7, whereby various *erythro*-3-fluorophenylalanines (10) have been prepared.[25] These compounds are of interest partly for determination of the effects of fluorine on stabilization of particular rotational conformations, but also because they could provide (experimental) inhibitors of the key enzyme phenylalanine ammonia lyase. This catalyses the loss of ammonia from phenylalanine and formation of cinnamate *en route* to the lignans, flavonoids, and phenylpropanoids.[26]

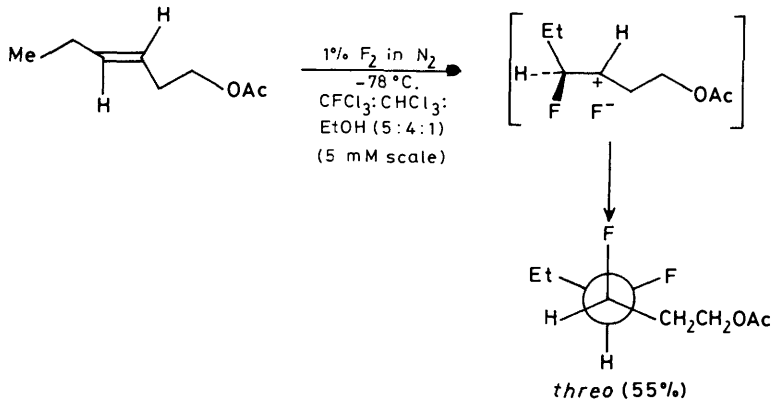
Geminal fluorination may be achieved by reaction of diazo compounds with

[23] D. H. R. Barton, J. Lister-James, R. H. Hesse, M. M. Pechet, and S. Rozen, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1105.

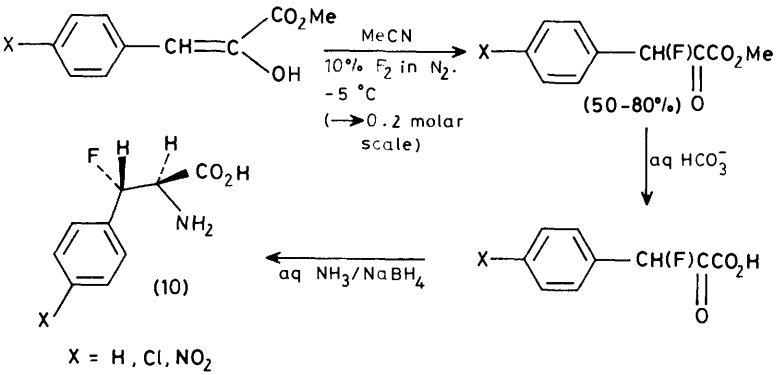
[24] S. Rozen and M. Brand, *J. Org. Chem.*, 1986, **51**, 3607.

[25] T. Tsushuna, K. Kawada, J. Nishikawa, T. Sato, K. Tori, T. Tsuji, and S. Misaki, *J. Am. Chem. Soc.*, 1984, **49**, 1163.

[26] See for example: J. Mann, 'Secondary Metabolism', 2nd Edn. Oxford University Press, Oxford, 1987, Chapter 4.



Scheme 6

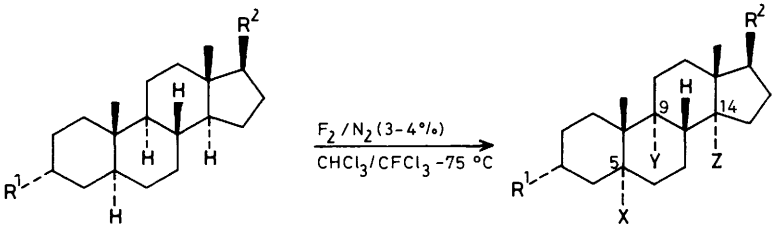


Scheme 7

F_2/N_2 in freons, for example the conversion of diazofluorene (11) into the difluoro derivative (12) (88%).[27] In a similar fashion, the somewhat exotic antibacterial compound pleuromutiline (13) can be converted into its diazo derivative, and thence into the *gem*-difluoro species (14) using fluorine in $CHCl_3$ at -60 °C in the presence of KF (31%).[28] This example demonstrates again that under the appropriate conditions, selective fluorination can be achieved even if a complex array of functionality is present.

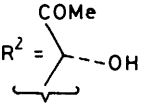
More remarkable and potentially very useful is the substitution of fluorine for hydrogen at unactivated carbon centres. The examples shown in Scheme 8 provide some idea of the scope of the methods introduced by Rozen.[29,30]

[27] T. P. Patrick, J. J. Sheibel, and G. L. Cantrell, *J. Org. Chem.*, 1981, **46**, 3917.
[28] H. Vyplet, *Chimia*, 1985, **39**, 304.
[29] S. Rozen and G. B. Shushan, *J. Org. Chem.*, 1986, **51**, 3522.
[30] S. Rozen and C. Gal, *J. Org. Chem.*, 1987, **52**, 2769.



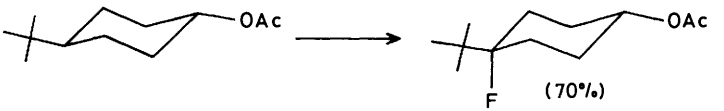
(a) $R^1 = R^2 = H$ — X = Z = H, Y = F (20%) (9-α-F); X = Y = H, Z = F (15%) (14-α-F)

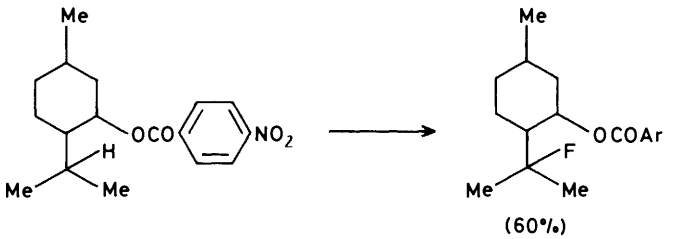
(b) R^1 = OAc, R^2 = H — 9-α-F (30%); Y = Z = H, X = F (30%) (5-α-F)

(c) R^1 = OAc, R^2 =  — 9-α-F (60%)

(d) R^1 = OAc, R^2 = =O — 9-α-F (40%); 5-α-F (30%)

(all reactions carried out on the 1–2 m mole scale)



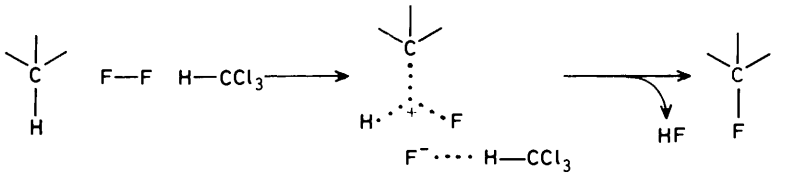


Scheme 8

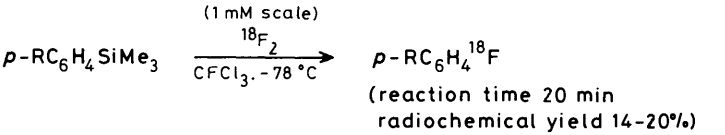
Predictions about regioselectivity may be made on the basis of the contribution of *p* hybridization to the tertiary C–H bond, and the close proximity of an oxygen functionality clearly disfavours electrophilic substitution.

As to the mechanism of substitution, at least with chloroform as solvent, free radical side-reactions are minimized and retention of configuration is observed, and the mechanism proposed by Rozen (Scheme 9) involving electrophilic fluorine, seems reasonable.

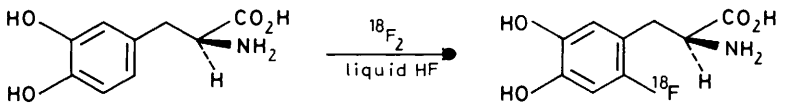
Finally, there is much current interest in the use of the positron emitter ^{18}F ($t_{\frac{1}{2}}$



Scheme 9



Scheme 10



Scheme 11

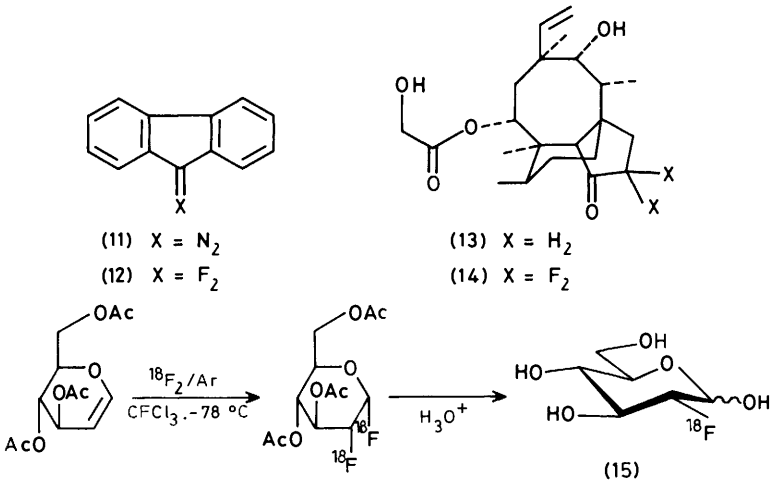
110 minutes) in the body scanning technique known as positron emission tomography (PET).[31] Obviously, introduction of the isotope must be rapid, and the route shown in Scheme 10 seems to offer a useful method for the production of ^{18}F-labelled aryl fluorides.[32]

The fluorination of 3,4-dihydroxyphenylalanine (DOPA) (Scheme 11)[33] and the synthesis of 2-deoxy-2-[^{18}F]fluoro-D-glucose (15) (Scheme 12)[34] are of more immediate biological interest. The product shown in Scheme 11, 6-[^{18}F]fluoro-L-DOPA, is used to follow the production of the essential brain amine dopamine (the decarboxylation product of DOPA), and compound (15) is used as a tracer for examination of glucose metabolism.

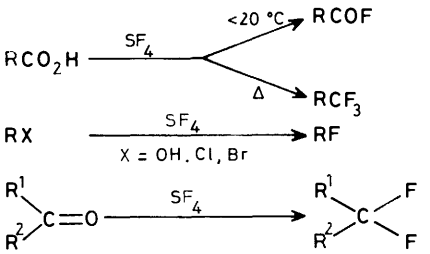
B. Sulphur Tetrafluoride.—SF_4 was first introduced by Dupont in 1960, and reviews covering early work (pre-1972[35]) as well as more recent work[16,17] are available. Its main uses are depicted in Scheme 13.

When used in conjunction with Lewis acids or liquid HF, reaction temperatures and times may often be reduced, and these species usually act catalytically. Reactions of SF_4/HF mixtures with amino alcohols are particularly effective, and

[31] M. M. Ter-Pogossian, M. E. Raichle, and B. E. Sobel, *Sci. Am.*, 1980, **243**, October issue, p. 140.
[32] P. Di Raddo, M. Diksic, and D. Jolly, *J. Chem. Soc., Chem. Commun.*, 1984, 159.
[33] G. Firnau, R. Chirakal, and E. S. Garnett, *J. Nucl. Med.*, 1984, **25**, 1228.
[34] T. Ido, C.-N. Wan, V. Casella, J. S. Fowler, A. P. Wolf, M. Reivich, D. E. Kuhl, *J. Labelled Compd. Radiopharm.*, 1978, **14**, 175.
[35] G. A. Boswell, W. C. Ripka, R. M. Schribner, and C. W. Tullock, *Org. React. (N.Y.)*, 1974, **21**, 1.



Scheme 12



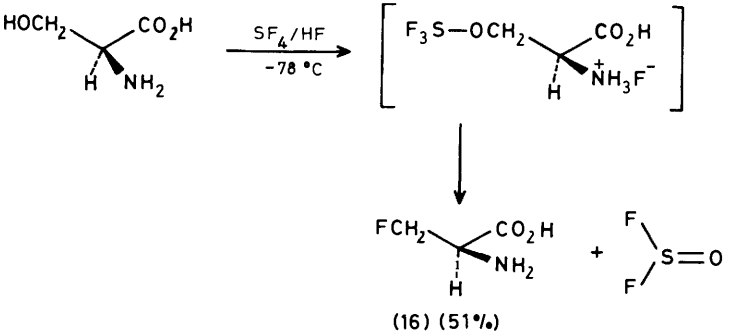
Scheme 13

the synthesis of 3-fluoroalanine (16) provides a good example of the methodology (Scheme 14).[36]

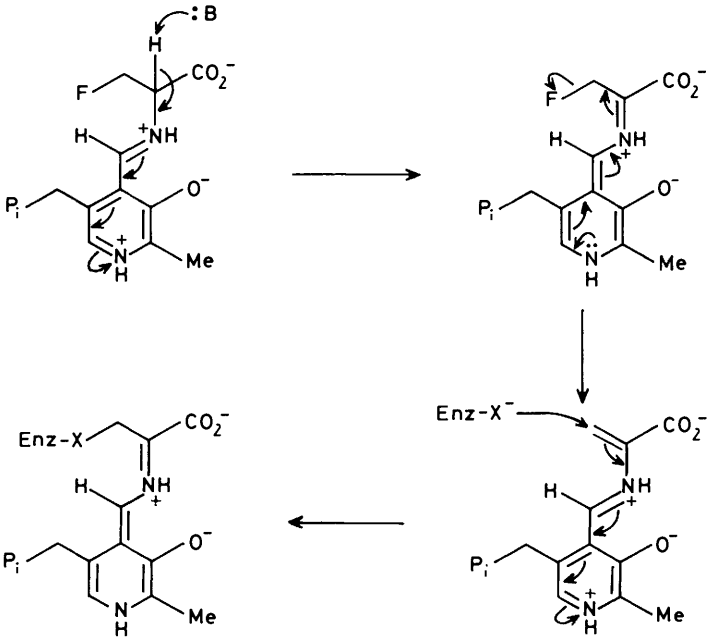
The HF protonates the amino function and suppresses side-reactions with the electrophilic reagent; and more recent studies[37] have shown that high dilutions (<0.5M of the amino acid in HF) almost eliminates dimerization of the first intermediate, which normally competes with the main pathway. In this work (*S*)-3-fluoro-2-deuterioalanine was prepared from the corresponding 2-deuterioserine on a 0.25 molar scale and in a yield of 80%! The product, fludalanine, is an effective antibacterial agent, and like 3-fluoroalanine serves as a suicide substrate for bacterial alanine racemase—one of the key enzymes for cell wall biosynthesis. The mode of action is shown in Scheme 15.

The *threo*- and *erythro*-3-fluoroglutamic acids (17*t* and 17*e*) have been prepared

[36] J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, 1975, **40**, 3808.
[37] P. J. Reider, R. S. E. Conn, P. Davis, V. J. Grenda, E. J. J. Grabowski, and A. J. Zambito, *J. Org. Chem.*, 1987, **52**, 3326.



Scheme 14

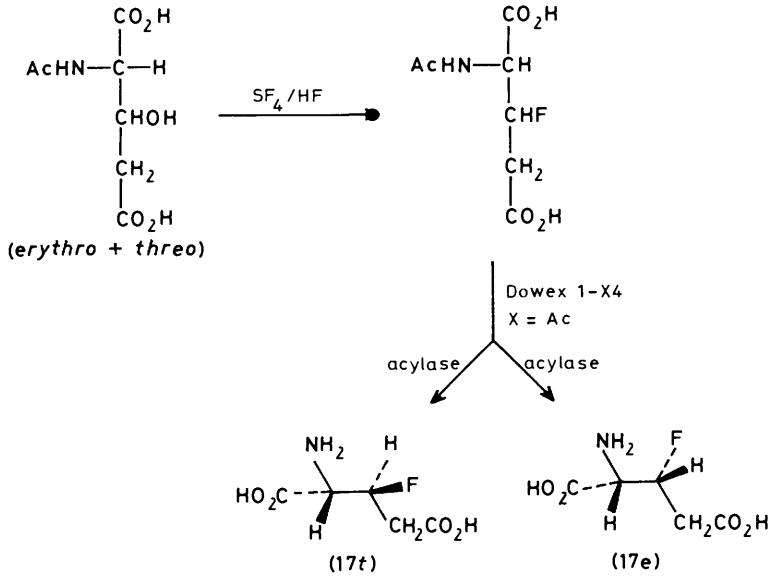


Scheme 15

in a similar fashion, and this work demonstrated that the fluorination proceeded predominantly with inversion of configuration Scheme 16.[38] These amino acid analogues are also potential inhibitors for pyridoxal phosphate-dependent enzymes, in this case those using glutamic acid as substrate.

Delicate functionality can also be preserved in these reactions as demonstrated

[38] A. Vidal-Cros, M. Gaudry, and A. Marquet, *J. Org. Chem.*, 1985, **50**, 3163.



Scheme 16

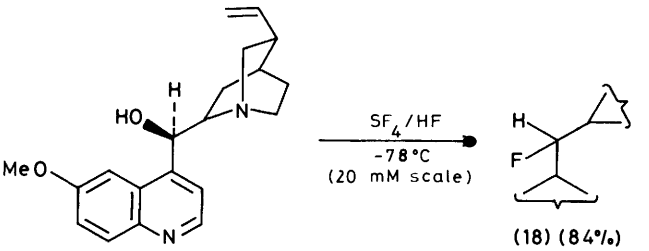
by the synthesis of the quinine derivative (18) (Scheme 17).[39]

Reaction of carbonyls with SF_4 almost invariably requires more forcing conditions, but particularly good yields of gem-difluoro compounds can be obtained using aryl carboxylic acids, as shown in Scheme 18.[40–46]

The synthesis of 3,3-difluorochlorambucil (19) (also shown in Scheme 18) is also of note, because the reaction was carried out on a reasonable scale and in good yield. The product (19) had a better therapeutic index (*i.e.* better ratio of anti-tumour activity to acute toxicity) than chlorambucil.

The major drawbacks of SF_4 are its volatility (b.pt. -38 °C), and its toxicity (comparable to phosgene), and reactions often require the use of sealed, stainless steel vessels. Its reactions with simple alcohols also proceed, in most instances, in

[39] J. Kollonitsch, S. Marburg, and L. M. Perkins, *J. Org. Chem.*, 1979, **44**, 771.
[40] B. G. Oksenenko, M. M. Shakirov, V. D. Shteingarts, *J. Org. Chem. USSR* (*Engl. Transl*), 1976, **12**, 1307.
[41] R. V. Grigorash, V. V. Lyalin, L. A. Alekseeva, and L. M. Yagupol'skii, *J. Org. Chem. USSR* (*Engl. Transl.*), 1975, **11**, 456.
[42] V. V. Lyalin, R. V. Grigorash, L. A. Alekseeva, L. M. Yagupol'skii, and A. I. Burmakov, *J. Org. Chem. USSR* (*Engl. Transl.*), 1975, **11**, 1073.
[43] B. V. Kunshenko, L. A. Alekseeva, V. G. Lukamanov, and L. M. Yagupol'skii, *J. Org. Chem. USSR* (*Engl. Transl.*), 1974, **10**, 896.
[44] G. H. Rasmusson, A. Chen, and G. E. Arth, *J. Org. Chem.*, 1973, **38**, 3670.
[45] N. N. Muratov, A. I. Burmakov, B. V. Kunshenko, L. A. Alekseeva, and L. M. Yagupol'skii, *J. Org. Chem. USSR* (*Engl. Transl.*), 1982, **18**, 1220.
[46] C. W. Buss, P. L. Coe, and J. C. Tatlow, *J. Fluorine Chem.*, 1986, **34**, 83.



Scheme 17

poor yield, and for these reasons the modified reagent diethylamino sulphur trifluoride (DAST) is now preferred.

C. Diethylamino Sulphur Trifluoride.—This reagent (20) (and a host of similar ones) were prepared by Middleton using the general method shown in Scheme 19.[47]

It is relatively easy to handle (b.pt. 46—47 °C at 10 mm Hg), and can be stored in plastic bottles at room temperature or below for long periods without significant decomposition. It is also commercially available around £5 per gramme.

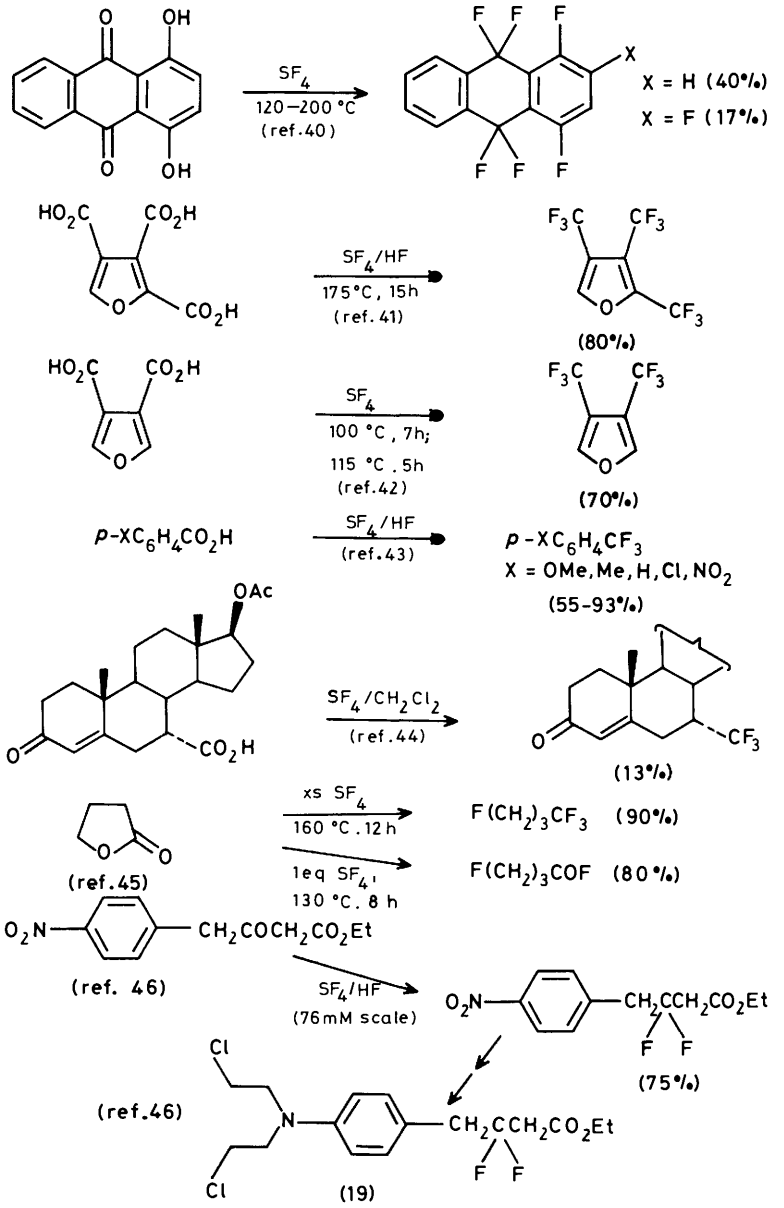
In his mini-review of its uses[47] Middleton described most of the key features of DAST chemistry, and the primary reactions are depicted in Scheme 20. The reactions with alcohols are probably the most important, especially since these conversions are difficult with SF_4, and they proceed in good yield using solvents like dichloromethane, $CFCl_3$, and diglyme, at temperatures ranging from −78 °C to room temperature and above. The reactions usually occur with inversion of stereochemistry, though retention of configuration and rearrangements are also common. Dehydration to form alkenes, though of much less significance than with SF_4, is also a common side-reaction.

The effect of changing to one of the bis-dialkylamino sulphur difluoride reagents is to reduce the amount of rearrangement, and this can be further enhanced by changing to a less polar solvent. These various experimental results have been explained through consideration of the likely intermediates (21) and (22) (Scheme 21).

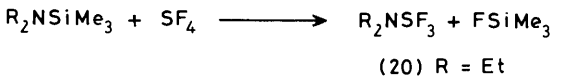
The ion pair containing two amino groups is likely to lose fluoride more easily, and should therefore have a shorter lifetime with consequent reduction of carbocation-type reactions. An explanation that takes into account the comparative stabilities of the intermediates (21) has also been considered.[47]

The commercial availability of DAST has led to a rapid expansion in its use, especially for natural product synthesis. Numerous syntheses of fluoro analogues of geraniol (23) and other isoprenoid precursors have been executed in order to probe the specificity of the enzymes involved in isoprenoid biosynthesis and to delineate the mechanisms of the biosynthetic reactions. Good reviews of this work are provided by Schlosser[48] and Poulter,[49] and although much of this chemistry

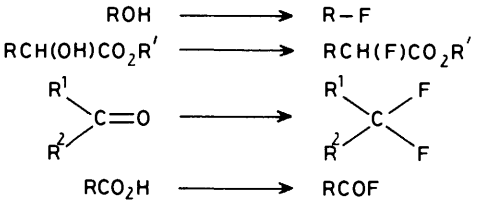
[47] W. J. Middleton, *J. Org. Chem.*, 1975, **40**, 574.
[48] M. Schlosser, *Tetrahedron*, 1978, **34**, 3.
[49] C. D. Poulter and H. C. Rilling, *Acc. Chem. Res.*, 1978, **11**, 307.


SF4
120–200 °C
(ref.40)
X = H (40%)
X = F (17%)
SF4/HF
175°C, 15h
(ref. 41)
(80%)
SF4
100 °C, 7h;
115 °C, 5h
(ref.42)
(70%)
p-XC6H4CO2H
SF4/HF
(ref.43)
p-XC6H4CF3
X = OMe, Me, H, Cl, NO2
(55-93%)
SF4/CH2Cl2
(ref.44)
(13%)
xs SF4
160 °C, 12h
F(CH2)3CF3 (90%)
1eq SF4
130 °C, 8 h
F(CH2)3COF (80%)
(ref.45)
(ref. 46)
SF4/HF
(76mM scale)
(75%)
(ref.46)
(19)

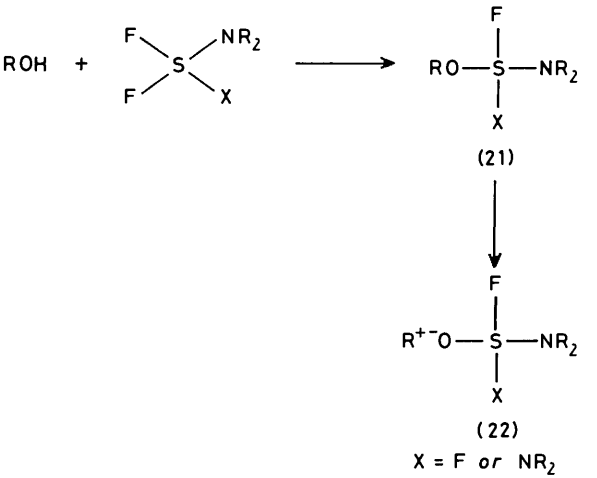
Scheme 18



Scheme 19



Scheme 20



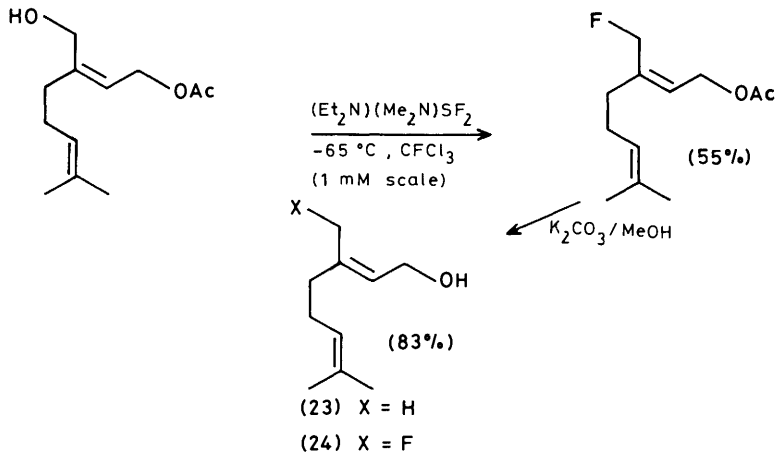
Scheme 21

employed commercially available fluorinated compounds, one good example of the use of bis(dialkylamino) sulphur difluoride reagent is shown in Scheme 22.[50] The route allows easy access to 3-fluoromethylgeraniol (24).

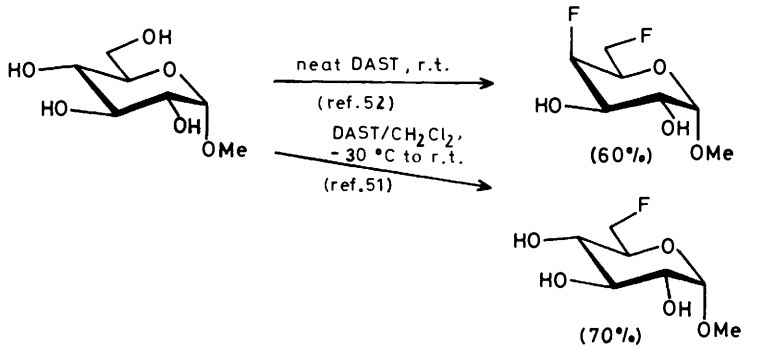
It is in the area of carbohydrate chemistry where most use has been made of DAST, and some idea of the potential selectivity can be obtained from Scheme 23.[51,52]

The whole area of fluoro-carbohydrate synthesis has been reviewed (to 1981)[53] and clearly many of the compounds have been prepared in order to probe or

[50] C. D. Poulter, P. L. Wiggins, and T. L. Plummer, *J. Org. Chem.*, 1981, **46**, 1532.
[51] P. J. Card, *J. Org. Chem.*, 1983, **48**, 393.
[52] C. W. Somawardhana and E. G. Brunngraber, *Carbohydr. Res.*, 1983, **121**, 51.
[53] A. A. E. Penglis, *Adv. Carbohydr. Chem. Biochem.*, 1981, **38**, 195.



Scheme 22



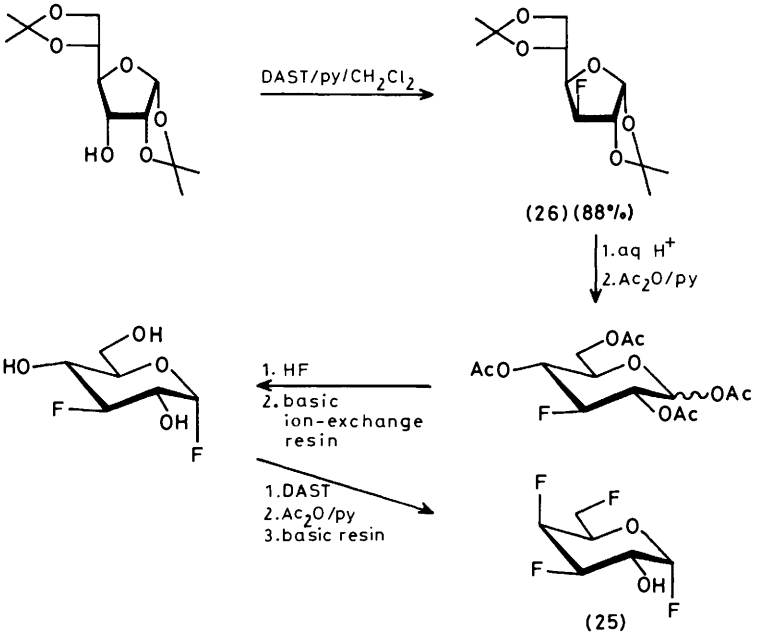
Scheme 23

interfere with metabolic processes, though polyfluorinated compounds like the galactose derivative (25) (Scheme 24)[54] may also be of value for ^{19}F (n.m.r.) and ^{18}F (PET) studies.

The 3-deoxy-3-fluoroglucofuranose derivative (26) has been employed in an elegant chemico-enzymatic synthesis of 2-deoxy-2-fluoroarabinose 5-phosphate (27) (Scheme 25).[55] The use of hexokinase for phosphorylation, together with the strong ATP-regeneration system based upon phosphoenolpyruvate and pyruvate kinase, is particularly interesting.

Given the importance of amino sugars as key constituents of antibiotics and other biologically interesting molecules, much attention has been paid to the

[54] G. H. Klemm, R. J. Kaufman, and R. S. Sidhu, *Tetrahedron Lett.*, 1982, **23**, 2927.
[55] D. G. Drueckhammer and C.-H. Wong, *J. Org. Chem.*, 1985, **50**, 5912.



Scheme 24

synthesis of azidofluoro sugars, and a recent paper by Lukacs and co-workers provides a useful summary of the potential of this chemistry.[56] Degradation and reduction of azido sugars also gives access to a whole range of β-fluoroamino sugars.

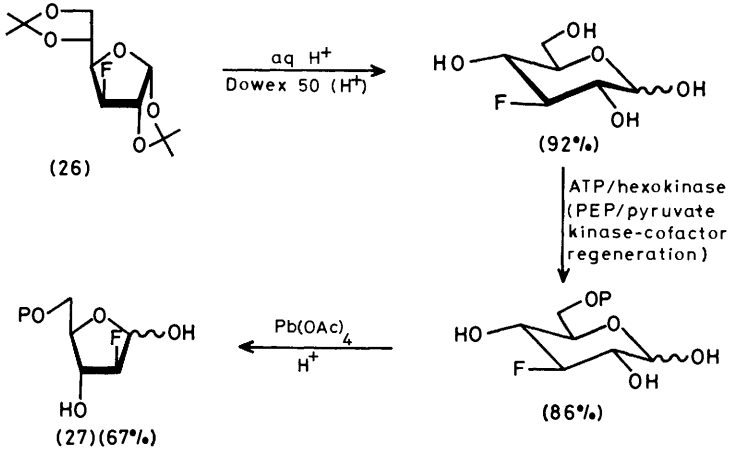
One feature of this work was the demonstration that vicinal diaxial azido alcohols undergo fluorination with DAST with retention of configuration, and this chemistry was employed by the same group for a synthesis of 2′-*C*-fluoro-β-daunomycin (28, X = F) (Scheme 26).[57]

The compound was prepared in the hope of improving the stability of the glycoside linkage of the parent daunomycin (28, X = H), a potent and broad spectrum anti-cancer agent. In the event, the analogue has similar cytostatic activity against the P388 mouse leukaemia *in vitro*, but was considerably less active against the same tumour *in vivo*.

The rearrangement reaction shown in Scheme 26 was also of use in the synthesis of the 2-α-fluorooleandrose derivative (29) shown in Scheme 27. The 2-β-fluorooleandrose derivative (30) was also prepared using DAST, and both fluoro

[56] R. Faghih, F. C. Escribano, S. Catillon, J. Garcia, G. Lukacs, A. Olesker, and T. T. Thang, *J. Org. Chem.*, 1986, **51**, 4558.

[57] S. Castillon, A. Dessinges, R. Faghih, G. Lukacs, A. Olesker, and T. T. Thang, *J. Org. Chem.*, 1985, **50**, 4913.



Scheme 25

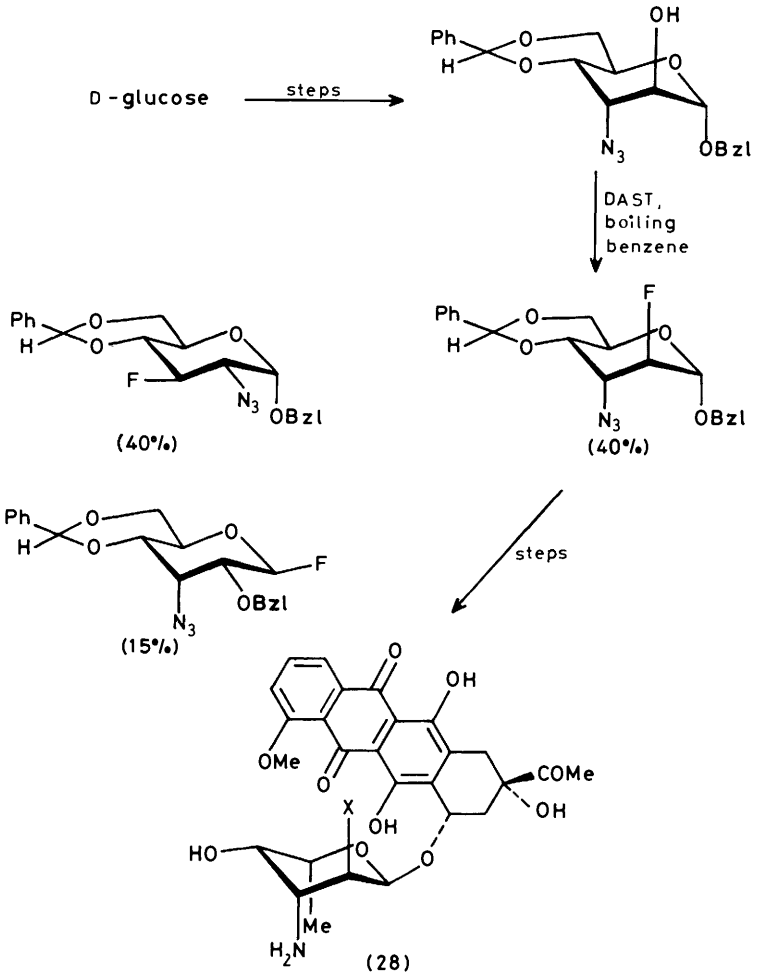
sugars were then employed for the preparation of *C*-2″-α-fluoro- and *C*-2″-β-fluoroavermectins (31a and 31b).[58]

Once again the rationale was to strengthen the glycosidic linkage of the parent compound, which is under development as an acaricide (toxic to intestinal worms) and insecticide. Both compounds had interesting biological properties, with potency similar (in some screens) to that of the parent compound.

Given the ease of access to a range of fluoro sugars, this has allowed the synthesis of a plethora of novel nucleosides. The one shown in Scheme 28[59] is notable on two counts: first that DAST can be employed for the introduction of both fluorine atoms and secondly because the final product (32) has excellent antiviral activity against both herpes simplex type 1 virus (HSV-1—the kind that causes cold sores), and against varicella zoster virus (VZV—the one responsible for chicken pox and shingles). In addition, the analogue was not cytotoxic except at high doses, in contrast to the analogue with a bromine atom in the side-chain.

Several carbocyclic nucleoside analogues containing fluorine have been reported recently by the Glaxo group (Scheme 29),[60,61] and although most of them were essentially devoid of useful activity, analogue (33, X = CH_2) was 100 × more potent than the most widely prescribed anti-viral agent acyclovir against both HSV-1 and HSV-2 (the agent responsible for genital herpes). The corresponding deoxyarabinose analogue (33, X = O) was inactive.

[58] C. Bliard, F. C. Escribano, G. Lukacs, A. Olesker, and P. Sarda, *J. Chem. Soc., Chem Commun.*, 1987, 368.
[59] H. Griengl, E. Wanek, W. Schwartz, W. Streicher, B. Rosenwirth, E. DeClercq, *J. Med. Chem.*, 1987, **30**, 1199.
[60] K. Biggadike, A. D. Borthwick, D. Evans, A. M. Exall, B. E. Kirk, S. M. Roberts, L. Stephenson, P. Youds, A. M. Z. Slawin, and D. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1987, 251.
[61] S. M. Roberts, personal communication.

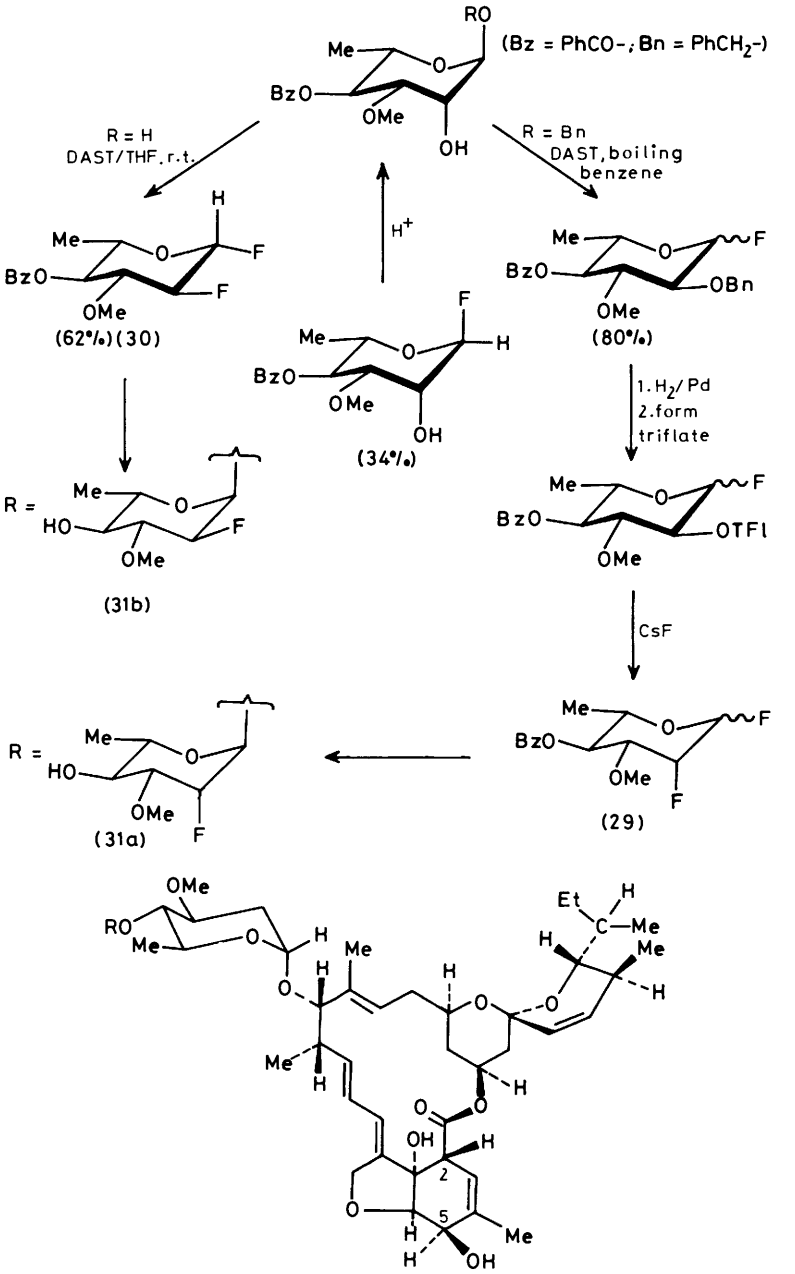


Scheme 26

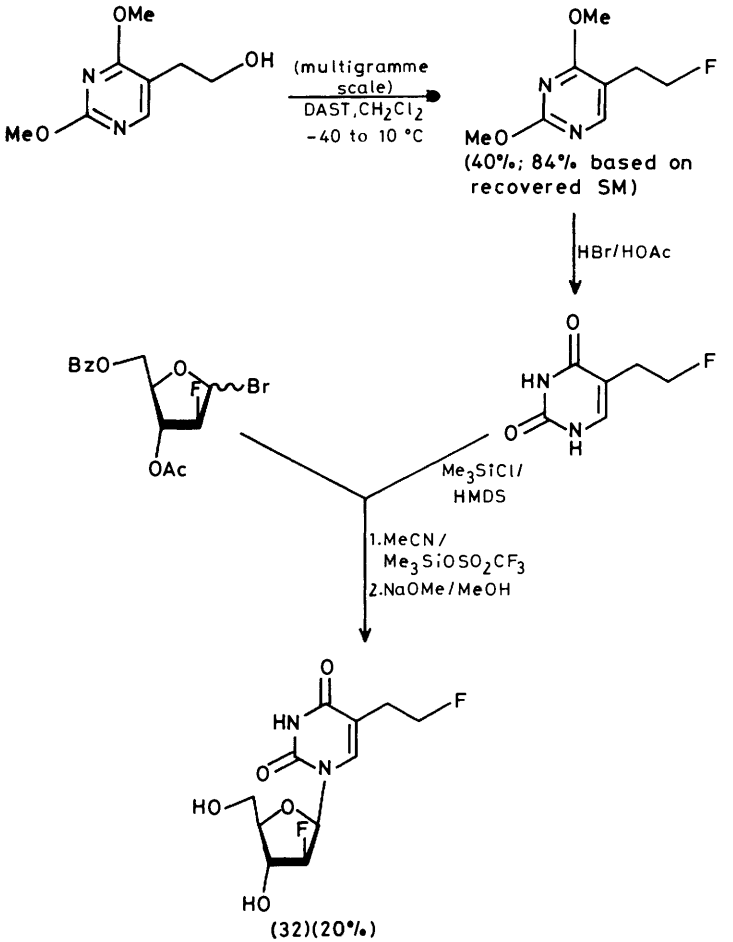
The use of DAST for the introduction of fluorine into the steroid nucleus has been comprehensively investigated by Meakins and co-workers, and their results are summarized in Scheme 30.[62] They employed DAST in dichloromethane for reactions with hydroxyls, and neat reagent at 80 °C for periods of 2—48 hours for reactions with ketones.

The selective reaction of an aldehyde in the presence of a ketone was used in the

[62] T. G. C. Bird, G. Felsky, P. M. Fredericks, Sir E. R. H. Jones, and G. D. Meakins, *J. Chem. Res.*, 1979, (*S*) 388, (*M*) 4728.


RO
(Bz = PhCO-; Bn = PhCH2-)
Me
BzO
OMe
OH
R = H
DAST/THF, r.t.
R = Bn
DAST, boiling
benzene
H+
(62%)(30)
(80%)
(34%)
1. H2/Pd
2. form
triflate
CsF
R =
HO
(31b)
(31a)
(29)
OTfl
Et
H
C
Me
OH
2
5

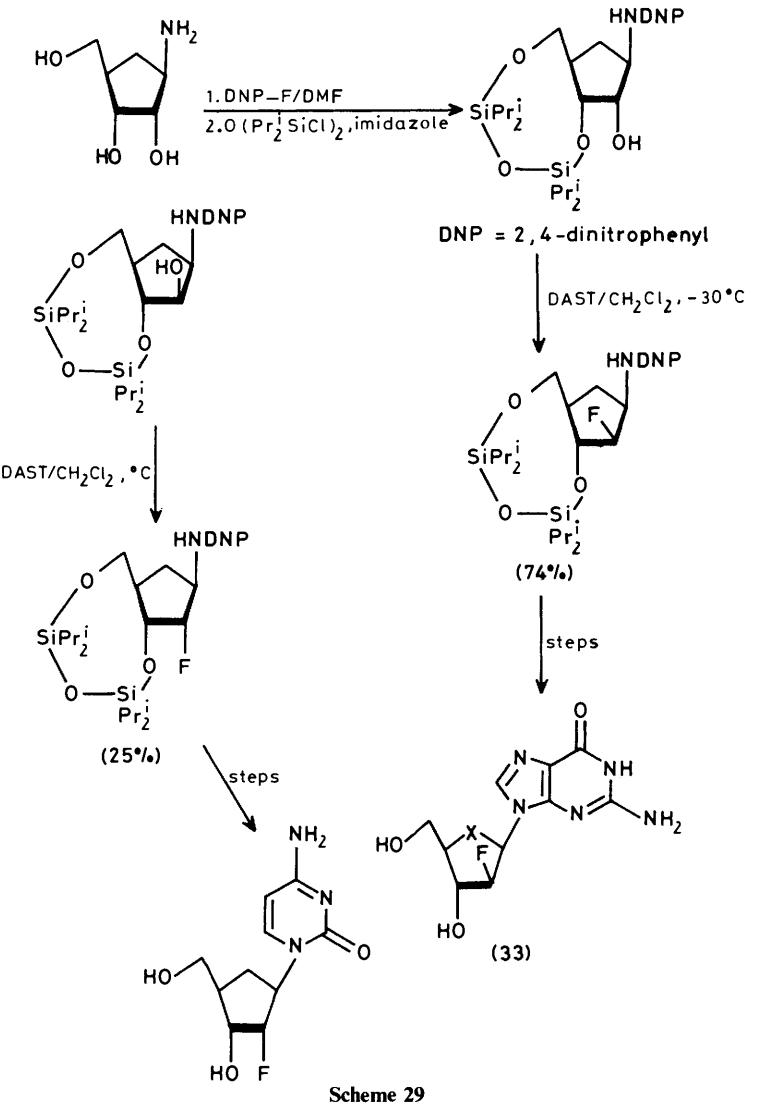
Scheme 27



Scheme 28

synthesis of 19,19-difluoroandrost-4-ene-3,17-dione (34) (Scheme 31).[63] This compound has modest activity as an inhibitor of the enzyme aromatase (the enzyme that mediates oxidative loss of the C-19 methyl of androstenedione *en route* to estrogens), and is believed to function as an acylating agent after metabolism to the acyl fluoride (35).[64] Interestingly, in the conversion shown in Scheme 31, small amounts of the rearranged steroid (36) were also obtained, and this compound lost HF on standing to yield the novel homo-estrogen (37).

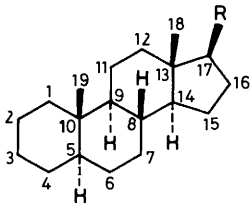
[63] J. Mann and B. Pietrzak, *J. Chem. Soc., Perkins Trans. 1*, 1987, 385.
[64] P. A. Marcotte and C. H. Robinson, *Cancer Res. (suppl.)*, 1982, **42**, 3322s.



Scheme 29

Investigation of the metabolism of vitamin D_3 and attempts to produce analogues that have modified effects on calcium and phosphorus metabolism have also employed fluoro-steroid chemistry. Two representative syntheses are shown in Schemes 32 and 33.[65,66] The 24,24-difluoro-25-hydroxy-vitamin D_3 (38) is

[65] S. Yamada, M. Ohmori, and H. Takayama, *Tetrahedron Lett.*, 1979, 1859.
[66] W. G. Dauben, B. Kohler, and A. Roesle, *J. Org. Chem.*, 1985, **50**, 2007.

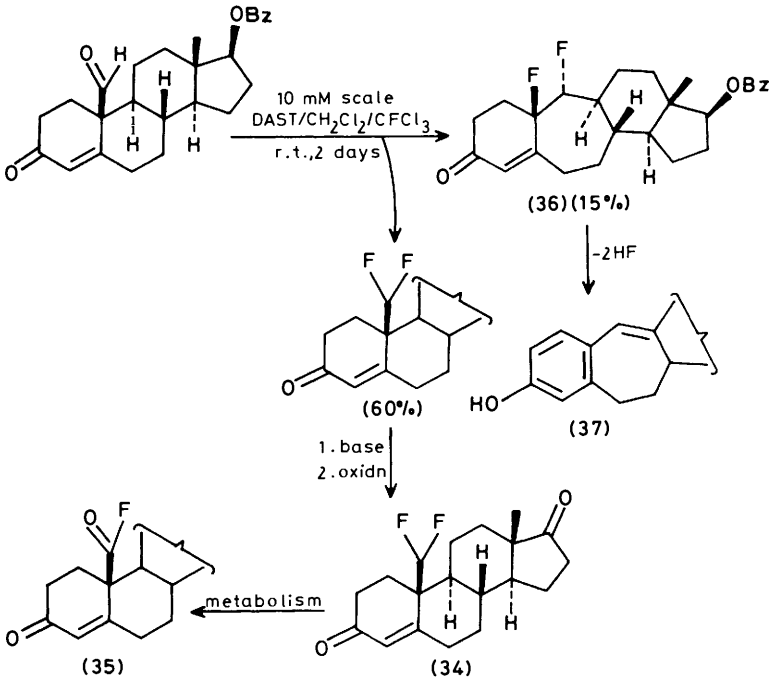


5-α-androstane R = H

5-α-pregnane R = $\overset{21}{Me}—\overset{20}{CH_2}—$

Monofluorination at carbons 3,6,7,12,16,and 17;
difluorination at carbons 3, 6,7,12,16,17,and 20

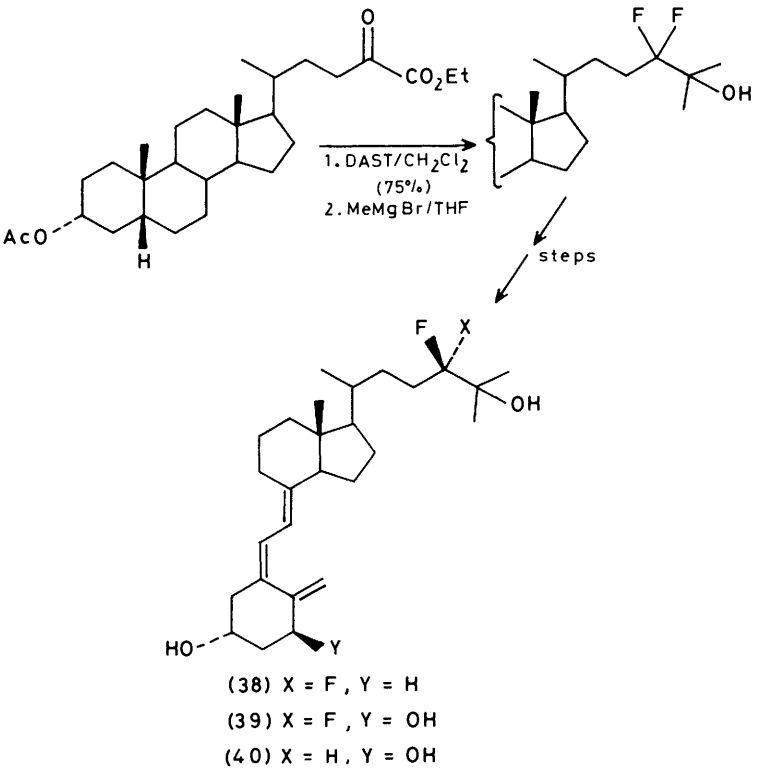
Scheme 30



Scheme 31

metabolized in kidneys to the corresponding 1-α-hydroxy metabolite (39), and this has been shown to be *ca.* 4× more potent than the natural metabolite.[67] Interestingly, the mono-(24*R*)-fluoro metabolite (40) (obtained from the (24*S*)-alcohol) possessed not only good anti-rachitogenic activity with a prolonged

[67] R. A. Corradino, H. F. DeLuca, Y. Tanaka, N. Ikekawa, and Y. Kobayashi, *Biochim. Biophys. Res. Commun.*, 1980, **96**, 1800.



(38) X = F, Y = H

(39) X = F, Y = OH

(40) X = H, Y = OH

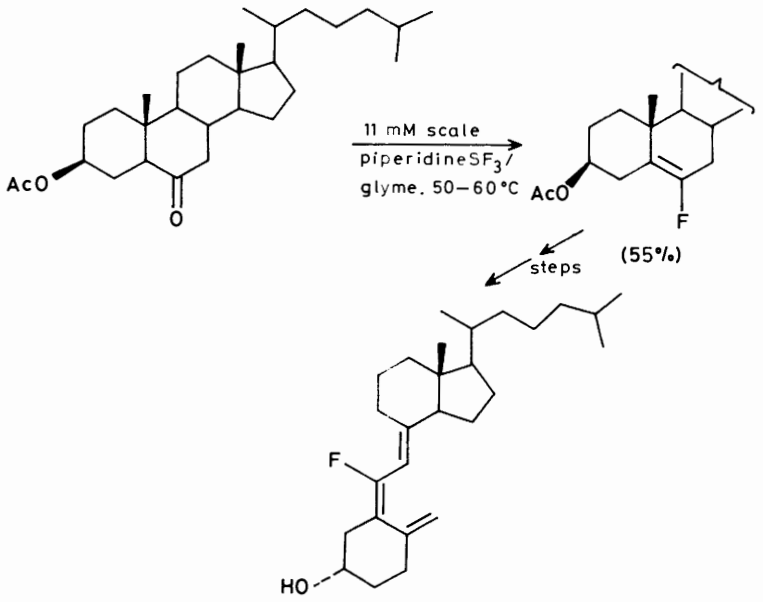
Scheme 32

biological half-life, but also inhibited the proliferation and differentiation of certain tumour cells.

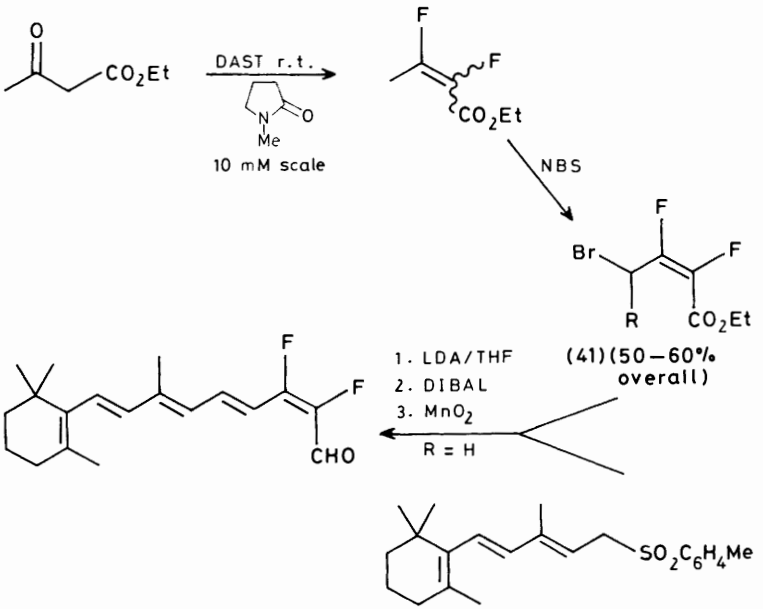
Finally, several difluororetinal analogues have been prepared for investigation of vision chemistry, and experimental use in the treatment of skin disorders including acne. Of particular interest is the recent work by Asato and Liu (Scheme 34)[68] since their methodology is applicable to the synthesis of a range of 2,3-difluoro-4-substituted butenoates (41).

Apart from the reactions with alcohols, ketones, and aldehydes, DAST also reacts with carboxylic acid chlorides and related species to yield the corresponding acyl fluorides. Representative examples are given in Scheme 35.[69] Reaction with carboxylic acids also yield acid fluorides, and an example is shown in Scheme 36.[70]

[68] A. E. Asato and R. S. H. Liu, *Tetrahedron Lett.*, 1986, **27**, 3337.
[69] L. N. Markovski and V. E. Pashinnik, *Synthesis*, 1975, 801.
[70] J. Mann and B. Pietrzak, unpublished results.



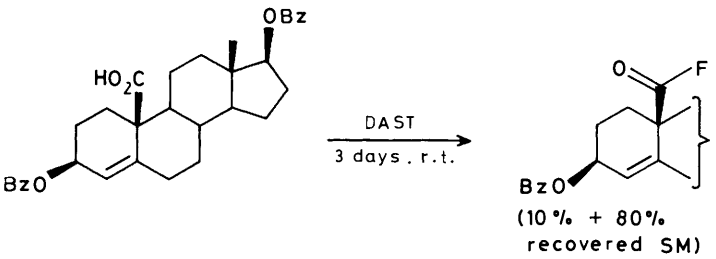
Scheme 33



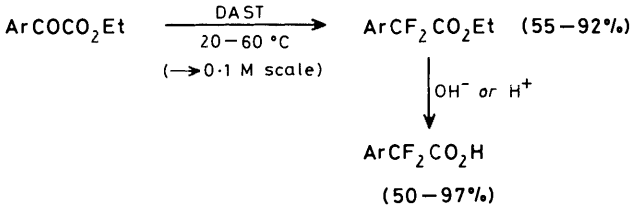
Scheme 34

$$\begin{aligned} &RCOCl \longrightarrow RCOF \quad (70-80\%) \\ &RSOCl \longrightarrow RSOF \quad (85-90\%) \\ &RSO_2Cl \longrightarrow RSO_2F \quad (70-80\%) \\ &(RO)_2POCl \longrightarrow (RO)_2POF \quad (70\%) \end{aligned}$$

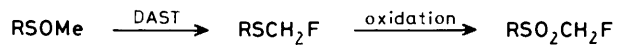
Scheme 35



Scheme 36



Scheme 37



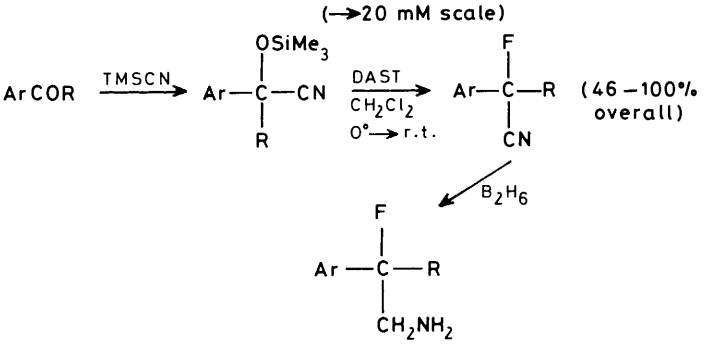
Scheme 38

As noted already, esters are completely inert, and this allows the synthesis of otherwise inaccessible α,α-difluoro-arylacetic acids Scheme 37.[71]

The seminal paper by Middleton[47] truly heralded a new erea in fluorine chemistry, and the reactions illustrated in the preceding pages are but a selection of those accomplished. In addition, the reaction of DAST with other functional groups has not been investigated in any depth, and new and useful methodology remains to be discovered and exploited. Recent discoveries are shown in Schemes 38 and 39.[72,73].

One recently described fluorosulphur reagent should be mentioned in this section, and that is tris(dimethylamino)sulphonium difluorotrimethylsilicate

[71] W. J. Middleton and E. M. Bingham, *J. Org. Chem.*, 1980, **45**, 2883.
[72] J. R. McCarthy, N. P. Peet, M. E. LeTourneau, and M. Inbasekaran, *J. Am. Chem. Soc.*, 1985, **107**, 735.
[73] M. E. LeTourneau and J. R. McCarthy, *Tetrahedron Lett.*, 1984, **25**, 5227.



Scheme 39

$(Me_2N)_3S^+ Me_3SiF_2^-$. This reagent (TASF) was first described by Middleton [74] and is a hygroscopic solid that is freely soluble in the common organic solvents. To date it has mainly been used as a source of fluoride for displacement of triflates in carbohydrates,[75] and the relatively brief reaction times involved should mean that the methodology will be of use for the introduction of ^{18}F into organic compounds.

C. 2-Chloro-1,1,2-trifluorotriethylamine.—This reagent (CTT) was really the forerunner of DAST, since it is primarily used for the fluorination of sensitive alcohols. It was first synthesized in 1959 by the route shown in Scheme 40(a),[76] and its mechanism of action is similar to that of DAST.

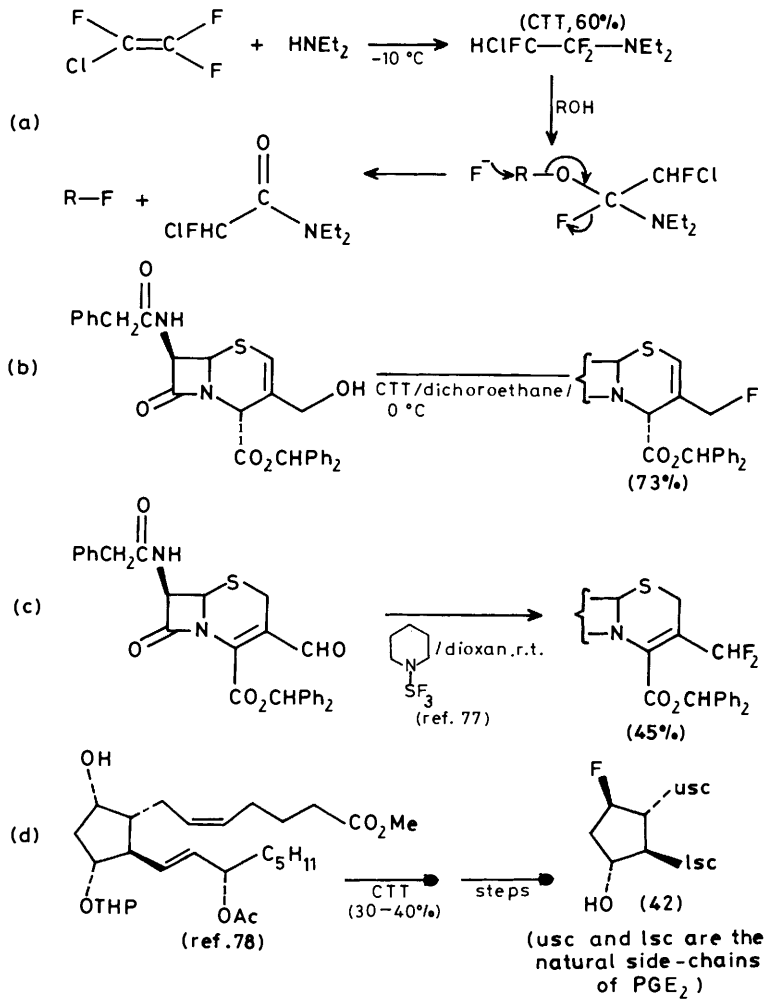
It is a very hygroscopic liquid (b.pt. 33 °C at 6 mm Hg), and can only be stored for a limited time at room temperature, but it has been used for the fluorination of a wide range of alcohols. A few representative examples are shown in Scheme 40(b—d), and it can be seen that the reagent is tolerant of a range of functionality.

The 9-β-fluoro-PGE_2 analogue (42)[78] was 3—4 × more potent than PGE_2.

Several related reagents have been synthesized, and the one due to Ishikawa[79] (43) is probably the most useful owing to its increased stability. Its synthesis and one representative reaction are shown in Scheme 41.

One final novel use of (43) is worthy of note. Acid fluorides corresponding to certain insect pheromone aldehydes were prepared, and shown to act as pheromone mimics (Scheme 42).[80] They probably react irreversibly with an amino group of the protein receptor; the effects on the insect were truly bizarre leading to 'hyperactivity and irreversible extention of the genitalia'!

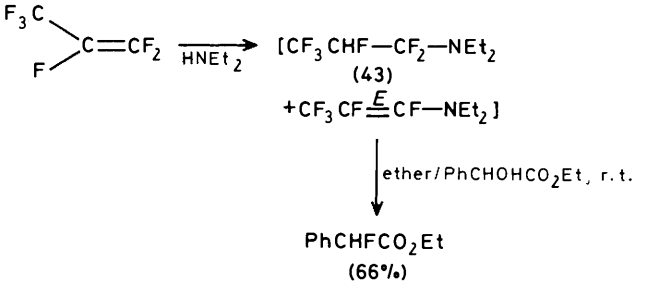
[74] W. J. Middleton, U.S. Patent, 1976, 3 940 402.
[75] B. Doboszewski, G. W. Hay, and W. A. Szarek, *Can. J. Chem.*, 1987, 65, 412.
[76] N. N. Yarovenko and M. A. Raksha, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1959, **29**, 2125.
[77] B. Müller, H. Peter, P. Schneider, and H. Bickel, *Helv. Chim. Acta*, 1975, **58**, 2469.
[78] C. E. Arroniz, J. Gallina, E. Martinez, J. M. Muchowski, E. Velarde, and W. H. Rooks, *Prostaglandins*, 1978, **16**, 47.
[79] A. Takaoka, H. Iwakiri, and N. Ishikawa, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3377.
[80] G. D. Prestwich, J. F. Carvalho, Y.-S. Ding, and D. E. Hendricks, *Experientia*, 1986, **42**, 964.



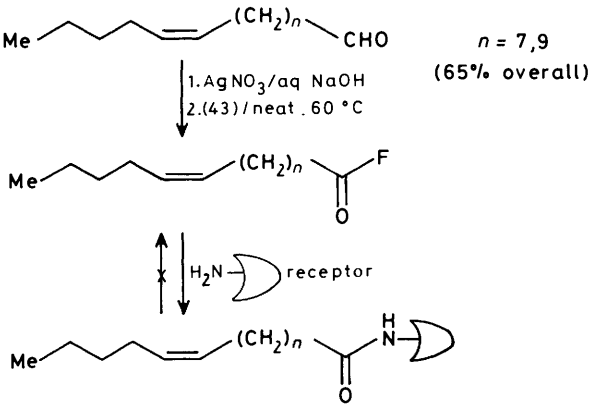
Scheme 40

D. Hydrogen Fluoride.—Anhydrous hydrogen fluoride is one of the classical fluorinating agents, but though cheap and readily available its volatility (b.pt. 19.6 °C) and corrosiveness provide obstacles to its utility. It has, however, been widely used especially with steroids where reactions with epoxides are notable for their synthetic utility and mechanistic interest. A representative example is shown in Scheme 43.[81] The key 9-α-fluorosteroids mentioned earlier were first prepared in this way.

[81] M. Neeman and J. S. O'Grodnick, *Can. J. Chem.*, 1974, **52**, 2941.



Scheme 41



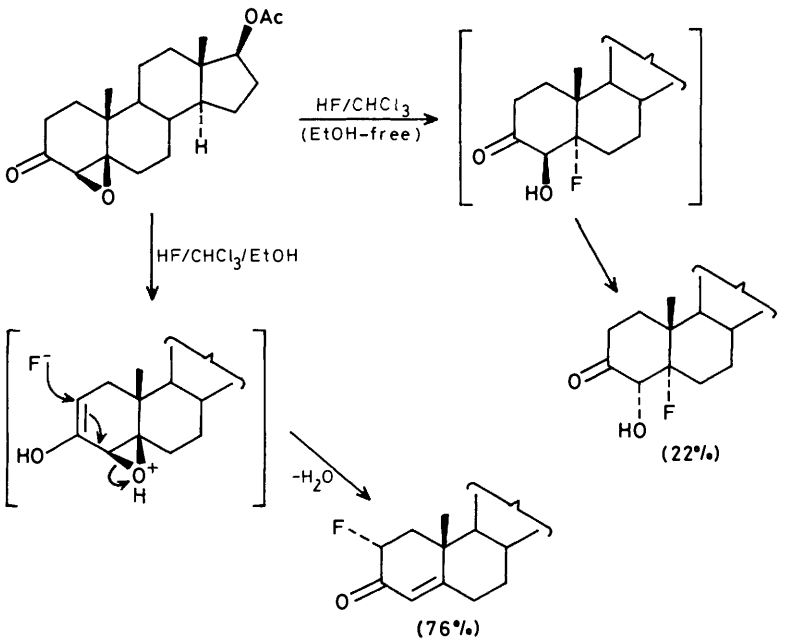
Scheme 42

The introduction of pyridinium poly(hydrogen fluoride), $(HF)_x$py, a stable liquid of approximate composition 30% pyridine and 70% HF, by Olah in 1973,[82] provided the impetus for the investigation of numerous new applications. The reagent does not lose HF below about 50 °C and is also less likely to cause polymerization since the HF has reduced acidity in the presence of pyridine. A summary of most of the chemistry is given in Scheme 44; the majority of the reactions were first reported by Olah.[83]

The formation of 9-α-fluoro-15-keto-cholestenol (44)[85] is of interest, since it demonstrates rather well the preference for reaction with a tertiary alcohol. The product exhibited marked hypocholesteremic activity in a number of animal species.

The product 6-fluoroandrostendione (45)[86] was a potent inhibitor of human placental aromatase *in vitro*, but was estrogenic *in vivo* (in rats).

[82] G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 1973, 779, and 785.
[83] G. A. Olah, J. T. Welch, Y. D. Vankar, M. Nojima, I. Kerekes, and J. A. Olah, *J. Org. Chem.*, 1979, **44**, 3872.
[84] G. A. Olah and M. Watkins, *Org. Synth.*, 1978, **58**, 75.
[85] E. J. Parish and G. J. Schroepfer, *J. Org. Chem.*, 1980, **45**, 4034.
[86] M. G. B. Drew, J. Mann, and B. Pietrzak, *J. Chem. Soc., Perkin Trans. 1.*, 1985, 1049.



Scheme 43

The reaction of the reagent with amino acids in the presence of sodium nitrite, as well as being of considerable synthetic utility, has also been shown to proceed with a high degree of stereoselectivity.[87]

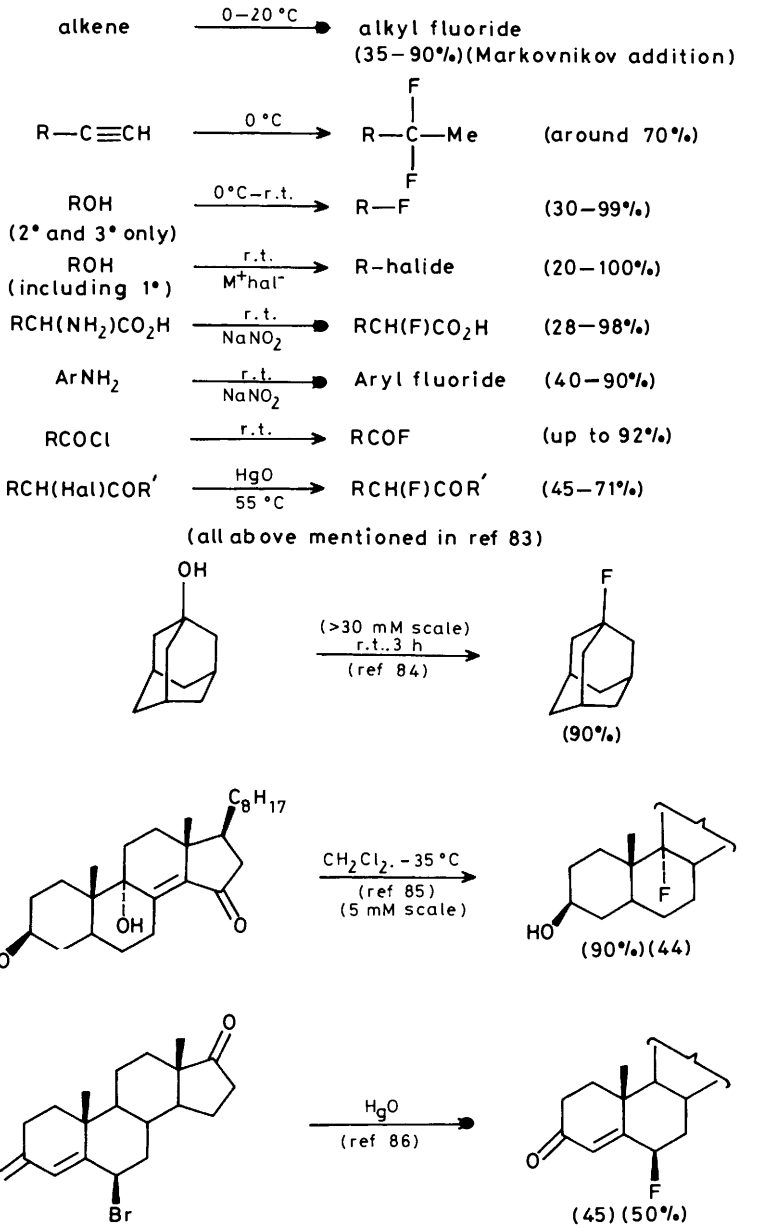
Over the past few years there has been increasing interest in the use of $(HF)_x$py for the generation of halogen fluorides. Olah originally reported[83] halogenofluorination of alkenes using *N*-halogenosuccinimides in conjunction with $(HF)_x$py, or through the use of bromine or iodine and silver nitrate with $(HF)_x$py. Yields were generally good.

Two more recent methods using orthothioesters (Scheme 45[88]) and thioketals (Scheme 46[89]) are of interest, especially the second method since this offers an alternative to the use of SF_4 for the conversion of aldehydes and ketones into *gem*-difluoro-compounds.

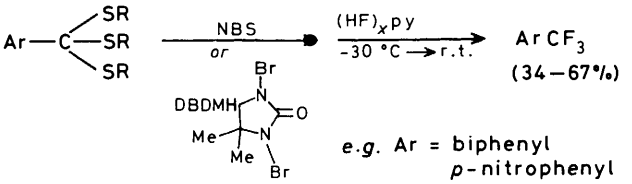
Of more biological interest is the synthesis (Scheme 47[90]) of the fluorovinyl analogue of γ-aminobutyric acid (GABA) (46) (one of the major mammalian neurotransmitters).

The parent vinyl-analogue is a selective enzyme-activated inhibitor of GABA

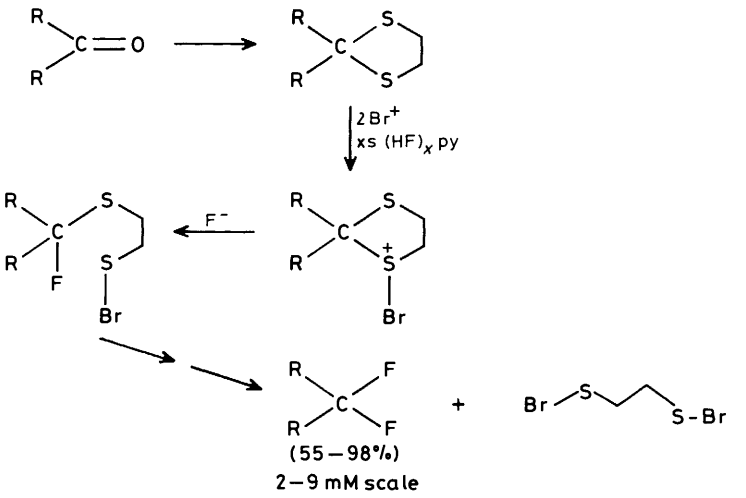
[87] F. Faustini, S. De Munari, A. Panzeri, V. Villa, and C. A. Gandolfi, *Tetrahedron Lett.*, 1981, **22**, 4533.
[88] D. P. Matthews, J. P. Whitten, and J. R. McCarthy, *Tetrahedron Lett.*, 1986, **27**, 4861.
[89] S. C. Sondej and J. A. Katzenellenbogen, *J. Org. Chem.*, 1986, **51**, 3508.
[90] M. Kolb, J. Barth, J.-G. Heydt, and M. J. Jung, *J. Med. Chem.*, 1987, **30**, 267.


alkene
0–20 °C
alkyl fluoride
(35–90%)(Markovnikov addition)
R—C≡CH
0 °C
R—C(F)(F)—Me
(around 70%)
ROH
(2° and 3° only)
0 °C–r.t.
R—F
(30–99%)
ROH
(including 1°)
r.t.
M+hal−
R-halide
(20–100%)
RCH(NH2)CO2H
r.t.
NaNO2
RCH(F)CO2H
(28–98%)
ArNH2
r.t.
NaNO2
Aryl fluoride
(40–90%)
RCOCl
r.t.
RCOF
(up to 92%)
RCH(Hal)COR′
HgO
55 °C
RCH(F)COR′
(45–71%)
(all above mentioned in ref 83)
OH
(>30 mM scale)
r.t., 3 h
(ref 84)
F
(90%)
C8H17
OH
HO
O
CH2Cl2, −35 °C
(ref 85)
(5 mM scale)
F
HO
(90%)(44)
O
O
Br
HgO
(ref 86)
O
F
(45) (50%)

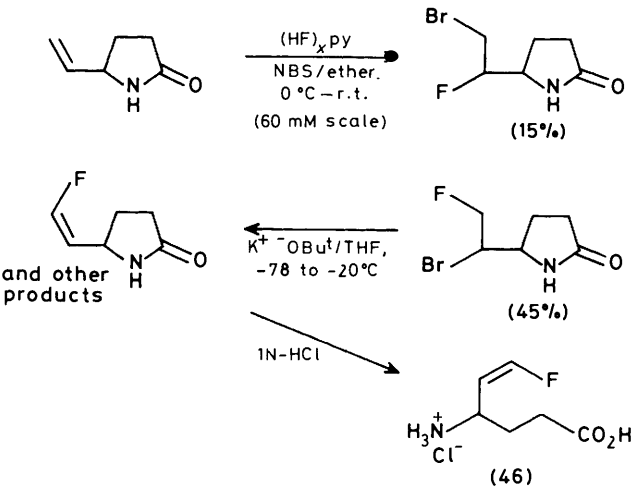
Scheme 44



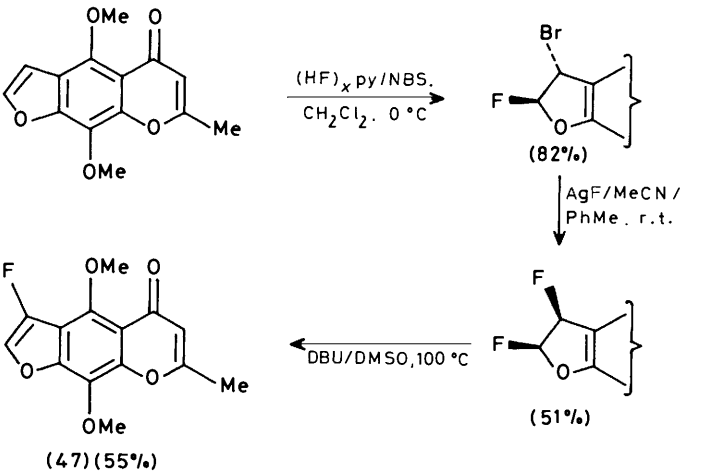
Scheme 45



Scheme 46



Scheme 47



Scheme 48

transaminase (another pyridoxal phosphate containing enzyme), and it was hoped that introduction of fluorine would increase the electrophilicity of the inhibitor. In the event the fluoro analogue was equipotent with the parent analogue, and the two compounds have potential as anti-epileptic drugs.

The synthesis of 3-fluorokhellin (47) (Scheme 48[91]) is also of interest given khellin's long association with folk medicine and the recent demonstration that it may have antiatherosclerotic activity.

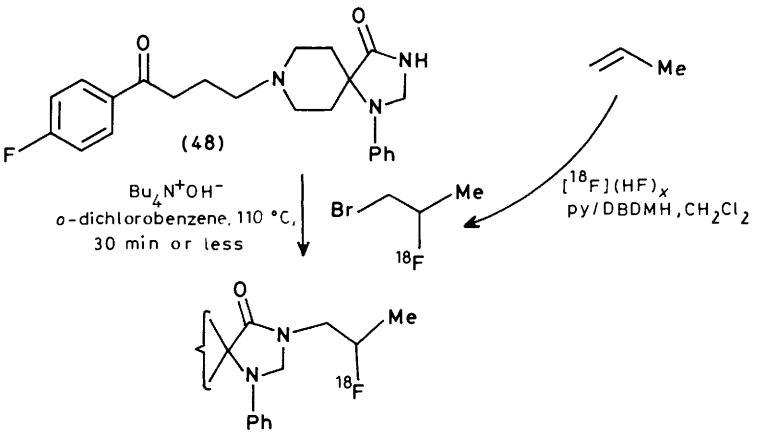
The same kind of methodology can be employed for the rapid construction of ^{18}F-labelled compounds (for PET), and a representative example is shown in Scheme 49.[92]

The substrate spiperone (48) is known to bind to dopamine receptors in the brain, and it is hoped that ^{18}F-labelled analogues will serve as imaging agents for areas of the brain rich in dopamine receptors.

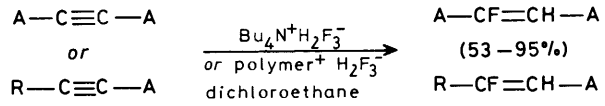
Finally, various modified forms of $(HF)_x$py are available, and one that uses triethylamine in place of pyridine has been shown to be useful for the synthesis of *trans*-halogenofluorides[93] and is claimed to be less corrosive than $(HF)_x$py. In addition, polymer-supported dihydrogen trifluoride and tetrabutylammonium dihydrogen trifluoride are effective hydrofluorinating agents (Scheme 50[94]).

Olah's reagent does not add HF to acetylene dicarboxylate, whilst these new reagents do not add to unactivated acetylenes. The explanation seems to lie in the extra nucleophilicity of the $H_2F_3^-$ ion. The reagents are made by addition of HF–KF or HF–KHF_2 to $Bu_4N^+F^-$ or to resin$^+$ F^-.

[91] S. A. Nash and R. B. Gammill, *Tetrahedron Lett.*, 1987, **28**, 4003.
[92] D. Y. Chi, M. R. Kilbourn, J. A. Katzenellenbogen, and M. J. Welch, *J. Org. Chem.*, 1987, **52**, 658.
[93] G. Alvernhe, A. Laurent, and G. Haufe, *Synthesis*, 1987, 562.
[94] P. Albert and J. Cousseau, *J. Chem. Soc., Chem. Commun.*, 1985, 961.



Scheme 49

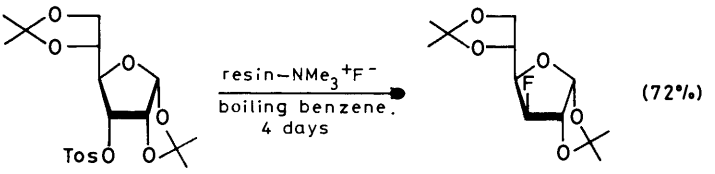


Scheme 50

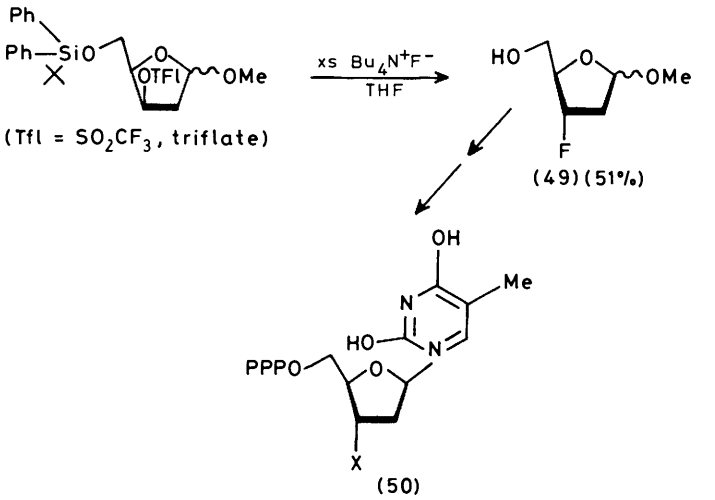
E. Fluoride.—Nucleophilic displacement of an halide by fluoride is amongst the cheapest and most widely employed methods for the introduction of fluorine. Swarts used silver fluoride in his synthesis of methyl fluoroacetate [1] but it is now more common to use KF, CsF, KF–HF, and tetralkylammonium fluorides. Displacement of tosylates, mesylates, and triflates is also routine. Anhydrous, polar, solvents (MeCN, DMF, glycols) are usually required for attaining an adequate concentration of dissolved fluoride, though the tetralkylammonium fluorides can be used in THF and other less polar solvents. Water reduces the nucleophilicity of fluoride, hence the need for anhydrous solvents. Recent innovations include the use of crown ethers, when KF may be used to good effect in benzene–acetonitrile mixtures (*e.g.* ref. 95); polymer-supported fluoride is also claimed to give clean S_N2 reactions with halides and sulphonates (Scheme 51 [96,97]). KF–CaF_2 mixtures are also beneficial for displacement of halides.[98,99]

A number of recent examples of biological interest or which have potential medical applications are outlined below. There are numerous syntheses of

[95] Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 1982, 85.
[96] S. Collona, A. Re, G. Gelbard, and E. Cesarotti, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2248.
[97] G. Cainelli and F. Manescalchi, *Synthesis*, 1976, 472.
[98] J. H. Clark, A. J. Hyde, and D. K. Smith, *J. Chem. Soc., Chem. Commun.*, 1986, 791.
[99] J. Ichihara, T. Matsuo, T. Hanafusa, and T. Ando, *J. Chem. Soc., Chem. Commun.*, 1986, 793.



Scheme 51



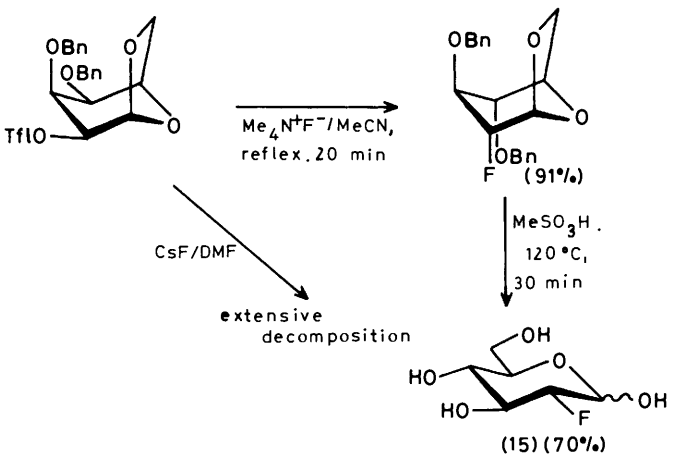
Scheme 52

deoxyfluoro sugars that have been made by this general methodology, though there is a tendency for elimination reactions to occur when KF and CsF are employed, and the best way to avoid this seems to be the use of tetralkylammonium fluorides in conjunction with triflates. The syntheses of the 3-fluoro-2,3-dideoxy-D-*erythro*-pento furanoside (49) (Scheme 52 [100]) and of 2-deoxy-2-fluoro-D-glucose (15) (Scheme 53 [101]) are exemplary.

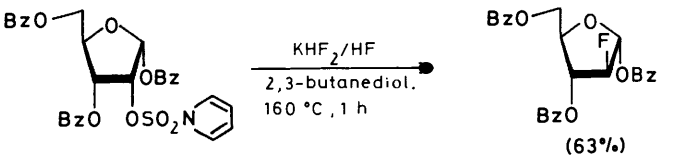
Compound (50, X = F) derived from (49) is of interest because it claimed to be a better inhibitor of the reverse transcriptase of the HIV (AIDS) virus than the triphosphate of AZT (50, X = N_3).[102]

If a particularly good leaving group is employed, the cheaper KF–HF may even be used, and the conversion shown in Scheme 54 has been carried out on the one mole scale![103]

[100] G. W. J. Fleet and J. C. Son, *Tetrahedron Lett.*, 1987, **28**, 3615.
[101] T. Haradahira, M. Maeda, Y. Kai, and M. Kojima, *J. Chem. Soc., Chem. Commun.*, 1985, 364.
[102] Y.-C. Cheng, G. E. Dutschman, K. F. Bastow, M. G. Sarngadhara, and R. Y. C. Ting, *J. Biol. Chem.*, 1987, **262**, 2187.
[103] C. H. Tann, P. R. Brodfuehrer, S. P. Brundidge, C. Sapino, and H. G. Howell, *J. Org. Chem.*, 1985, **50**, 3644.



Scheme 53



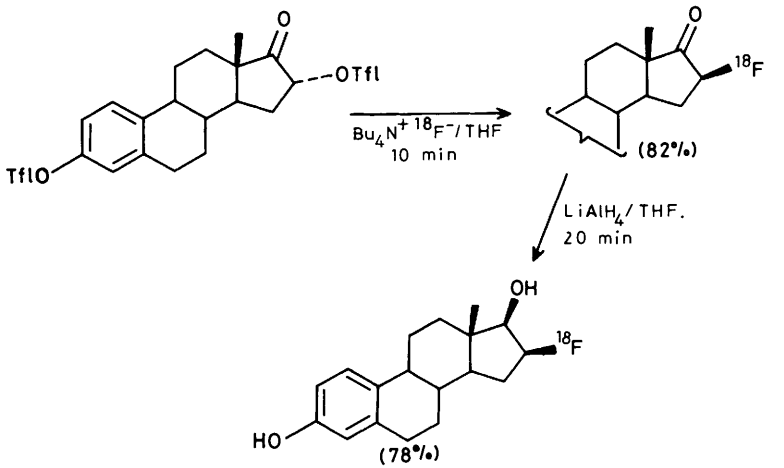
Scheme 54

These reactions are generally rapid, and once again the possibility of using them for the introduction of ^{18}F has been explored. For example, fluoro-estrogens have been prepared for use as imaging agents in breast tumours (Scheme 55).[104] The presence of estrogen receptors is a good indication of whether the tumour is estrogen-dependent or not, and this information is vital since it will influence the choice of chemotherapy.

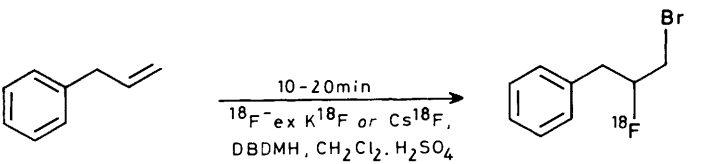
Two other methods are illustrated in Schemes 56 and 57.[105,106]

Finally in this section on fluoride displacements, the chemoselective fluorination shown in Scheme 58[107] and the neat four-step synthesis of 2′-deoxy-5-fluoromethyl-uridine (51, X = CH_2F) and the corresponding difluoromethyl derivative (51, X = CHF_2) (Scheme 59[108]) are of particular note.

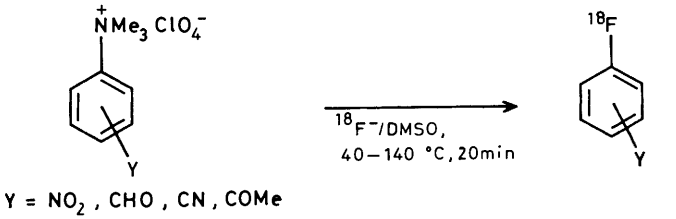
[104] D. O. Kiesewetter, J. A. Katzenellenbogen, M. R. Kilbourn, and M. J. Welch, *J. Org. Chem.*, 1984, **49**, 4900.
[105] D. Y. Chi, J. A. Katzenellenbogen, M. R. Kilbourn, and M. J. Welch, *J. Nucl. Med.*, 1985, **26**, P37.
[106] G. Angelini, M. Speranza, A. P. Wolf, and C.-Y. Shiue, *J. Fluorine Chem.*, 1985, **27**, 177.
[107] M. Shimizu, Y. Nakahara, and H. Yoshioka, *Tetrahedron Lett.*, 1985, **26**, 4207.
[108] J. Matulic-Adamic and K. A. Watanabe, *J. Chem. Soc., Chem. Commun.*, 1985, 1535.



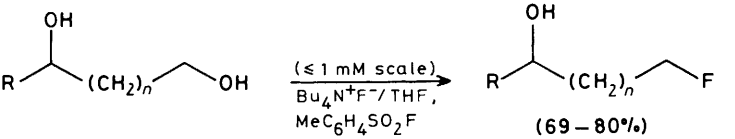
Scheme 55



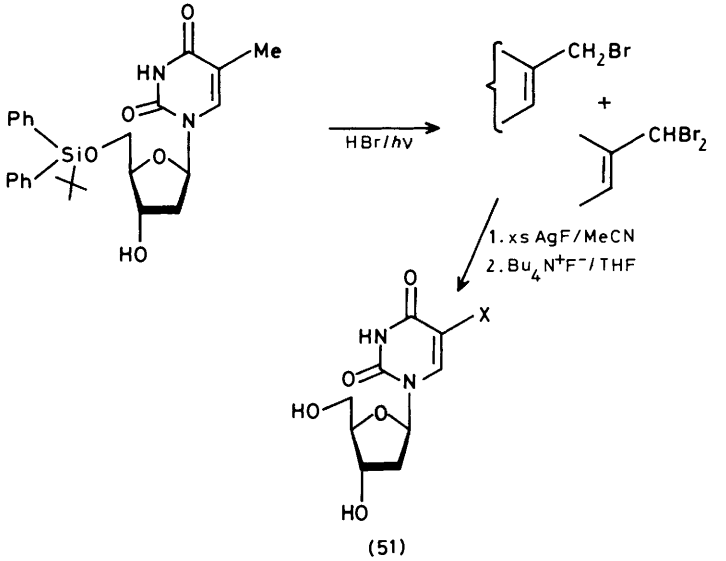
Scheme 56



Scheme 57



Scheme 58



(51)

Scheme 59

Returning to silver fluoride, this is often employed where displacements are to be carried out on delicate systems, and the synthesis of 7-fluoro-PGI_2 (52) shown in Scheme 60[109] provides a good recent example of the methodology.

The prostacyclin analogue (as the sodium salt) was not only biologically active (50% inhibition of ADP-induced rabbit platelet aggregation at a dose of 0.05 μg ml^{-1}), but had a biological half-life of more than one month when stored in pH 7.4 buffer. Prostacyclin has a half-life of minutes when stored under the same conditions.

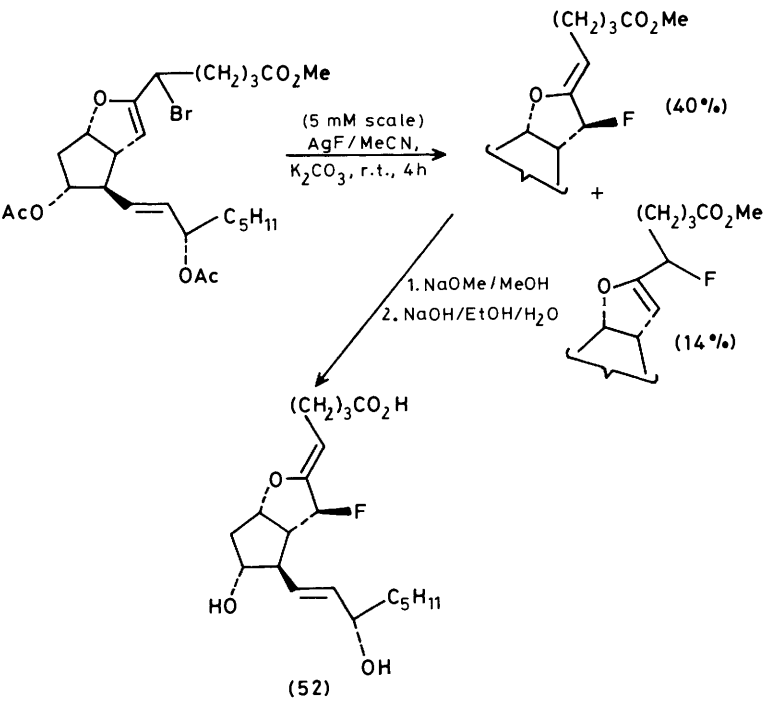
The fluoro-GABA analogue (53) was also prepared using a silver fluoride displacement (Scheme 61[110]) and caused irreversible inhibition of the enzyme GABA aminotransferase from pig brain.

In addition to displacement of halides and sulphonates, fluoride reagents will also react with epoxides to produce fluorohydrins, as for example in the synthesis of the 2-deoxy-2-fluoro-arabinose analogue (54) shown in Scheme 62.[61] This compound was required for an alternative route to the new Glaxo anti-viral agent (33) (see Scheme 29).

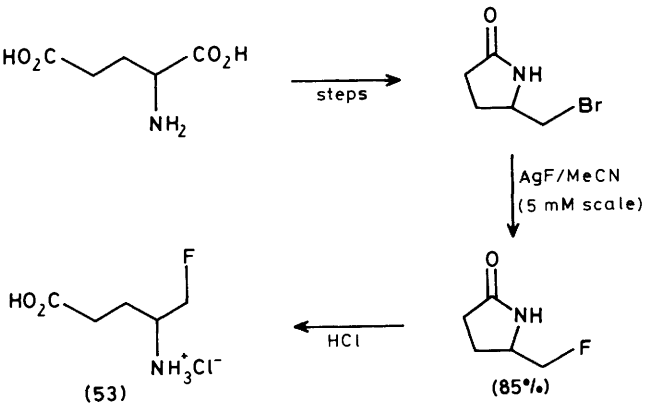
A number of other reagents have been introduced during the past 25 years, but all have somewhat limited utility. The most versatile of these are tetrafluoroboric acid (and silver tetrafluoroborate), perchloryl fluoride, hypofluorites, caesium fluoroxysulphate, and xenon difluoride.

[109] K. Bannai, T. Toru, T. Oba, T. Tanaka, N. Okamura, K. Watanabe, A. Hazato, and S. Kurozumi, *Tetrahedron*, 1986, **42**, 6735.

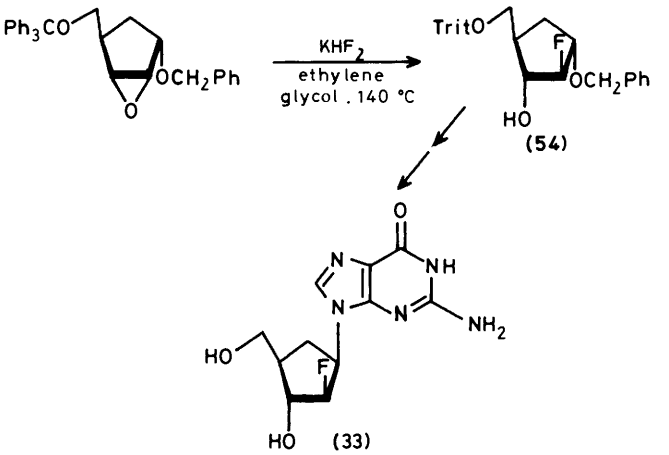
[110] R. B. Silverman and M. A. Levy, *Biochim. Biophys. Res. Commun.*, 1980, **95**, 250; *J. Org. Chem.*, 1980, **45**, 815.



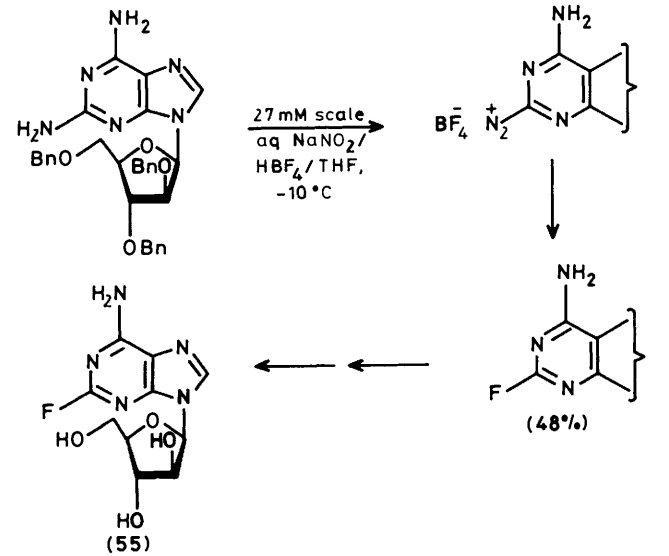
Scheme 60



Scheme 61



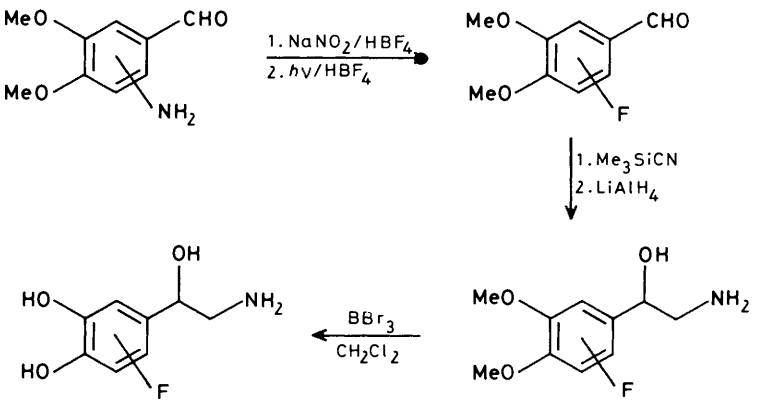
Scheme 62



Scheme 63

F. Tetrafluoroboric Acid and Silver Tetrafluoroborate.—The classical reaction between tetrafluoroboric acid and aryl diazonium salts is illustrated by the synthesis of 9-β-D-arabinofuranosyl-2′-fluoro-2′-deoxyadenine (55) (Scheme 63[111])—an experimental anti-cancer agent.

[111] J. A. Montgomery, S. D. Clayton, and A. T. Shortnacy, *J. Heterocycl. Chem.*, 1979, **16**, 157.



Scheme 64

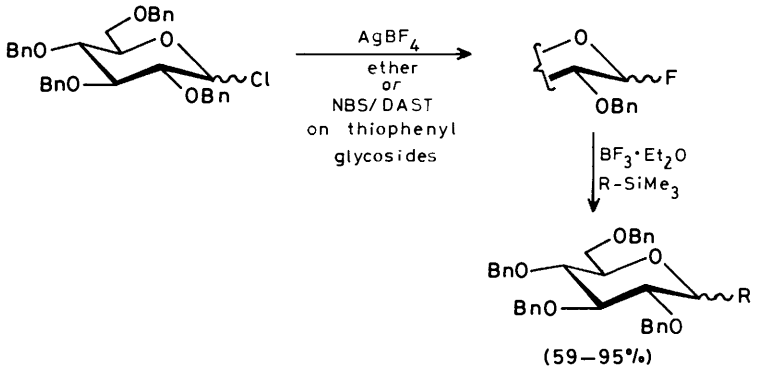
For labile diazonium species, a photochemical variant has also been employed with some success[112] and this method has been used to prepare key fluoro-aryl aldehydes for elaboration into fluoro analogues of norepinephrine (noradrenaline) (Scheme 64[113]).

Two main types of adrenergic receptors, *i.e.* α and β (and subclasses), are distributed throughout the body, and different biological affects are produced following their interactions with noradrenaline and adrenaline (the *N*-methyl-derivative). The search for specific inhibitors or stimulators of these responses is a continuing theme of medicinal chemistry research, hence it was of interest that the 2-fluoro-noradrenaline analogue was an almost pure β-adrenergic agonist, the 6-fluoro analogue an α-adrenergic agonist, and the 5-fluoro analogue possessed both activities.

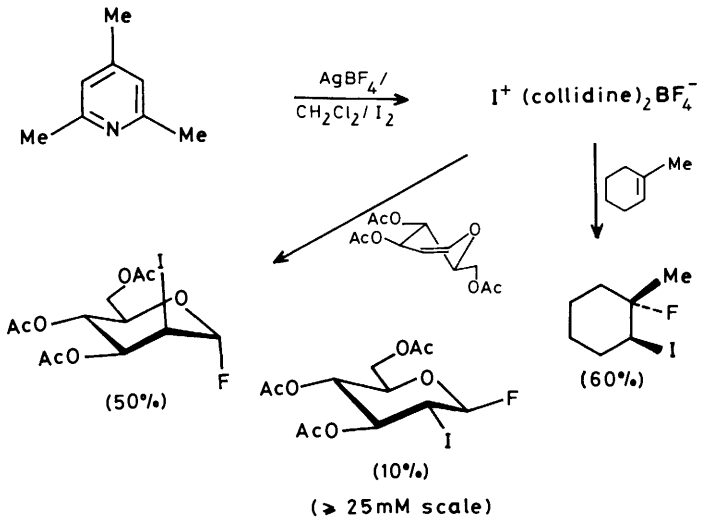
Silver tetrafluoroborate has been used to prepare α-fluorocarbonyl compounds from the corresponding α-bromocarbonyls.[114] It has also been used to synthesize glycosyl fluorides from the corresponding chlorides, and these species are of utility for the construction of *C*-glycosides as illustrated in Scheme 65.[115] *N*-, *O*-, and *S*-glycosides can also be prepared using this methodology.[116]

Finally, a very recent method of iodofluorination using bis(*sym*-collidine)-iodine(I) tetrafluoroborate appears to be preparatively useful Scheme 66.[117]

[112] J. C. Reepmeyer, K. L. Kirk, and L. A. Cohen, *Tetrahedron Lett.*, 1975, 4107.
[113] K. L. Kirk, D. Cantacuzene, Y. Nimitkitpaisan, D. McCulloh, W. L. Padgett, J. W. Daly, and C. R. Creveling, *J. Med. Chem.*, 1979, **22**, 1493.
[114] A. J. Fry and Y. Migron, *Tetrahedron Lett.*, 1979, 3357.
[115] K. C. Nicolaou, A. Chucholowski, R. E. Dolle, and J. E. Randall, *J. Chem. Soc., Chem. Commun.*, 1984, 1153.
[116] Ref. 115, p. 1155.
[117] R. D. Evans and J. H. Schauble, *Synthesis*, 1987, 551.



Scheme 65



Scheme 66

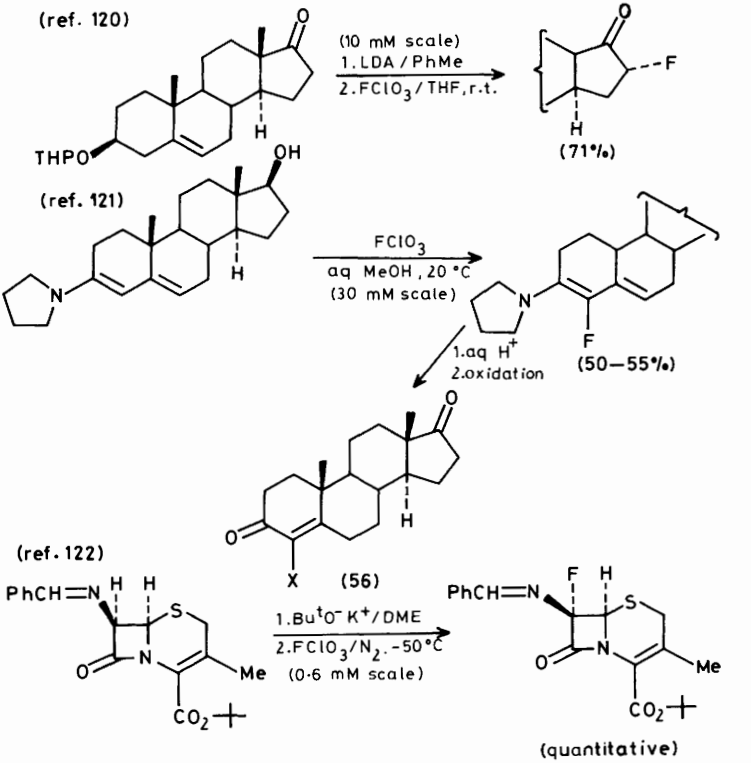
G. Perchlorylfluoride.—This reagent (b.pt. −47 °C) is commercially available and relatively inexpensive (£3 per gramme) but has been somewhat underused, partly because of its non-selectivity as a fluorinating agent but also because a number of serious explosions have occurred whilst using it (see *e.g.* ref. 118). These explosions have been attributed to the formation of chlorates which then react with organic solvents. The accidents have usually occurred when large amounts of the reagent have been condensed into a reaction mixture: if, however, the gas is bubbled slowly (often with nitrogen) through the reaction mixture, the hazard is greatly reduced.

[118] M. B. Glinski, J. C. Freed, and T. Durst, *J. Org. Chem.*, 1987, **52**, 2749.

These reservations aside, the reagent has been used widely as an electrophilic fluorinating agent, especially with steroids, and this work has been reviewed by Djerassi.[119] Some representative examples of its use are assembled in Scheme 67.

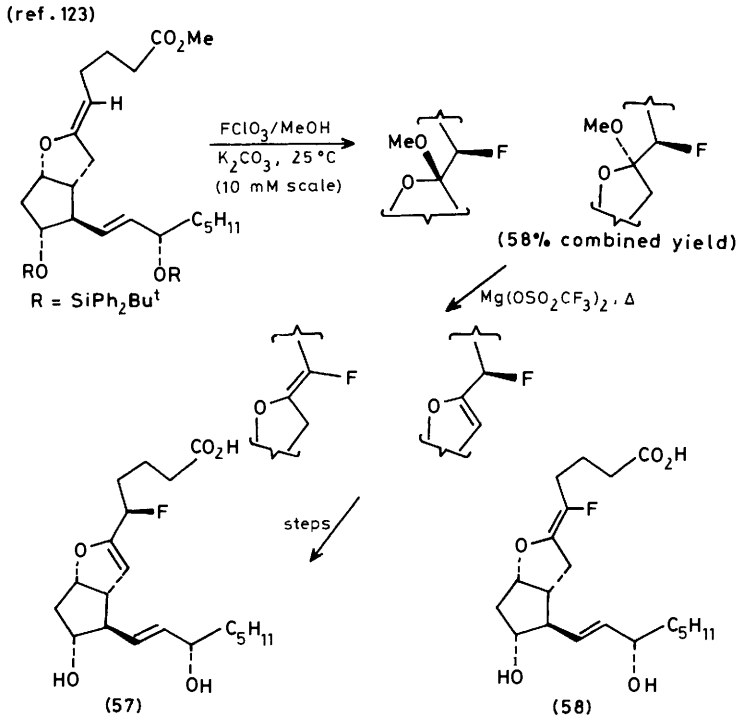
4-Fluoro-androstendione (56, X = F) was prepared as a potential aromatase inhibitor—the corresponding 4-hydroxy species (56, X = OH) is a clinically effective agent for the treatment of hormone-dependent breast cancer. In the event the agent was very potent both *in vitro* and *in vivo* (rats), but offers no advantages over the 4-hydroxy compound.[121]

The two 5-fluoroprostacyclin analogues (57) and (58) were approximately equipotent with PGI_2 in platelet aggregation assays, but were more stable under physiological conditions.[123]



Scheme 67

[119] C. Djerassi, 'Steroid Reactions', Holden Day, San Francisco, 1963.
[120] M. Schlosser and G. Heinz, *Chem. Ber.*, 1969, **102**, 1944.
[121] M. G. Rowlands, A. B. Foster, J. Mann, B. Pietrzak, J. Wilkinson, and R. C. Coombes, *Steroids*, in press.
[122] W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.*, 1973, **38**, 943.
[123] S. W. Djuric, R. B. Garland, L. N. Nysted, R. Pappo, G. Plume, and L. Swenton, *J. Org. Chem.*, 1987, **52**, 978.

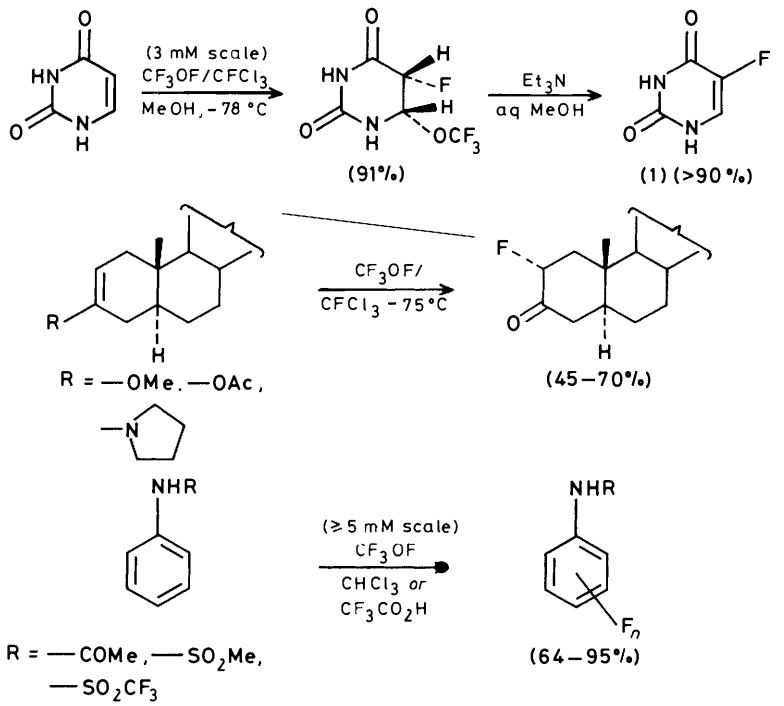


Scheme 67 cont.

H. Trifluoromethyl Hypofluorite and Acetyl Hypofluorite.—In 1968 Barton, Hesse, and co-workers first described the use of trifluoromethyl hypofluorite (fluoroxytrifluoromethane) for the introduction of fluorine into organic molecules;[124] comprehensive reviews of this early work have been published.[125,126] The reagent was prepared from carbon monoxide and excess fluorine using a silver fluoride catalyst, but it is now more common to use a caesium fluoride catalyst.

The reagent is a toxic gas (b.pt. −97 °C), is commercially available (*ca.* £10 per gramme), and behaves as a potent electrophile (more so than $FClO_3$). Most of its reactions can be divided into two categories: electrophilic addition to carbon–carbon double bonds, and electrophilic substitution of tertiary hydrogens. The syntheses of 5-fluorouracil (1),[127] 2-α-fluorosteroids,[124] and fluoroaromatic compounds[128] shown in Scheme 68 are representative of the first category. The reactions probably proceed *via* an addition–elimination mechanism.

[124] D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *J. Chem. Soc., Chem. Commun.*, 1968, 804.
[125] D. H. R. Barton, *Pure Appl. Chem.*, 1977, **49**, 1241.
[126] R. Hesse, *Isr. J. Chem.*, 1978, **17**, 60.
[127] M. J. Robins, M. MacCoss, S. R. Naik, and G. Ramani, *J. Am. Chem. Soc.*, 1976, **98**, 7381.
[128] M. J. Fifolt, R. T. Olczak, and R. F. Mundhenke, *J. Org. Chem.*, 1985, **50**, 4576.



Scheme 68

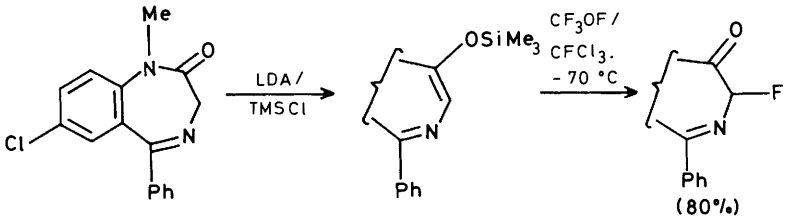
A more recent example of this methodology is given in Scheme 69[129] and demonstrates how enol silyl ethers of aldehydes, ketones, esters, acids, and amides can be converted into α-fluorocarbonyl compounds. The product of the reaction shown is the 3-fluoro analogue of diazepam (Valium).

The other main class of reactions is exemplified by the syntheses shown in Scheme 70.[130]

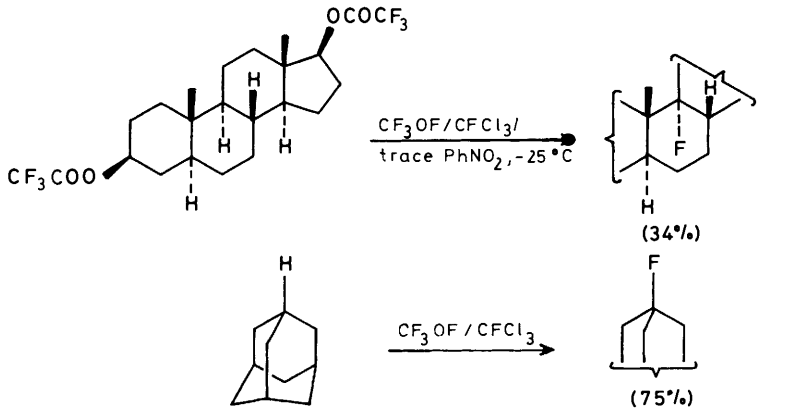
Although many of these reactions are clean, the relative expense of CF_3OF has precluded its large-scale use, and the introduction of acetyl hypofluorite by Rozen[131] in 1981 has provided an inexpensive means of synthesizing a wide range of fluoro-organic compounds. Much of Rozen's work has been reviewed,[15,132,133] but the salient features are worth including here.

Acetyl hypofluorite is prepared by passing a stream of fluorine diluted with nitrogen (to a final concentration of 5—10% fluorine) through a mixture of sodium

[129] W. J. Middleton and E. M. Bingham, *J. Am. Chem. Soc.*, 1980, **102**, 4845.
[130] D. H. R. Barton, R. H. Hesse, R. E. Markwell, M. M. Pechet, and S. Rozen, *J. Am. Chem. Soc.*, 1976, **98**, 3036.
[131] S. Rozen, O. Lerman, and M. Kol, *J. Chem. Soc., Chem. Commun.*, 1981, 443.
[132] O. Lerman, Y. Tor, and S. Rozen, *J. Org. Chem.*, 1981, **46**, 4629.
[133] S. Rozen, O. Lerman, M. Kol, and D. Hebel, *J. Org. Chem.*, 1985, **50**, 4753.



Scheme 69

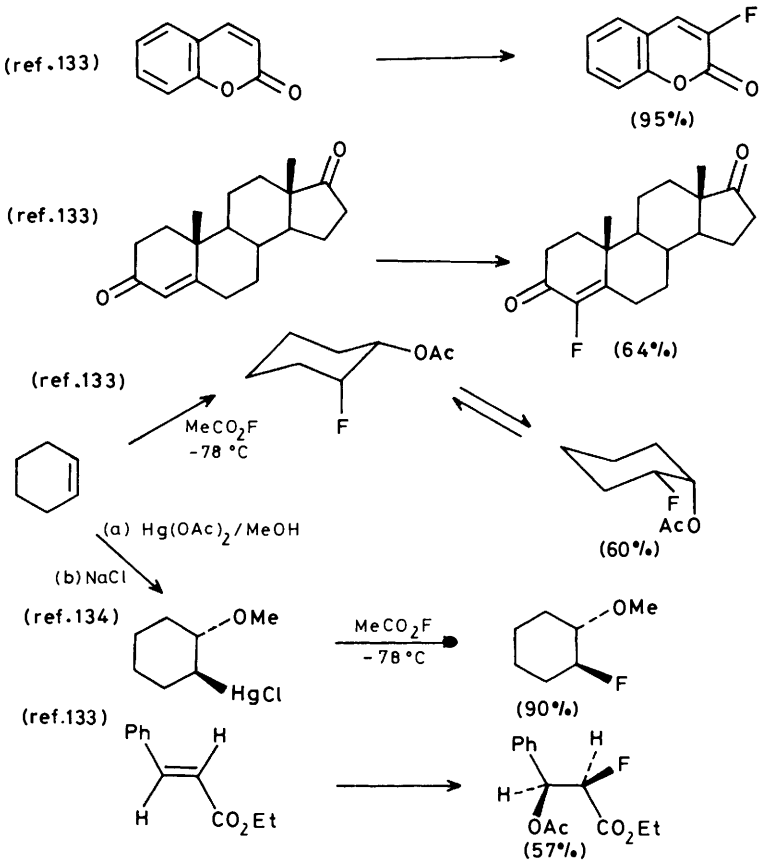


Scheme 70

acetate, glacial acetic acid, and trichlorofluoromethane at −78 °C. The synthesis has been carried out on the 30—50 mmole scale, with reported yields of 50—80%. The reagent reacts smoothly and predictably with alkenes at −78 °C to generate acetylated fluorohydrins, which frequently lose acetic acid. Representative examples are shown in Scheme 71 and a good tabular survey is also given in ref. 15. The two complementary reactions shown for cyclohexene are particularly noteworthy.

The reagent also reacts with a wide range of aromatic compounds, and best results are obtained with electron-rich aryl species. This methodology has obvious potential for the introduction of ^{18}F, and a few recent examples are given in Scheme 72. The last method is of particular promise.

[134] D. Hebel and S. Rozen, *J. Org. Chem.*, 1987, **52**, 2588.
[135] O. Lerman, Y. Tor, D. Hebel, and S. Rozen, *J. Org. Chem.*, 1984, **49**, 806.
[136] M. J. Adam, T. J. Ruth, S. Jivan, and B. D. Pate, *J. Fluorine Chem.*, 1984, **25**, 329.
[137] D. M. Jewett, J. F. Potocki, and R. E. Ehrenkaufer, *J. Fluorine Chem.*, 1984, **24**, 477.
[138] O. Lerman and S. Rozen, *J. Org. Chem.*, 1983, **48**, 724.
[139] S. Rozen and Y. Menahem, *J. Fluorine Chem.*, 1980, **16**, 19.
[140] M. J. Adam, *J. Chem. Soc., Chem. Commun.*, 1982, 730.



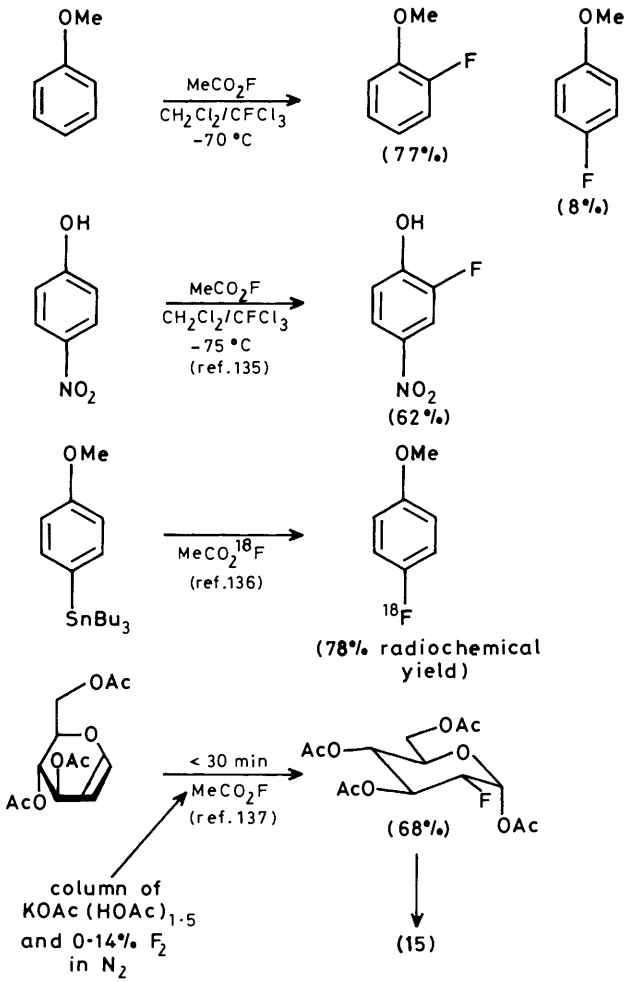
Scheme 71

As with CF_3OF, useful reactions also occur with carbonyl derivatives, *i.e.* with lithium enolates and enol ethers, and good yields of α-fluorocarbonyl compounds or acetylated fluorohydrins are obtained Scheme 73.

Much of this chemistry can probably also be adapted for use with ^{18}F, and acetyl hypofluorite (and related species like trifluoroacetyl hypofluorite) seem set to expand to rival the other major fluorinating agents like DAST and $(HF)_x$py.

I. Caesium Fluoroxysulphate.—In 1981 Appelman demonstrated that passing fluorine through an aqueous solution of caesium sulphate produced the stable, ionic hypofluorite caesium fluoroxysulphate ($CsSO_4F$) (Scheme 74[141]).

[141] D. P. Ip, C. D. Arthur, R. E. Winans, and E. H. Appelman, *J. Am. Chem. Soc.*, 1981, **103**, 1964.

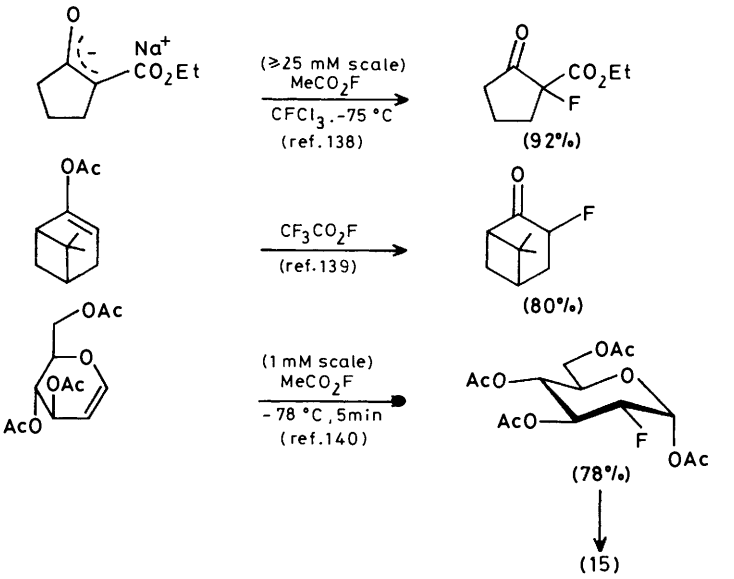


Scheme 72

Aromatic compounds are especially susceptible to fluorination by this reagent, and reaction with cyclic enol acetates is also of synthetic utility (Scheme 75).

The stereochemistry of the reactions with aryl alkenes was explored by Stavber and Zupan.[145] The variable ratio of *syn* and *anti* products, coupled with the

[142] S. Stavber and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 1981, 148.
[143] S. Stavber and M. Zupan, *J. Org. Chem.*, 1985, **50**, 3609.
[144] S. Stavber and M. Zupan, *J. Chem. Soc., Chem. Commun.*, 1981, 795.
[145] S. Stavber and M. Zupan, *J. Org. Chem.*, 1987, **52**, 919.



Scheme 73

$$Cs_2SO_4 + F_2 \longrightarrow CsSO_4F + CsF$$

Scheme 74

regioselectivity observed, suggested that (at least in MeOH) a carbocation mechanism may be involved.

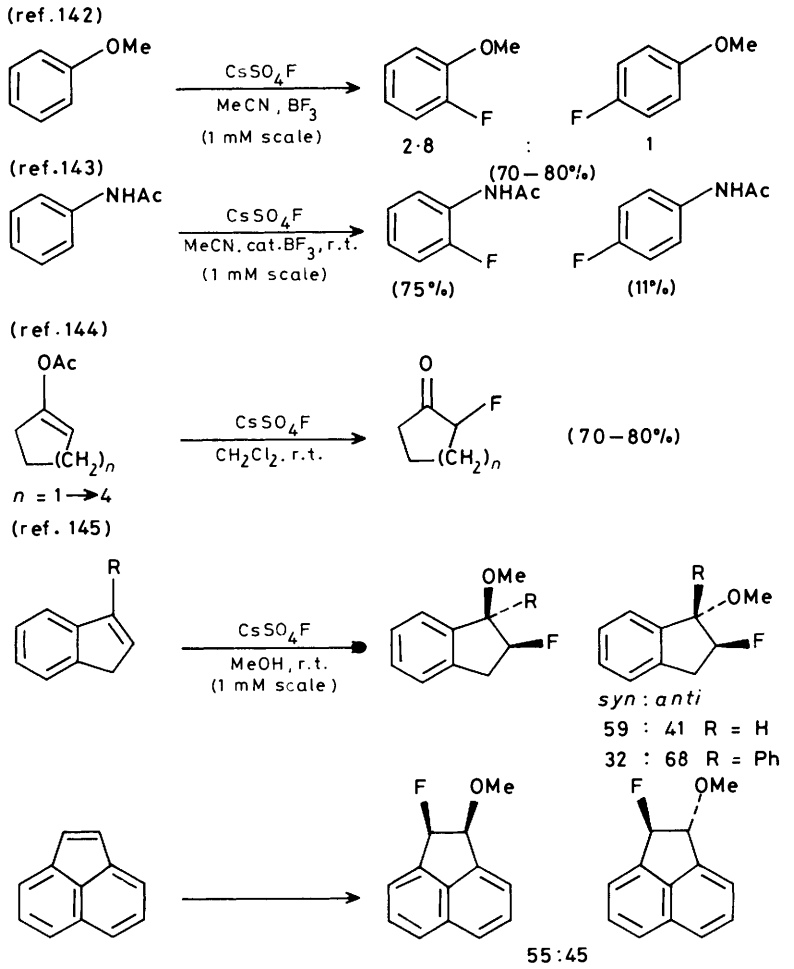
In this same paper the authors compared the reactions of CF_3OF, CF_3CO_2F, xenon difluoride (*vide supra*), and $CsSO_4F$ with (*E*)-and (*Z*)-stilbenes. In methanol or HF, CF_3OF and $CsSO_4F$ produced rather similar results, with a predominance of *syn* products (*i.e. vic*-methoxy fluorides or difluorides); xenon difluoride in combination with HF yielded a predominance of *anti*-products; and trifluoroacetyl hypofluorite gave almost exclusively the *syn*-product.

Finally, as with $FClO_3$, explosions have occurred with $CsSO_4F$.[141]

J. Xenon Difluoride.—With the exception of the ionic fluorides, XeF_2 is one of the easiest fluorinating agents to use, though 25 years ago its existence would not even have been predicted. It is a white crystalline solid which is commercially available, although very expensive.

Most of the early work has been reviewed by Filler,[146] and a radical cation mechanism has been proposed for many of its reactions. Traces of HF, Lewis acids, and organic acids facilitate many of the reactions. It reacts with alkenes yielding *vic*-difluorides, though the utility of the method is limited by the occurrence of

[146] R. Filler, *Isr. J. Chem.*, 1978, **17**, 71.



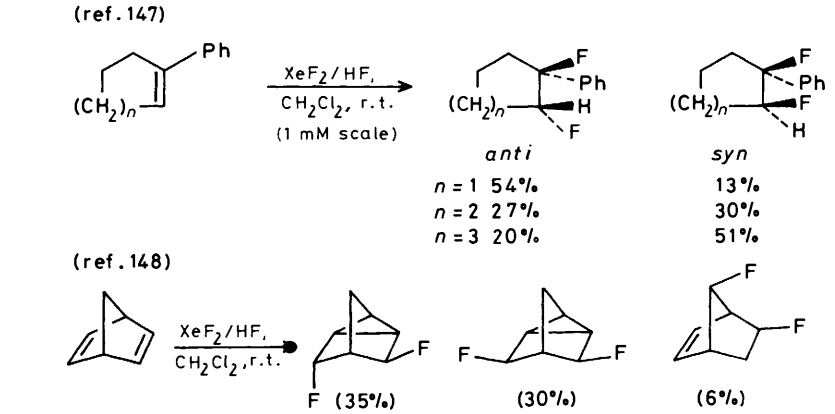
Scheme 75

rearrangement reactions. Typical processes are shown in Scheme 76.

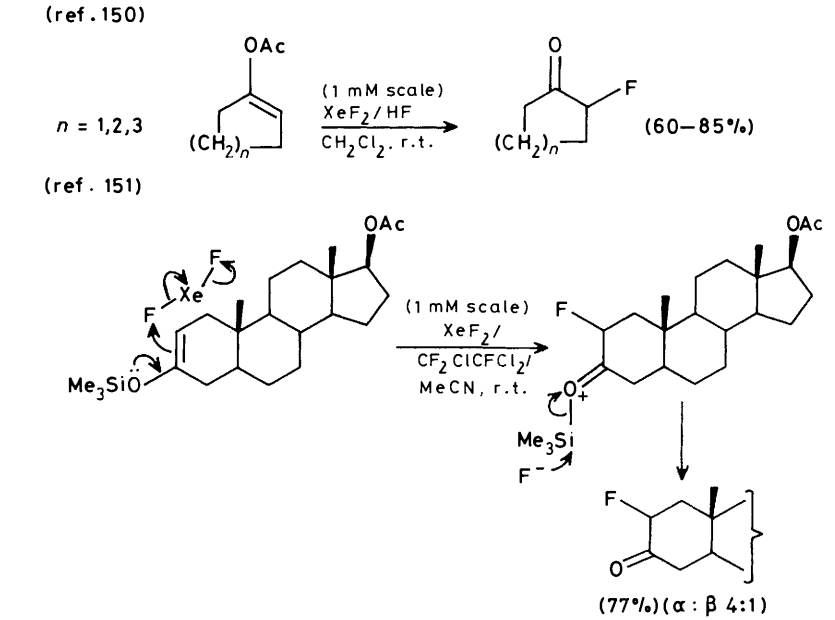
A slight predominance of *anti*-products is observed, though with cyclic alkenes the *syn*-isomer is favoured as the ring size increases.

Bromofluorination has also been carried out with XeF_2–Br_2 mixtures,[149] and with enol acetates and enol silyl ethers good yields of α-fluoro-carbonyl compounds have been obtained. Representative examples are given in Scheme 77.

[147] M. Zupan and B. Šket, *J. Org. Chem.*, 1978, **43**, 696.
[148] M. Zupan, A. Gregorčič, and A. Pollak, *J. Org. Chem.*, 1977, **42**, 1562.
[149] S. Stavber and M. Zupan, *J. Fluorine Chem.*, 1977, **10**, 271.



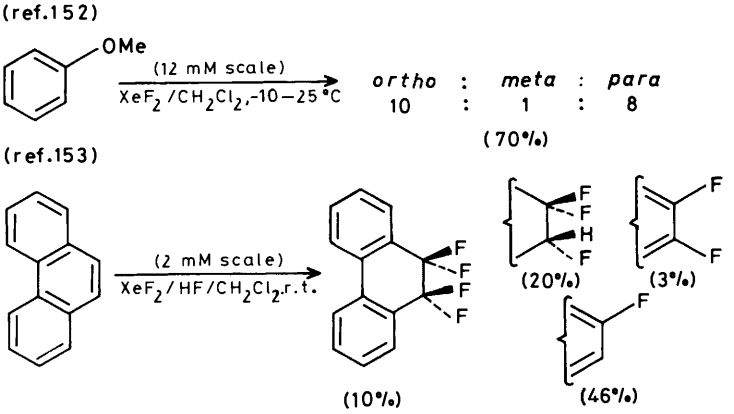
Scheme 76



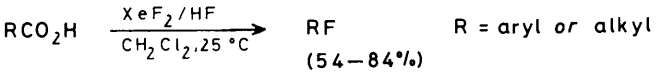
Scheme 77

Xenon difluoride will also replace hydrogens in certain saturated compounds, *e.g.* adamantane, and aromatic fluorination has also been extensively investigated. Some typical results are shown in Scheme 78.

[150] B. Zajc and M. Zupan, *J. Org. Chem.*, 1982, **47**, 573.
[151] T. Tsushima, K. Kawada, and T. T. Tsuji, *Tetrahedron Lett.*, 1982, **23**, 1165.
[152] S. P. Anand, L. A. Quarterman, H. H. Hyman, K. G. Migliorese, and R. Filler, *J. Org. Chem.*, 1975, **40**, 807.



Scheme 78



Scheme 79

One final unique reaction has great potential. This is the reaction of XeF_2 with carboxylic acids (Scheme 79[154]). This is formally equivalent to a Hunsdieker reaction, which of course cannot be used to prepare fluorides.

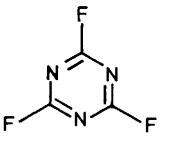
Other noble gas fluorides have been briefly investigated, but none compares with XeF_2 for ease of utility or predictability.

K. Miscellaneous.—Numerous other fluorinating agents have been described, but none have gained the widespread use and acceptance of those already mentioned. The reviews already cited[15,21] provide some information and leading references for reagents introduced before 1986, and so only particularly promising reagents will be discussed here.

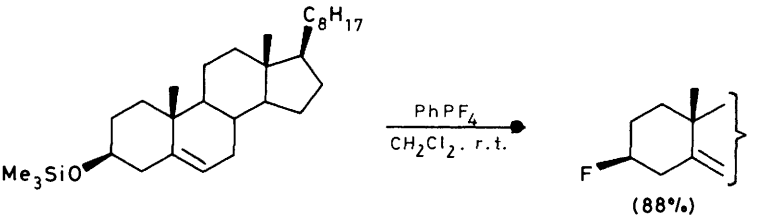
In a review[155] Olah recommends the use of cyanuric fluoride (60) for the conversion of carboxylic acids into acid fluorides. The employment of SCl_2 in conjunction with $(HF)_x$py for the generation of SF_4 *in situ* SeF_4 (b.pt. 106 °C) is also recommended as an alternative to SF_4, although its toxicity is an undoubted problem.

Various fluorophenylphosphoranes (Ph_nPF_{5-n}) have also been prepared by the reaction of the corresponding chlorides with AsF_3 or SbF_3.[156] The reaction shown

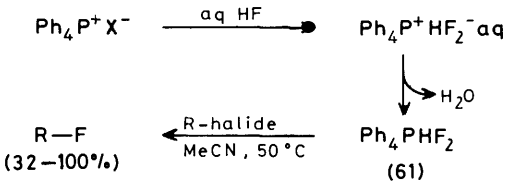
[153] M. Zupan and A. Pollak, *J. Org. Chem.*, 1975, **40**, 3794.
[154] T. B. Patrick, K. K. Johri, and D. H. White, *J. Org. Chem.*, 1983, **48**, 4158.
[155] G. A. Olah, *Acc. Chem. Res.*, 1980, **13**, 330.
[156] R. Schmutzler, *Inorg. Chem.*, 1964, **3**, 410.



(60)



Scheme 80



Scheme 81

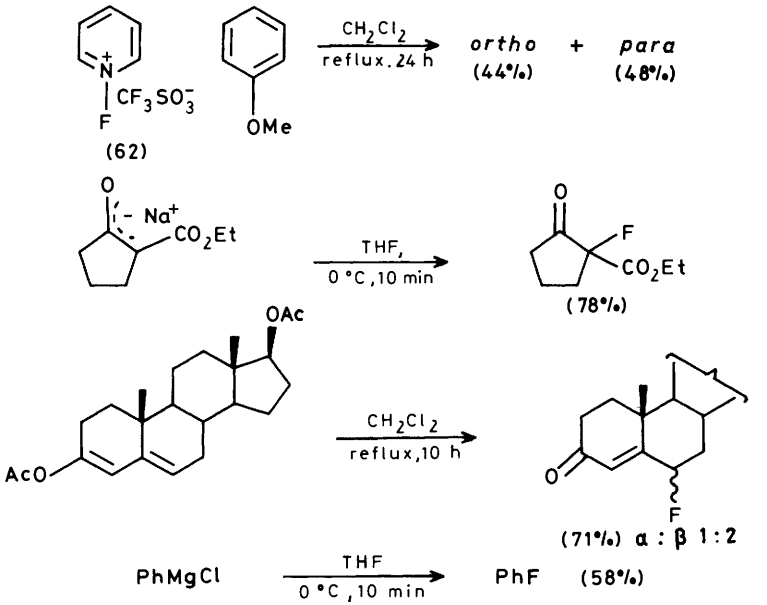
in Scheme 80 provides an example of an optimized conversion.[157] Elimination reactions are usually a serious problem with these reagents. The related species (61) looks more promising (Scheme 81[158]).

Finally, *N*-fluoropyridinium triflate (62) and derivatives appear to offer the promise of broad utility (Scheme 82[159]).

3 Conclusion

This review has concentrated on tried and tested methodology, with an emphasis on recent developments. It does have to be admitted, however, that most of the reagents have drawbacks of expense, toxicity, and explosiveness either alone or in combination. There is thus scope for the development of new reagents, and it remains a truism that the most 'painless' (though not necessarily the least expensive) way to introduce fluorine into a product molecule, is to have the atom(s) present in a commercially available starting material! The two syntheses of

[157] N. E. Boutin, D. U. Robert, and A. R. Cambon, *Bull. Soc. Chim. Fr.*, 1974, 2861.
[158] S. J. Brown and J. H. Clark, *J. Fluorine Chem.*, 1985, **30**, 251.
[159] T. Umemoto, K. Kawada, and K. Tomita, *Tetrahedron Lett.*, 1986, **27**, 4465.



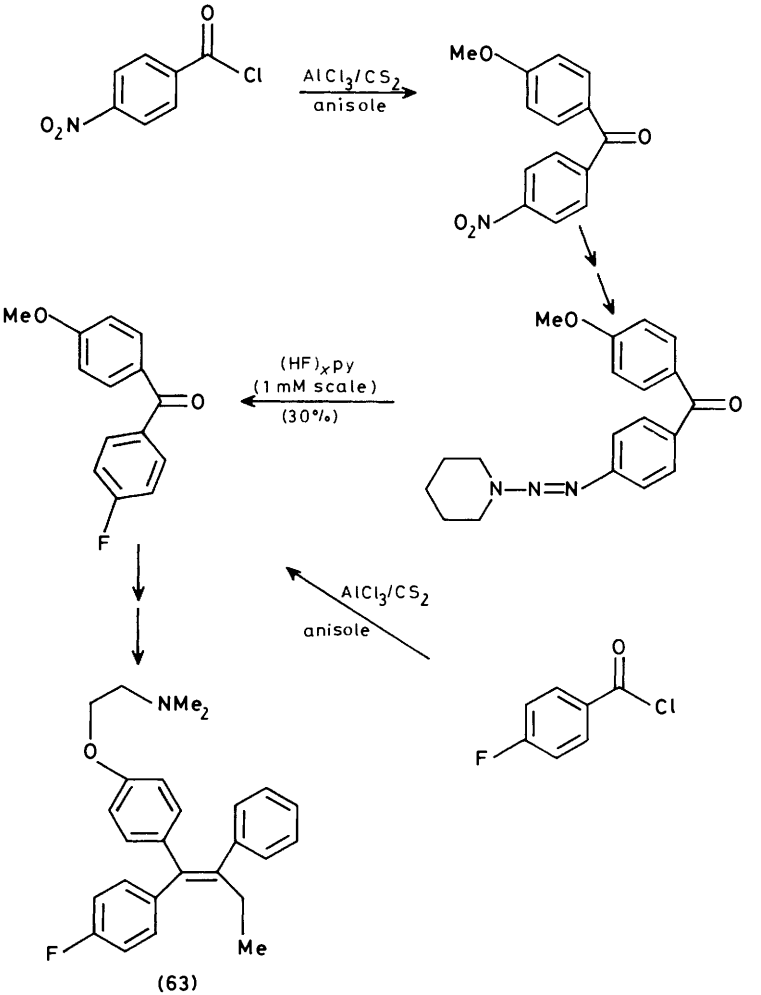
Scheme 82

fluorotamoxifen (63) shown in Scheme 83 (see p. 436)[160] illustrate the point, though it must be said that introduction of an ^{18}F atom for imaging studies necessitates a fluorination step. The parent compound tamoxifen is a potent non-steroidal estradiol antagonist (anti-estrogen), and is very effective in the treatment of hormone-dependent breast cancer.

Whatever strategy is chosen, the introduction of fluorine is almost invariably worth the effort (and expense), since the chemical and biological properties of the fluoro analogues are rarely without interest.

Acknowledgements. I thank Dr. Barbara Pietrzak for her many contributions to our work on fluoro-steroids and Professor Allan Foster for exciting my interest in fluorine chemistry in the first place.

[160] J. Shani, A. Gazit, T. Livshitz, and S. Biran, *J. Med. Chem.*, 1985, **28**, 1504.


O
Cl
O_2N
$AlCl_3/CS_2$
anisole
MeO
O
O_2N
MeO
O
N—N=N
$(HF)_x$py
(1 mM scale)
(30%)
MeO
O
F
$AlCl_3/CS_2$
anisole
O
Cl
F
NMe_2
O
F
Me

(63)

Scheme 83