ELECTROPHILIC FLUORINATION OF ORGANIC COMPOUNDS USING SELECTFLUOR™

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Declaration

The work described herein was carried out at the Chemistry Department, UMIST, between October 1992 and August 1997. It is solely the work of the author, except where indicated by reference, and includes no material carried out in collaboration. No part of this thesis has been, or will be, submitted for a degree or any other qualification at this, or any other, University.

Allan Popplewell

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UMIST, 12th August 1997

Acknowledgements

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My thanks must also go to all of the technical staff in the analytical laboratories, the fluorine laboratory and the stores at the Chemistry Department of UMIST for their efficient support services.

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Contents

Abstract

The aim of this research has been to investigate the scope and limitations of the electrophilic fluorinating reagent, Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate). This reagent was invented at UMIST and, at the start of the project, there was little information in the literature about its properties and reactivity. The work carried out during this project and described herein has demonstrated that Selectfluor™ is a versatile reagent, which is easily and safely prepared in high yield from inexpensive starting materials (although it is now commercially available for those researchers that do not have the facilities for handling elemental fluorine).

The most useful solvent for reactions involving Selectfluor™ is acetonitrile. The results of this research show that the reagent is reasonably stable in this solvent, but that slow decomposition and loss of fluorinating ability becomes significant when reaction temperatures in excess of 40 °C are required. Also demonstrated is the ability of Selectfluor™ to efficiently fluorinate 1,3-dicarbonyl compounds. This has been shown using examples from each of the main sub-classes (β-diketones, β-ketoesters, β-ketoamides and malonate esters).

The efficiency of the reagent as a source of "F+" inevitably means that it can also act as a fairly powerful oxidising agent. Indeed, the results of this work demonstrate that Selectfluor™ oxidises benzylic alcohols to benzaldehydes which are further converted to benzoyl fluorides. Whilst investigating the scope of this reaction with other alcohols an unusual ring closure was discovered where the nitrile solvent was incorporated between the hydroxyl and isopropyl groups of (–)-menthol. Further investigations showed that this transformation was limited to compounds containing a hydroxyl functionality β- to an isopropyl group. The oxazine resulting from the reaction with (–)-menthol was hydrolysed to the hydroxyamine, demonstrating the use of the new reaction as a method for effecting remote functionalisation of an alcohol with an amino group.

These results imply that readily oxidisable functionalities in the substrate (such as alcohol and amine groups) should be protected before the compound is treated with Selectfluor™. The protection of alcohols as silyl ethers was investigated. The results demonstrated that silyl ethers should be used only under mild conditions, as they are cleaved by the presence of Selectfluor™.

Using the information gathered during this research, a route for the total synthesis of the 2-fluoro analogue of A-factor (an inducer of cytodifferentiation in many streptomycetes) was designed. The synthesis of this compound was successfully achieved using the Selectfluor™ reagent for the fluorination step. The biological activity of this material will be compared to that of A-factor itself.

Glossary

Ac	acetyl
AHF	anhydrous hydrogen fluoride
AIBN	azoisobutyronitrile or azobis(1-cyano-1-methylethane)
aq.	aqueous
Ar	aryl
Ar FAB$^+$	positive fast atom bombardment with argon
Atm.	atmosphere(s) of pressure
b.p.	boiling point
br	broad
brine	saturated aqueous sodium chloride solution
Bu or Bu^n	*normal*-butyl
Bu^t	*tert*-butyl
c.	concentration
ca.	*circa* (Latin: "about")
cat.	catalytic (amount)
Celite®	high grade diatomaceous earth used as a filter aid
cf.	*confer* (Latin: "compare")
d	doublet
Δ(*delta*)	heat
Δδ	difference in the chemical shift of similar atoms from two diastereoisomers of the same compound
DAST	diethylaminosulfur trifluoride
d.e.	diastereoisomeric excess: [(A–B)/(A+B)]×100 expressed as a percentage where A & B are diastereoisomers
dec.	decomposes
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ed.	editor
e.e.	enantiomeric excess: [(*R*–*S*)/(*R*+*S*)]×100 expressed as a percentage where *R* & *S* are enantiomers
e.g.	*exempli gratia* (Latin: "for example")
eq. or equiv.	equivalent(s)
Et	ethyl
et al.	*et alia* (Latin: "and others")
etc.	*et cetera* (Latin: "and so on")
Expt.	Experiment
EWG	Electron withdrawing group
FMOC	*N*-Fluorenylmethoxycarbonyl
g	gas

hr	hour(s)
i.e.	*id est* (Latin: "that is")
in situ	in the reaction mixture [Latin: "in its (original) place"]
in vacuo	under vacuum
LDA	lithium diisopropylamide
Lit.	literature (reference)
m	multiplet
Me	methyl
m-	*meta-*
MHz	MegaHertz
min	minute(s)
ml	millilitre(s)
m.p.	melting point
m/z	mass to charge ratio measured by mass spectroscopy
N.B.	*nota bene* (Latin: "note well")
NH_3 CI^+	chemical ionisation with ammonia
NIS	*N*-iodosuccinimide
nm	nanometre(s)
NMR	nuclear magnetic resonance
no.	number
Nuc^-	general nucleophile
o-	*ortho-*
[O]	oxidation
p	page
p-	*para-*
petrol	the fraction of light petroleum-ether boiling between 40-60 °C
Ph	phenyl
pp	pages
ppm	parts per million
Py	pyridine
q	quartet
quant.	quantitative (>98%)
quin	quintet
R_f	retention factor
RT	room temperature (*ca.* 22 °C)
s	singlet
sat.	saturated
Selectfluor™	The family of 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts, with particular reference to 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (**9**)
sept	septet

SET	single electron transfer
sext	sextet
sulfolane	tetramethylenesulfone
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
temp.	temperature
Tf	trifluoromethylsulfonyl (CF_3SO_2)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
triflate	trifluoromethylsulfonate ($CF_3SO_2O^-$)
Ts	*p*-toluenesulfonyl
v/v	volume/volume ratio
wrt.	with respect to
w/v	weight/volume ratio
w/w	weight/weight ratio

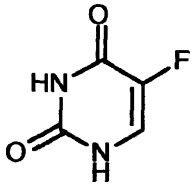
1. Introduction

"Dans les champs de l'observation le hasard ne favorise que les esprits préparés."
"Where observation is concerned, chance favours only the prepared mind."
-Louis Pasteur.

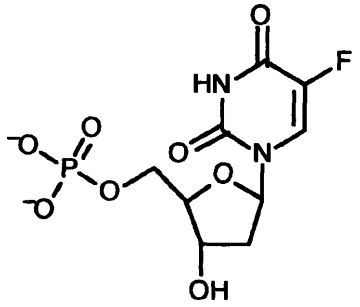
1.1 The importance of organofluorine chemistry

The C–F bond is, on average, only 27% longer than the C–H bond [*l*(C–F) ≈ 0·138 nm, *l*(C–H) ≈ 0·109 nm].[1] The small size of covalent fluorine means that, sterically, it behaves in a very similar way to hydrogen in organic molecules. However, being the most electronegative element in the periodic table, it most certainly does not resemble hydrogen electrostatically (Pauling electronegativities for fluorine and hydrogen are 4·0 and 2·1 respectively).[1] Consequently the physiological properties of fluoro-analogues of biologically active compounds can differ from their unfluorinated counterparts in a subtle way. That is, the fluoro-compound may have physical properties similar enough to the naturally-occurring molecule that the physiological system will use it in place of the original. However, the chemical properties of the fluoro analogue will often preclude its use as a direct replacement. For example monofluoroacetic acid owes its severe toxicity[2] to the fact that it mimics acetic acid, but interrupts the Krebs-Matius-Knoop tricarboxylic acid cycle.

This property of fluorinated naturally occurring compounds is used to good effect in anticancer chemotherapy. The family of chemotheraputic agents based on 5-fluorouracil (**1**) owe their activity to the fact that their metabolite [5-fluoro-2'-deoxyuridylate (**2**)] acts as a suicide inhibitor of thymidylate synthase.[3]



5-Fluorouracil (**1**)



5-Fluoro-2'-deoxyuridylate (**2**)

This enzyme is responsible for the methylation of 2'-deoxyuridylate (**3**) to form thymidine-5'-phosphate (**4**) within cells (**Fig. 1.1**). When **2** is the substrate the presence of fluorine in the 5-position prevents the elimination of the methylated compound from the enzyme. The enzyme is thus incapable of carrying out further reaction. If a cell cannot synthesise thymidine it dies. Rapidly growing cells, such as those in a tumour, require

more thymidine (and therefore more **4**), so each enzyme molecule encounters more 2'-deoxyuridylate (**3**). This increased activity raises the enzyme's chance of deactivation by taking up a molecule of 5-fluoro-2'-deoxyuridylate (**2**). This means that the introduction of **2** will deactivate the enzyme in tumour cells faster than it will in healthy cells so the growth of the tumour is inhibited relative to the surrounding, healthy tissue.

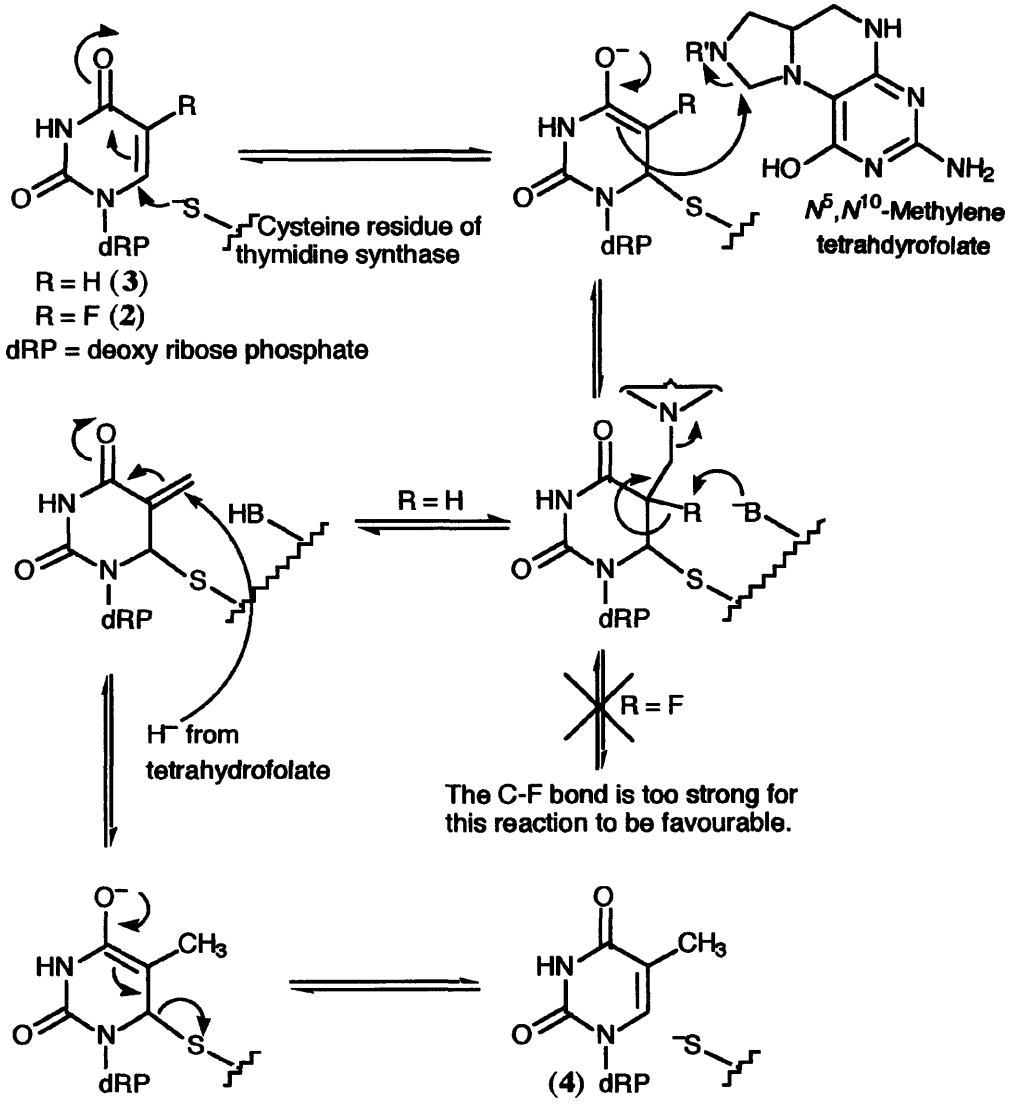
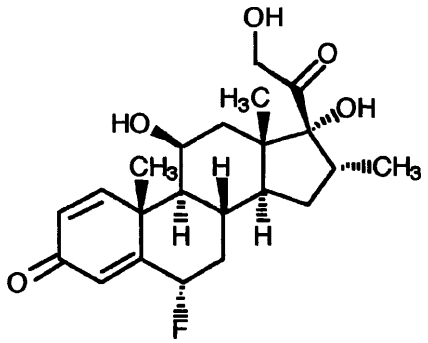
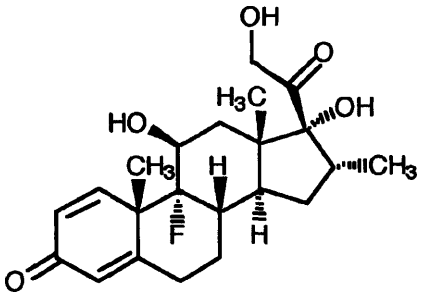


Fig. 1.1

The fluoro-analogue is not always harmful to physiological systems. In fact it is known that fluorosteroids can, in some cases, surpass naturally occurring hormones in their biological activity. Such is the case with the steroidal anti-inflammatory drugs[4] Paramethasone (**5**) and Dexamethasone (**6**). These are especially useful for the treatment of rheumatoid arthritis. They have a higher activity and are less prone to cause sodium retention in the patient than their unfluorinated counterparts.

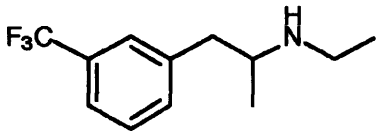


Paramethasone (**5**)



Dexamethasone (**6**)

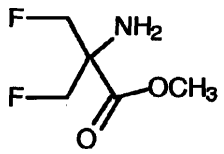
Replacement of hydrogen by fluorine usually increases the lipid solubility of a molecule. Consequently the molecule will be absorbed into and transported around an organism much more quickly. This is particularly useful for neuro-active drugs as it is often difficult for drugs to cross the blood-brain barrier due to their poor lipid solubility. Indeed, many fluorinated compounds exist for the treatment of such neurological disorders[5] as schizophrenia, depression, epilepsy and obesity. An example of such a drug is Fenfluramine (**7**) which is an anorectic (appetite depressant) used in the treatment of obesity.



Fenfluramine (**7**)

There is intense current interest in obtaining site-selectively fluorinated analogues of biologically active molecules[6] for use in both the agrochemical and pharmaceutical industries.

In the area of fluoro-steroids it has been shown that 9α-fluorohydrocortisone acetate and 9α-fluorocortisone acetate have eleven and nine times (respectively) the glucocortical activity of their unfluorinated counterparts.[7] Work on fluoroamino acids[8] has included the synthesis of 4,4-difluorothreonine[9] which has been shown to have *in vitro* anti-tumour activity comparable to that of 5-fluorouracil (**1**) whilst methyl 2-(fluoromethyl)-3-fluoroalanine[10] (**8**) has been used as a probe for measuring intracellular pH by ^{19}F NMR.[11]



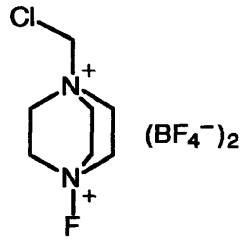
Methyl 2-(fluoromethyl)-3-fluoroalanine (**8**)

Notable effort is also apparent in the area of nucleosides such as the family of chemotherapeutic agents based on 5-fluorouracil[3] (**1**). Fluorination has also been carried

out at the C2' and C3' positions of the carbohydrate ring of nucleosides.[12] This work is described in **Section 1.8.3**. Work has also been published on the synthesis of some analogues of 20-fluorovitamin D. These have been found to have slight activity towards the selective destruction of human leukaemia cells.[13] The activity was sufficient to warrant further lead optimisation.

With this increased interest in fluorinated compounds has come a corresponding increase in the number of methods and reagents available for the site-selective introduction of fluorine into molecules. Many of these are outlined in later sections of this introduction.

The aim of this project is to investigate the scope and limitations of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate[14] (Selectfluor™)[15](**9**) as a site-selective fluorinating reagent. This is one of the more recently introduced members of the N–F class of electrophilic fluorinating reagents (see **Sections 1.6.9** and **1.8**).



Selectfluor™ (**9**)

1.2 Methods for introducing fluorine into organic molecules

There are many ways for chemists to introduce fluorine into organic molecules. Whilst it is appropriate to outline those methods relevant to this work, a comprehensive list of all of the methods is beyond the scope of this thesis, however, a good many of them are featured in some recent reviews.[16]

Fluorine atoms may be introduced into an organic molecule by way of F^-, $F^\bullet$ or F^+ synthon equivalents. They may also be introduced as a part of another fragment (R^-, $R^\bullet$, or R^+ where R contains fluorine).[17] However, this introduction will concentrate on the actual formation of the C–F bond. Some of the more widely used methods for achieving this are discussed briefly below:

1.3 F^- synthon equivalents

These reagents provide a source of fluoride ions which act as nucleophiles to displace a leaving group,[18] X (such as halide, tosylate and, in the case of aromatic substitution, nitro groups[19]), from the substrate molecule (**Fig. 1.2**).

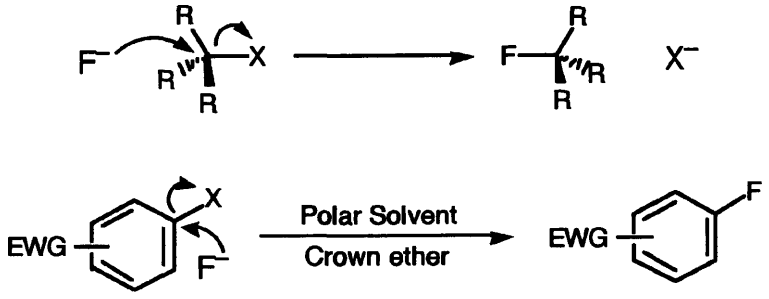


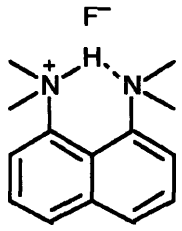
Fig. 1.2

A common source of F^- are the metal fluorides such as potassium fluoride[20] or caesium fluoride.[21] Due to their poor solubility these reagents usually require polar solvents (such as sulfoxides,[22] or sulfones[23]) and high temperatures,[24] although crown ethers[25] have been used as catalysts to increase their solubility and lower the temperature required for reaction.

Tetra-*n*-butylammonium fluoride[26] (TBAF) is most often used to displace a leaving group from an alkyl carbon. It has a much greater solubility in organic solvents and so may be used at lower temperatures in solvents of relatively low polarity such as THF. Hydrogen fluoride-pyridine complex[27] (Olah's reagent) and triethylamine trishydrofluoride[28] behave in much the same way as TBAF.

Anhydrous hydrogen fluoride (AHF) is often used to add H–F across unsaturated carbon-carbon bonds. Addition of the substrate to an excess of the acid can give good results,[29] but addition of the acid to the substrate usually results in a polymer.[30] This reagent is notoriously difficult to work with as it reacts with all but silver, copper and steel vessels. The effect of AHF on human skin has been well documented,[31] making this a reagent which should be used with extreme caution.

All of the above reagents are extremely hygroscopic and so require careful handling. This is due to the large hydration enthalpy of the fluoride ion [ΔH_{hyd} (F^-) = –506 kJmol^{-1}, *cf.* ΔH_{hyd} (Cl^-) = –364 kJmol^{-1}][1]. In the presence of even a slight amount of water the fluoride ion acquires a solvation shell. This prevents it from coming into contact with the substrate and so impairs its reactivity as a nucleophile. Reagents have been developed which address this problem. By attaching the fluoride ion to a larger group, such as hypervalent silicon, the hydration enthalpy is reduced and so the reagent becomes less hygroscopic. Such reagents include tris(dimethylamino)sulfonium difluorotrimethylsilicate [TAS fluoride, $(Me_2N)_3S^+$ $Me_3SiF_2^-$],[32] tetrabutylammonium difluorotriphenylstannate (Bu_4N^+ $Ph_3SnF_2^-$),[33] tetrabutylammonium difluorotriphenylsilicate (TBAT, Bu_4N^+ $Ph_3SiF_2^-$)[34] and proton sponge hydrofluoride (**10**).[35,36]



Proton sponge hydrofluoride (**10**)

Tetrafluoroborate salts can also be sources of F^- as in the Balz-Schiemann reaction[37] (**Fig. 1.3**). This reaction does not suffer the same problems with water as those which rely on fluoride ions. Indeed the reaction is carried out in an aqueous medium up until the last step, where the isolated, dry diazonium tetrafluoroborate salt is heated (usually in a sand bath) to give the corresponding fluoro compound with elimination of nitrogen and boron trifluoride

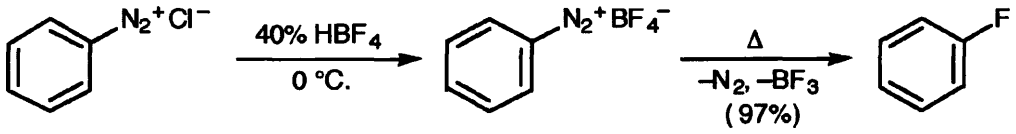


Fig. 1.3

Sulfur tetrafluoride[38] is a source of F^- that is used to convert alcohols to fluorides and ketones to difluorides. It is also used to synthesise trifluoromethyl groups from carboxylic acids (**Fig. 1.4**).

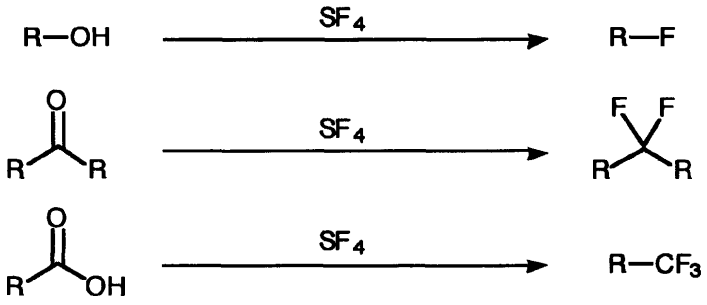


Fig. 1.4

Due to the low boiling point (–40·4 °C),[39] corrosive nature of sulfur tetrafluoride and the high temperatures (typically 100-200 °C) required the reactions must be carried out in a stainless steel pressure reactor. However, the required reaction temperature can be lowered by the addition of a Lewis acid catalyst[40] such as boron trifluoride, titanium tetrafluoride, phosphorus pentafluoride or hydrogen fluoride. The latter is often generated *in situ* by adding small amounts of water. A full description of the mechanisms of these reactions is beyond the scope of this review, but they have been extensively covered in the literature.[38,40]

Diethylaminosulfur trifluoride (DAST)[41] is increasingly being used in place of sulfur tetrafluoride. It is not as corrosive, has a much lower toxicity and is a liquid at room temperature (b.p. 30-32 °C @ 3 mmHg),[42] thus making it safer and easier to work with.

1.4 F• synthon equivalents

The fluorine radical is easily generated from elemental fluorine. This is due to the weak F–F bond [D(F–F) = 158 kJmol^{-1}].[1] However, due to the strength of both H–F and C–F bonds [D(H–F) = 562 kJmol^{-1}, D(C–F) = 484 kJmol^{-1} *cf.* D(C–H) = 412 kJmol^{-1}],[1] it is extremely reactive towards organic molecules. This reactivity results in a lack of selectivity towards the substrate, with hydrogen abstraction and C–F bond formation occurring at many sites in the molecule in an uncontrolled manner (**Fig. 1.5**).

Fig. 1.5

The energy released by this reaction is greater than that of a C–C bond [D(C–C) = 348 kJmol^{-1}].[1] This means that the reaction is often accompanied by fragmentation of the carbon chain. Consequently the use of elemental fluorine at ambient temperatures is usually reserved for the synthesis of perfluoro compounds.[43] It should be noted that, at lower temperatures, fluorine behaves as a source of "F+" (see **Section 1.5.5**).

An alternative way of generating fluorine radicals is electrochemical fluorination.[44] The substrate is electrolysed in the presence of anhydrous hydrogen fluoride. This is a complex process with a free radical mechanism and, as with elemental fluorine, is only really useful for the synthesis of perfluoro compounds. These are generally produced as a mixture due to carbon chain fragmentation in the process.

1.5 F+ synthon equivalents

This class of fluorinating reagent is used to insert a fluorine atom at a nucleophilic centre in a molecule (**Fig. 1.6**).

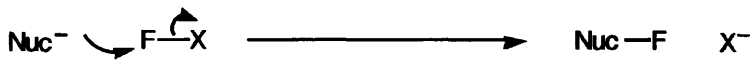
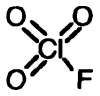


Fig. 1.6

In most useful syntheses the nucleophile is a carbanion, although it can also be a non-carbon group such as an alcohol or an amine. A brief review of the more commonly used classes of electrophilic fluorinating reagents is given below.[45]

1.5.1 Perchloryl fluoride:



Perchloryl fluoride (**1 1**)

Perchloryl fluoride[46] (**1 1**) was the first electrophilic fluorinating reagent to be discovered. It was first synthesised by the action of fluorine gas on potassium chlorate[47] (**Fig. 1.7**).

Fig. 1.7

The major disadvantage of this method is that it is difficult to separate the gaseous **1 1** from any unreacted fluorine that may be present. An easier and more efficient way of synthesising small quantities of **1 1** is *via* the reaction of potassium perchlorate with fluorosulfonic acid[48] (**Fig. 1.8**).

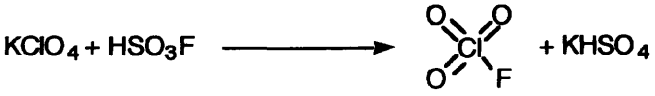


Fig. 1.8

This method produces **1 1** from a liquid and a solid, so contamination of the gaseous product is not such a problem. Perchloryl fluoride is synthesised on an industrial scale by the electrolysis of a solution of sodium perchlorate in liquid hydrogen fluoride.[49] It is a gas at well below room temperature (b.p. –46·7 °C)[39] and is extremely toxic.[50] It is also corrosive and must be stored in steel containers when not generated *in situ*. Perchloryl fluoride is also a powerful oxidising agent and care must be taken to avoid sparks, flames or even reaction hot-spots when it is in the presence of readily oxidisable materials such as organic compounds. Similarly, liquid **1 1** can become an explosion hazard if it comes into contact with organic compounds.[51] This explosion hazard also applies to the by-product (chloric acid or chlorate salts) formed in the reaction between **11** ı and organic nucleophiles.

The reactivity of **1 1** is not high, so fluorination reactions can only be performed on strongly nucleophilic substrates such as organometallic compounds,[52] metal enolates,[53] enol ethers[54] or enamines.[55]

The reaction with organometallic compounds is thought to proceed *via* a simple S_N2 process (**Fig. 1.9**).

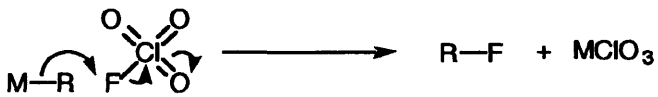


Fig. 1.9

The reaction with metal enolates, on the other hand, is thought to proceed *via* a five-membered transition state. This is formed when the oxygen atom of the carbonyl group attacks **1 1** at the central chlorine atom[56] (**Fig. 1.10**).

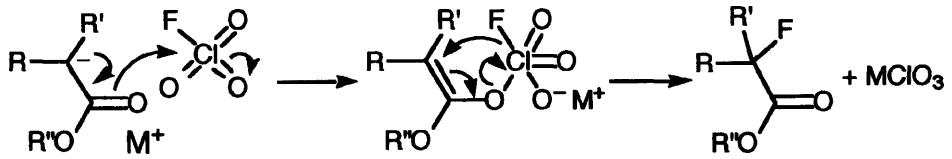


Fig. 1.10

The unoccupied d-orbitals on the chlorine atom can facilitate a single electron transfer (SET) mechanism (**Fig. 1.11**).

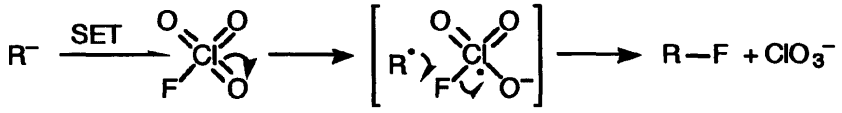


Fig. 1.11

When this mechanism is occurring, radical attack of R• at chlorine or oxygen can result in chlorinated and/or oxygenated products rather than the desired fluorinated product[56,57].

1.5.2 Xenon difluoride:

In 1962 Neil Bartlett discovered that xenon could be oxidised by platinum hexafluoride to give a yellow-orange solid,[58] $Xe^+[PtF_6]^-$. Shortly afterwards Claassen, Selig and Malm synthesised xenon tetrafluoride,[59] whilst a group under Hoppe reported xenon difluoride.[60]

The most efficient method for synthesising xenon difluoride in reasonable quantities is to place equimolar amounts of fluorine and xenon gases in a Pyrex bulb and allow them to stand in sunlight at 25 °C for several hours, during which time a solid is formed.[61] This solid may then be sublimed to give xenon difluoride as a waxy, white, stable crystalline solid (m.p. ≈ 140 °C).[39]

A recent article by M.A. Tius[62] describes the reactions of xenon difluoride in some detail. Essentially it reacts with nucleophiles in a similar manner to perchloryl fluoride (**1 1**).

Zupan has investigated the reactions of xenon difluoride with enol acetates and 1,3-dicarbonyl compounds to form α-fluoroalkanones.[63,64] He has shown that these reactions only proceed when catalysed by the addition of hydrogen fluoride or boron trifluoride etherate. Tius has converted vinyl stannanes to vinyl fluorides using xenon difluoride in the presence of silver (I) hexafluorophosphate[65] or silver (I) triflate.[66]

α-Fluoroalkanones may also be prepared by the action of xenon difluoride on silyl enol ethers. This reaction sometimes requires hydrogen fluoride pyridine [Py·$(HF)_x$] as a catalyst, but several steroids have been fluorinated in this manner[67] without any catalyst.

Stabilised carbanions such as metal enolates usually form dimers when reacted with xenon difluoride in the absence of any catalyst.[68] In this reaction xenon difluoride is clearly acting as an oxidising agent rather than a fluorinating agent (**Fig. 1.12**).

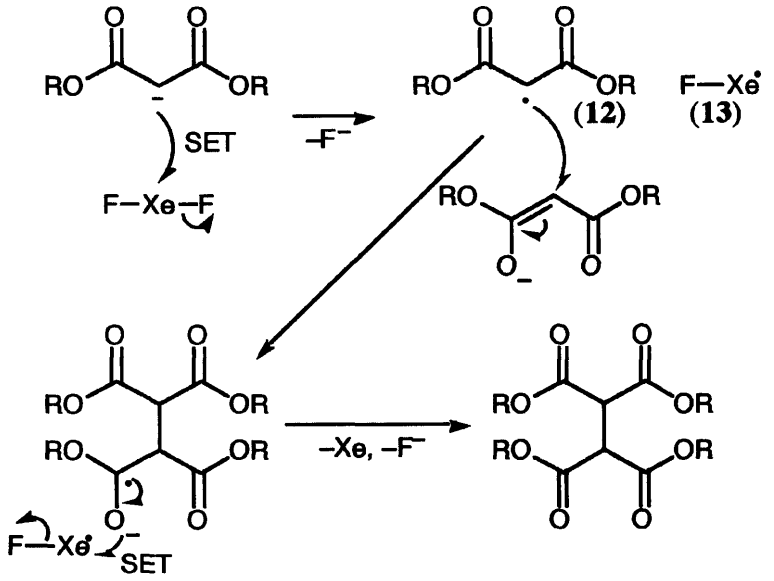


Fig. 1.12

Both of the radicals produced by electron transfer (**12** and **13**) are electron deficient so they only react with each other slowly. The malonate salt, however is electron rich so this species can be attacked by the malonate radical as shown.

The desired fluorinated products are only produced in useful yields when both boron trifluoride etherate and a sulfide are present. The catalysed reaction is thought to proceed through a fluorosulfonium salt (**14**) (**Fig. 1.13**).[68]

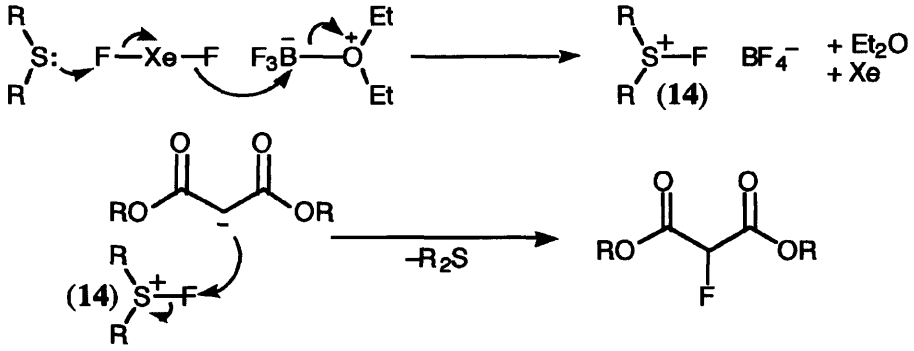


Fig. 1.13

An electron transfer mechanism has also been shown to occur in the reaction between aromatic compounds and xenon difluoride[69] (**Fig. 1.14**).

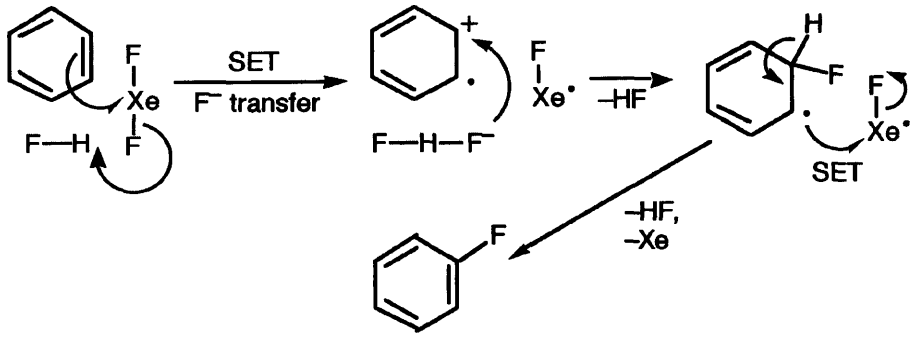


Fig. 1.14

One of the major disadvantages of xenon difluoride is that, at £60·00 for 5 g,[70] it is rather expensive. The xenon produced as a reaction by-product may be collected and recycled when work is being carried out on a large scale in order to reduce the cost.

1.5.3 Hypofluorites:

A recent review of fluorination reactions by reagents containing the OF group has been published by Rozen.[71] Some of the more commonly used reagents in this group are described below:

Fluoroxytrifluoromethane (sometimes called trifluoromethyl hypofluorite) was originally prepared in 1948 by Kellogg and Cady in 50% yield from a silver fluoride catalysed reaction between methanol and elemental fluorine.[72] There are now several other methods for the synthesis of fluoroxytrifluoromethane.[73] The most effective is the caesium fluoride catalysed reaction between carbon monoxide and fluorine[74] (**Fig. 1.15**).

$$2F_2 + CO \longrightarrow COF_2 + F_2 \xrightarrow{CsF} CF_3OF$$

Fig. 1.15

This compound was introduced to organic chemistry as a fluorinating reagent in 1968 by Barton and Hesse.[75,76,77] It is a toxic gas (b.p. –95 °C)[39] with a reactivity slightly greater than that of perchloryl fluoride (**1 1**). Fluoroxytrifluoromethane is a strong oxidising agent (similar to fluorine), but the risk of explosion when in contact with oxidisable materials is far less than with perchloryl fluoride. However, precautions must still be taken when working with this material. For example, work should be carried out in high dilution (with nitrogen) in inert solvents (such as chlorofluorocarbons) and at low temperatures behind a safety shield.

Low temperatures are also essential to avoid the initiation of free radical reactions. These can be a problem with this reagent due to the low dissociation energy of the O–F bond [$D(CF_3O–F)$ = 180 $kJmol^{-1}$]. The reaction mixture must also be well stirred to prevent any "hot-spots" from developing.

Most of the chemistry of fluoroxytrifluoromethane, up to 1977, is covered in the extensive reviews by Hesse[78] and Barton.[79] In addition to delivery of electrophilic

fluorine fluoroxytrifluoromethane can add across multiple bonds in one of two ways[76] (**Fig. 1.16**).

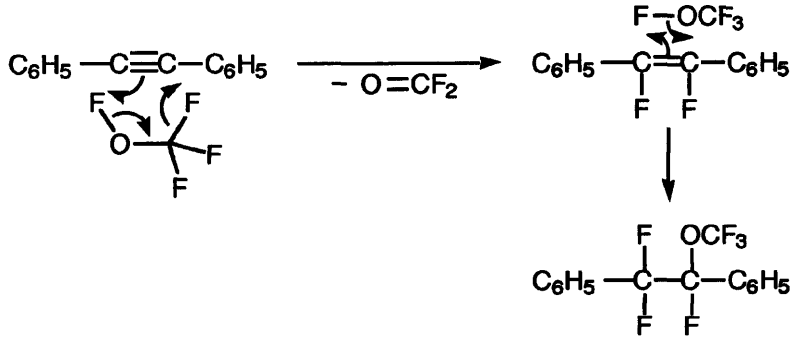


Fig. 1.16

This has been studied by DesMarteau[80] and has been used by Barton[77] to introduce a fluorine into positions 2 or 6 in steroids (**Fig. 1.17**).

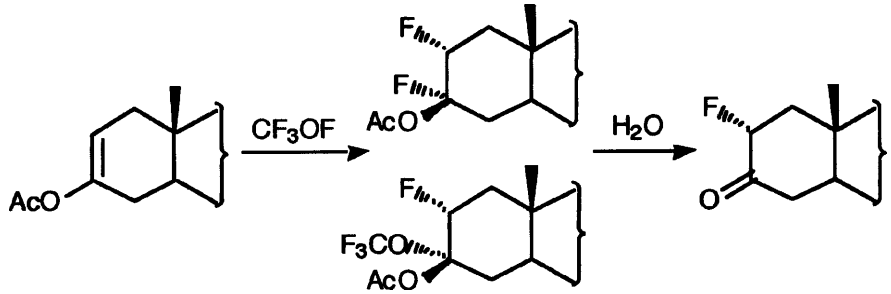


Fig. 1.17

The first acyl hypofluorite to be used synthetically was trifluoroacetyl hypofluorite. Rozen[81] and Lerman first synthesised this compound in 1979 by bubbling fluorine into a suspension of sodium trifluoroacetate in fluorotrichloromethane at –78 °C (**Fig. 1.18**).

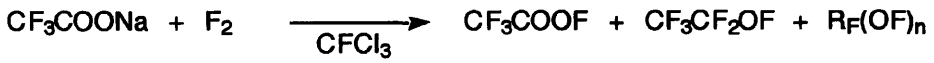


Fig. 1.18

The resulting solution usually contains a complex mixture of perfluoro hypofluorites, but may be used to effect fluorination reactions as if it were a single, homogeneous reagent. Under certain conditions it is possible to produce a solution containing mainly the trifluoroacetyl hypofluorite which can be used without further purification.[82] Either the mixture of hypofluorites or the crude trifluoroacetyl hypofluorite can be used to effect the fluorination of enol acetates[83] (to give α-fluoroketones) or *syn*-addition across multiple bonds[82] (**Fig. 1.19**). This latter reaction is thought to proceed in two steps *via* a solvent-cage trapped α-fluorocarbocation. Good regioselectivity is obtained because the carbocation is stabilised more effectively by the α-phenyl group than it would be by the electron-deficient *para*-carbomethoxybenzene group if the other regioisomer of the carbocation intermediate were to be formed.

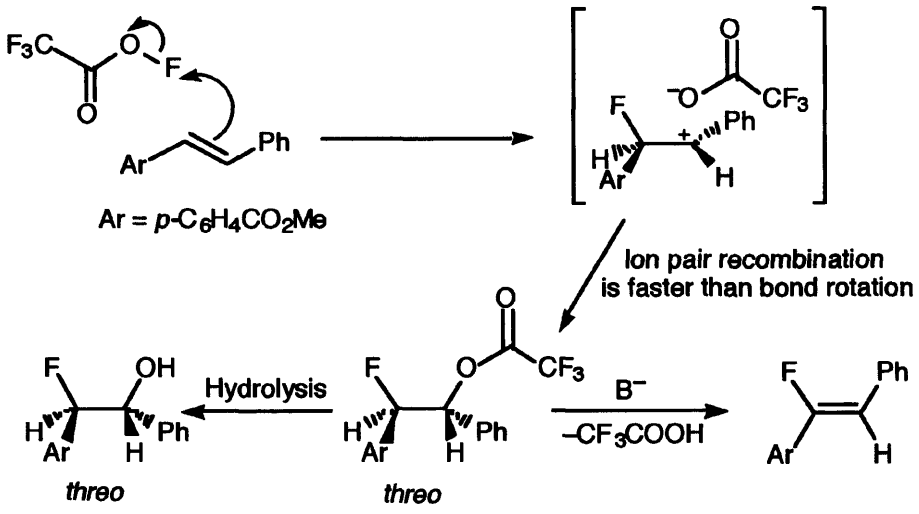


Fig. 1.19

Acetyl hypofluorite was synthesised in 1981 by Rozen and Lerman.[84,85] They used a similar procedure to that used in the synthesis of trifluoroacetyl hypofluorite. That is, fluorine was bubbled into a suspension of sodium acetate in fluorotrichloromethane and acetic acid (≈10:1) at –75 °C. The resulting solution was successfully used to fluorinate various alkoxy aromatic compounds and acetanilide.[85] It was also shown that this reagent adds in a *syn*-manner across olefinic double bonds.[84,86]

Being generated from elemental fluorine and used *in situ*, acetyl hypofluorite provides a fast and efficient method for the synthesis of ^{18}F substituted compounds.[87] These compounds are used to study drug uptake and distribution patterns by using positron emitting transaxial tomography.[88] To use this technique, the compound to be studied must be synthesised and introduced into the organism in a very short space of time. This is due to the short half-life of the ^{18}F nucleus (110 min).

Acetyl hypofluorite is less reactive than any of the other fluoroxy reagents. Consequently it will only react with 1,3-dicarbonyl compounds possessing considerable enolic character, giving only moderate yields. When the substrate has little or no enol character, (in monoketones or dialkyl malonates, for example) a reaction is only possible if the metal enolate of the substrate is used.

It has been shown that acetyl hypofluorite reacts cleanly and efficiently with metal enolates of ketones[89] and with organotin compounds.[90] Such reactions are not possible with other, more reactive fluoroxy reagents as they tend to result in tars.[91] This is due to the more reactive nature of metal enolates of monoketones when compared to metal enolates of 1,3-dicarbonyl compounds.

1.5.4 Caesium fluoroxysulfate ($CsSO_4F$):

In 1979 Appelman synthesised caesium fluoroxysulfate ($CsSO_4F$) by bubbling elemental fluorine (in a stream of nitrogen) into aqueous caesium sulfate.[92] Appelman[93] and Zupan[94] showed that the reagent could be used to fluorinate aromatic ring systems in a reasonably efficient manner (**Fig. 1.20**).

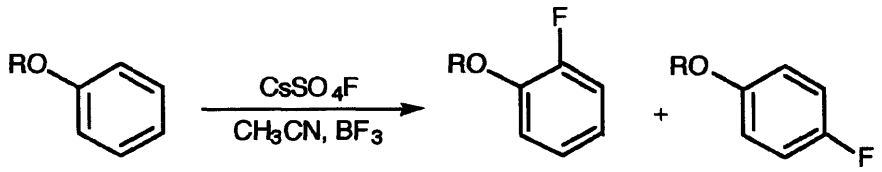
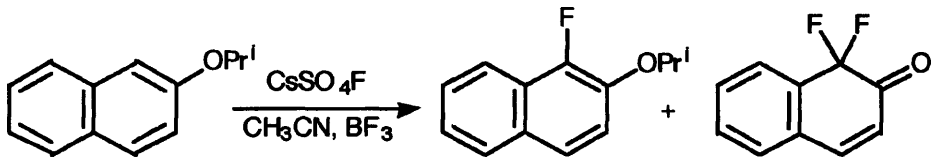


Fig. 1.20

Zupan also noticed that difluoroketones were also produced in a side-reaction with certain aromatic substrates (such as 2-*iso*-propoxynaphthalene)[94] (**Fig. 1.21**).



62 : 38

Fig. 1.21

Monofluoroketones can be synthesised by reacting caesium fluoroxysulfate with enol acetates[64,95] or ketones.[64] Caesium fluoroxysulfate also reacts with organometallic compounds such as aryltrialkyltin derivatives to give the corresponding aryl fluoride[96] in a site-selective manner (*cf.* the reaction with alkoxybenzenes above where mixtures of *ortho-* and *para-* substituted products were obtained).

Caesium fluoroxysulfate is powerful oxidant, and reactions on substrates containing heteroatoms often result in oxidation rather than fluorination[97] (**Fig. 1.22**).

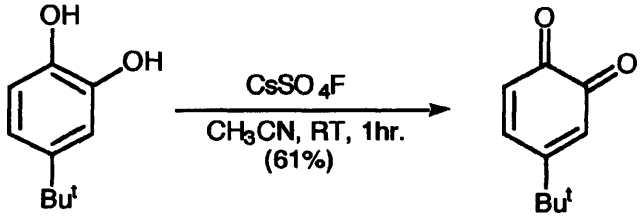


Fig. 1.22

Caesium fluoroxysulfate is prone to explode when subjected to mechanical pressure or even upon contact with a metal spatula.[94] This clearly means that the reagent is not easy to transport, and so is usually generated and purified shortly prior to use. The risk of explosion also precludes the use of this reagent in large scale reactions.

1.5.5 Elemental fluorine:

As mentioned earlier (**Section 1.4**, p 7) elemental fluorine can be a rather unselective and harsh reagent.[98] However, when it is used in high dilution and at low temperatures it may be used to effect site selective fluorination.[99] These reactions mostly result in the addition of fluorine across a polarised double bond rather than electrophilic fluorination of a nucleophile. This has successfully been used to introduce fluorine into steroids,[100] particularly where the steroid contains an α,β-unsaturated carbonyl group.[101] Addition of

fluorine across a carbon-carbon double bond is used in one of the most important industrial applications of elemental fluorine. This is the synthesis of 5-fluorouracil[102,103] (1) (**Fig. 1.23**), which is an important anticancer chemotherapeutic agent. It is also the key intermediate for several other anticancer chemotherapeutic agents.

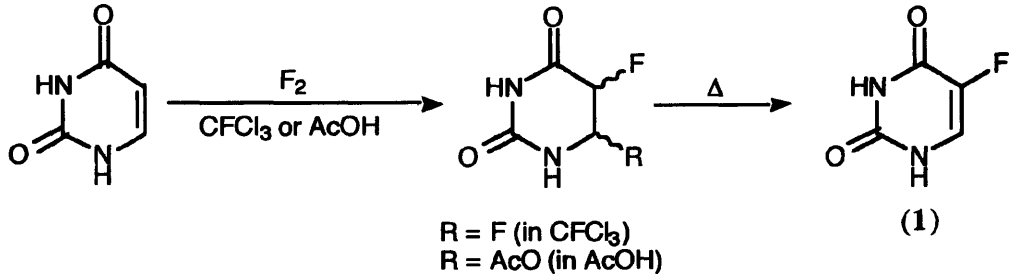


Fig. 1.23

Until recently, reactions of elemental fluorine with nucleophiles was limited to such substrates as organotin compounds,[90,104] silyl enol ethers[105] and pyruvic acid derivatives[106] (**Fig. 1.24**). When the substrate possesses substantial enol character (R = Ar or acyl), fluoro pyruvates were isolated in moderate to good yields, but where the enol content was low (R = Alkyl), a complex mixture of products was formed.

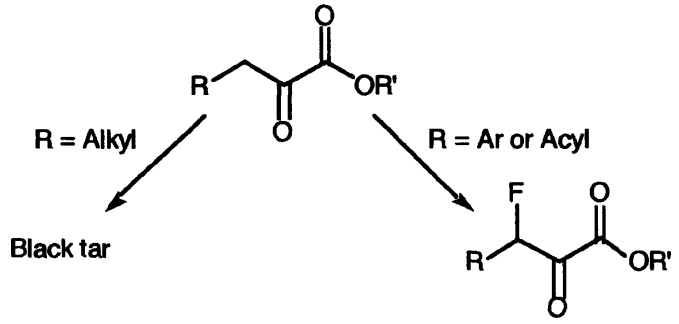


Fig. 1.24

Rozen has described remote functionalisation during the fluorination of cyclohexanol derivatives[107] (**Fig. 1.25**). This was followed by a similar studies on acyclic compounds,[108] rings of various sizes[109] and the use of carbonyl as the remote activation group.[110] This work is summarised in two, more recent, publications.[111,112]

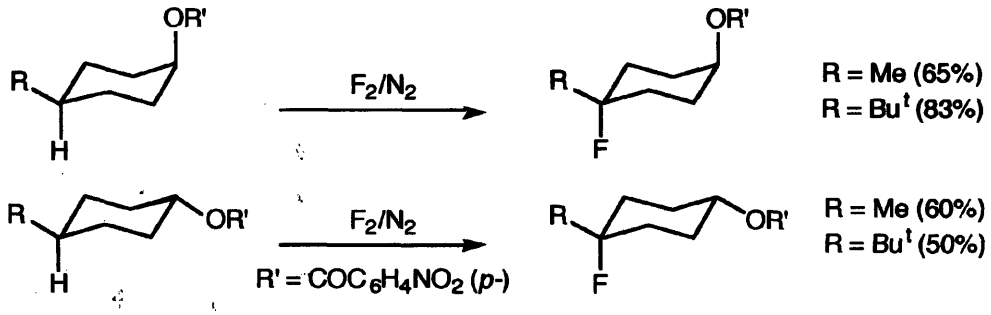


Fig. 1.25

Much progress has been made recently by Chambers and co-workers in "taming" elemental fluorine as a useful source of electrophilic fluorine. They have shown that the fluorination of aromatic compounds is best achieved by using strong protonic acids as the solvent for the reaction. By bubbling a stream of 10% fluorine in nitrogen through a solution of 4-fluorobenzoic acid in formic acid at room temperature they obtained 3,4-difluorobenzoic acid in 66% yield.[113] This is increased to 84% when concentrated sulfuric acid is used as a solvent.[114] The same procedure has been used to monofluorinate 1,3-dicarbonyl compounds (cyclic and acyclic) in 10% to 90% yields.[115] The lower yields were due to side-products formed by fluorination in the 2- or 4-position (**15** and **16** respectively) (**Fig. 1.26**). Difluorination at the 2-position was more of a problem for the cyclic diketones.

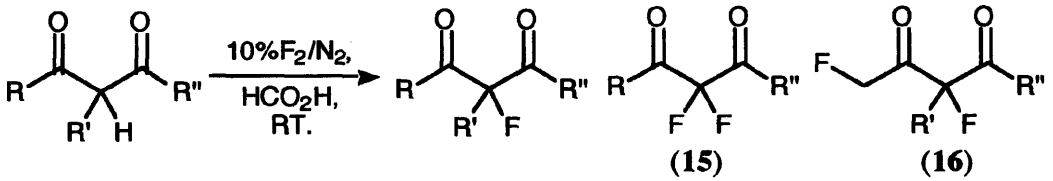


Fig. 1.26

Chambers later reported that diesters, such as malonates do not react with fluorine under these conditions,[116] although the sodium salts of some malonates were successfully fluorinated at –15 °C in acetonitrile.[117] In the same article he proposes a concerted reaction mechanism for the conversion where fluorine reacts with the enol form of the dicarbonyl compound (**Fig. 1.27**). The cyclic 2-fluoro-1,3-diketones were reported to crystallise in the enol form, of which crystal structures have been obtained.[118]

Fig. 1.27

Using acetonitrile as a solvent for room temperature fluorination of 1,3-dithiolanes Chambers has reported yields of 52% to 68% for the formation of the corresponding *gem*-difluorides[119] (**Fig. 1.28**). Iodine is used as a catalyst for this reaction.

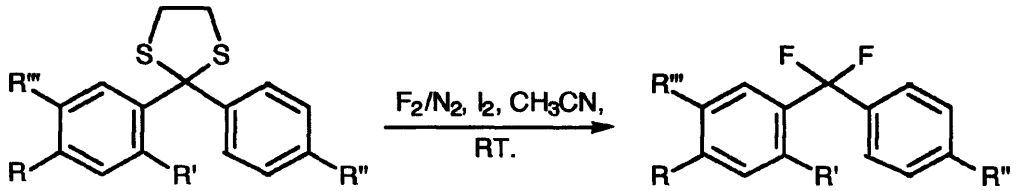


Fig. 1.28

The yields for these reactions were optimised further and reported as 69% to 87% in a later article.[120] There was no reaction when R''' = CF_3 or when R = NO_2. The reaction is probably effected by IF, formed *in situ*, rather than by F_2. The I_2/F_2 mixture has also been used to iodinate aromatic systems.[121]

Elemental fluorine is a gas at well below room temperature (b.p. –188·0 °C)[39] and is extremely toxic.[122] Contact with organic compounds at room temperature may result in combustion due to the powerfully oxidative nature of this reagent. Should elemental fluorine come into contact with the skin, a severe thermal burn may result. This can be further complicated by the hydrolysis of the fluorine into hydrogen fluoride by moisture on the skin surface. The dangers of hydrogen fluoride burns have already been mentioned (**Section 1.3**, p 5).

1.5.6 N–F Fluorinating reagents:

In this class of electrophilic fluorinating reagents[123,124] the fluorine atom is attached to a nitrogen atom which is, in turn, attached to an electron withdrawing system such as a carbonyl or sulfonyl group (**Fig. 1.29**).

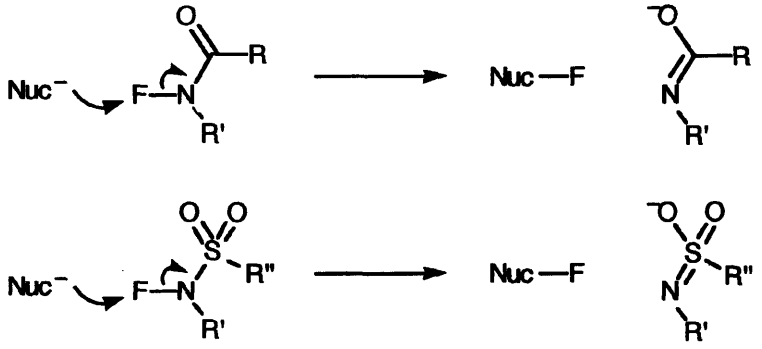


Fig. 1.29

Alternatively the fluorine may be attached to a quaternary ammonium atom with a positive charge (**Fig. 1.30**).

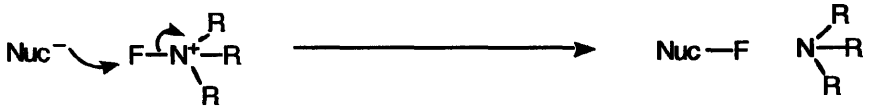


Fig. 1.30

There has been much activity in this area over the past ten years with many different reagents being developed. It is the aim of this project to investigate the reactivity of one of the latest of these reagents with particular emphasis on the site-selective fluorination of organic compounds.

The N–F reagents are usually reasonably stable liquids or solids. This means that they can be weighed more easily into a reaction, and the precise amount of reagent added can be known. Their greater stability also means that they can be handled and transported without undue risk.

1.6 A brief history of the N–F fluorinating reagents

1.6.1 The early N–F fluorinating reagents:

In 1949 Simons synthesised perfluoro-*N*-fluoropiperidine (**17**) as a colourless, volatile liquid (b.p. 49 °C) in 8% yield by ECF of pyridine.[125] In 1962 the yield was increased to 14% by using 2-fluoropyridine in place of pyridine[126] (**Fig. 1.31**). This was the first compound reported for use as an N–F fluorinating reagent.[127]

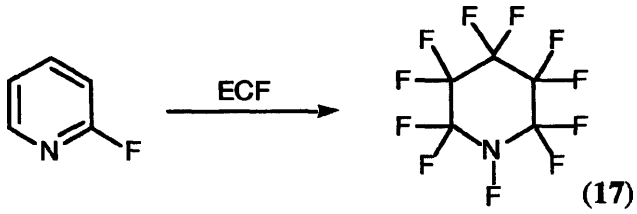


Fig. 1.31

A major drawback with this reagent is the fact that the compound (**18**) which results from nucleophilic attack is, itself, susceptible to attack by nucleophiles[128,131] (**Fig. 1.32**).

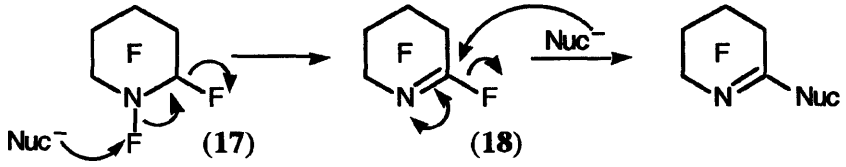


Fig. 1.32

In 1957 Simmons' group synthesised perfluoro-*N*-fluoromorpholine (**19**) by performing ECF on morpholine[129] (**Fig. 1.33**). The synthesis was optimised by Burling in 1964 to give a 14% yield of the N–F compound.[130] This is also a colourless, volatile liquid (b.p. 35 °C).

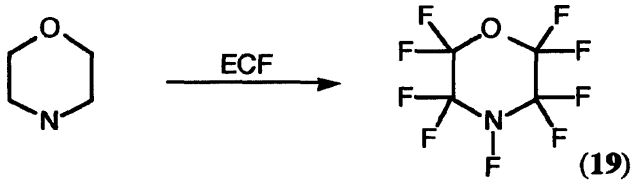


Fig. 1.33

Both of these reagents are stable liquids with long shelf-lives, but they were not very widely used. This lack of use was due to their high cost and the difficult nature of preparation (ECF is carried out in anhydrous hydrogen fluoride). Their reactions with nucleophiles (such as enol ethers, sodium malonates and organometallic compounds) usually proceeded in poor (often <50%) yields.[128,130,131] However, a suitable alternative was not discovered until 1983.

1.6.2 *N*-Fluoro-2-pyridone:

In 1983 Purrington and Jones synthesised *N*-fluoro-2-pyridone (**20**)[132] (**Fig. 1.34**) and demonstrated its use as an electrophilic fluorinating reagent.

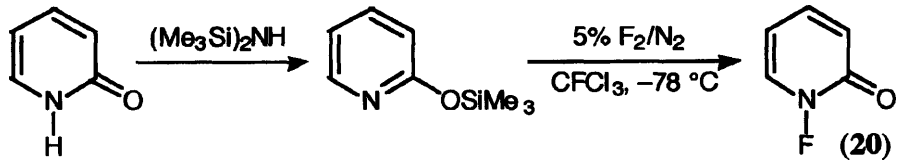


Fig. 1.34

This reagent is a non-toxic, non-explosive solid (m.p. 50-53 °C), but it is not stable enough for long term storage. In fact its shelf-life is only one week when stored in a domestic freezer. The reagent also gave poor yields when reacted with nucleophiles such as sodium malonates and organometallic compounds.[132,133] However, the short shelf life and poor reaction yields have detracted from the usefulness of this reagent.

1.6.3 Barnette reagents:

In 1984 Barnette synthesised a series of *N*-fluorosulfonamides[134] (**Fig. 1.35**).

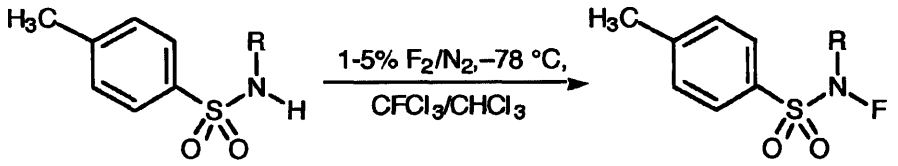


Fig. 1.35

The yields for this reaction varied from 5% (R = cyclohexyl) to 59% (R = Me). The preparation yield for the reagent where R = Bu^t was only 14%, but this reagent was the most effective for the fluorination of nucleophiles.

The Barnette reagents reacted in yields of up to 90% with nucleophiles such as enol acetates, metal salts of alkylnitro compounds organometallics, and aromatic rings. The reagent also fluorinated vinyl lithium compounds with retention of configuration.[135]

The first useful and commercially available N–F fluorinating reagent had arrived, but the poor yield in its preparation meant that it was quite expensive.[136]

1.6.4 *N*-Fluoropyridinium salts:

In 1947 Simons used pyridine and 2-fluoropyridine as moderators (see also **Section 1.5.3** Hypofluorites above) in liquid phase aromatic substitutions at low temperatures.[137] The structures of the intermediates in these reactions were not specified.

In 1963 Banks and Thomas noticed that the fluorinated pyridine solution underwent an exotherm at –30 °C when allowed to warm up slowly.[138] They postulated that a pyridine:fluorine complex was responsible for the fluorination reaction (**Fig. 1.36**).

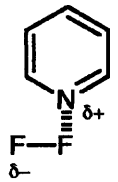


Fig. 1.36

In 1965 Meinert reported the preparation of $(Py–F)^+ F^-$ as a colourless precipitate[139] which was only stable at temperatures below –2 °C. Above this temperature the compound violently decomposed to give a brown oil containing 2-fluoropyridine.

No further investigation of this area was reported until 1983 when Gakh generated the complex and reacted it *in situ* with anions of alkylnitro compounds.[140] He demonstrated that reaction occurred at the ring rather than at the fluorine atom to give 2- or 4-pyridyl derivatives of the starting nitro compounds.

In 1986 a breakthrough came when Umemoto prepared some stable *N*-fluoropyridinium compounds.[141,142,143] This was achieved by replacing the fluoride counter-ion with a non-nucleophilic one such as triflate or tetrafluoroborate (**Fig. 1.37**).

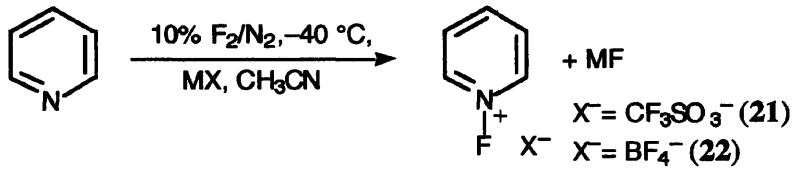


Fig. 1.37

In the studies it was found that the triflate (**21**) (80% preparation yield) was most reactive of the salts.[142] Several substituted pyridines were also investigated, the most reactive of which was found to be 1-fluoro-2,3,4,5,6-pentafluoropyridinium triflate.[144,145] This was even capable of fluorinating benzene.[146] These reagents were used to perform fluorination on aromatic rings, enol ethers, sodium malonates and organometallic compounds. Yields for these reactions were poor to excellent.[142,143,147] Good yields were also obtained in the fluorination of some alkyl-arylsulfides[148] (**Fig. 1.38**).

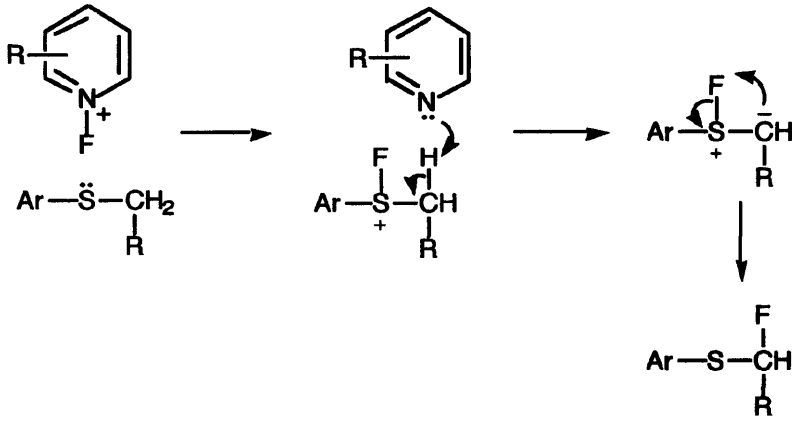
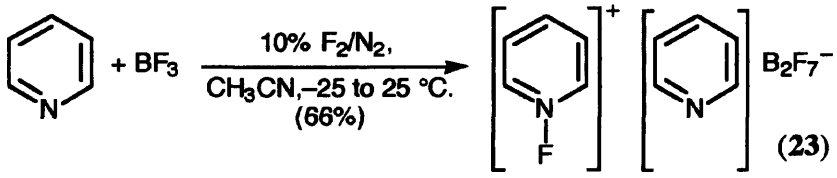


Fig. 1.38

Umemoto's group suggested that all fluorination reactions using pyridinium fluorides proceed *via* a SET mechanism[146,148] similar to that of xenon difluoride (p 9), but they did not offer any reasons for this.

In 1990 Van Der Puy and his group synthesised and patented *N*-fluoropyridinium heptafluorodiborate or Accufluor™ NFPy[149] (**23**) (**Fig. 1.39**). This reagent reacted with enol compounds in good to excellent yields.[150]



(**23**)

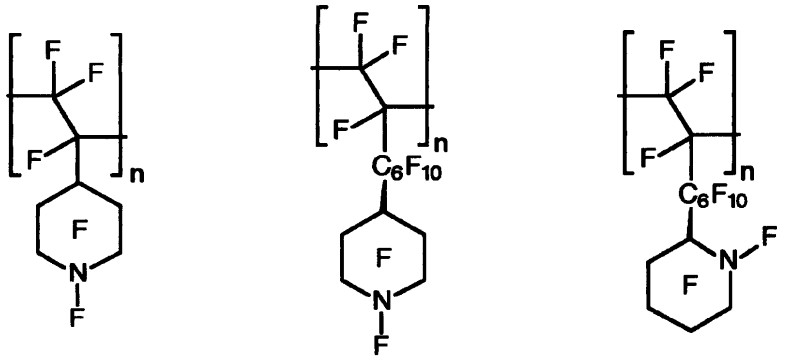
Fig. 1.39

The melting point of this complex (m.p. = 196-197 °C) suggested that it was unlikely to be the same compound as that isolated by Umemoto [m.p. for $(Py–F)^+$ BF_4^- is 90-91 °C].[142]

So it can be seen that this class of electrophilic fluorinating reagents is reactive enough to be useful in many reactions, but stable enough to store for reasonable periods.

1.6.5 Polymeric N–F fluorinating reagents:

In 1986 Banks reported the use of some polymeric electrophilic fluorinating reagents.[151] It was hoped that these reagents could be used as a recyclable source of fluorine. These contained a perfluoro-*N*-fluoropiperidine group as the active site. This was attached to a cross-linked perfluoroalkyl backbone (**Fig. 1.40**).



(**24**) (**25**) (**26**)

Fig. 1.40

The presence of the perfluoro-*N*-fluoropiperidine group means that these reagents were also prone to the side reaction (see **Fig. 1.32**, p 18) which removes the electrophile from the reaction mixture. Indeed, the sodium salt of diethyl phenylmalonate was fluorinated with a yield of only 23% in the best case when using polymer **26**.

1.6.6 *N*-Fluorosulfonamides and sulfonimides:

These were introduced in 1987 by DesMarteau.[152] He prepared a series of *N*-fluorobis[(perfluoroalkyl)sulfonyl]imides (**Fig. 1.41**).

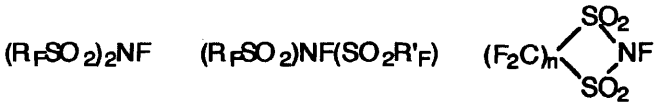


Fig. 1.41

The most efficient and the most reactive of these compounds was found to be the first in the series, *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (**27**) (**Fig. 1.42**).

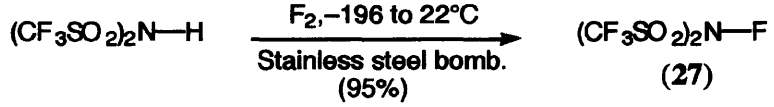


Fig. 1.42

N-fluorobis[(trifluoromethyl)sulfonyl]imide (**27**) is a stable, colourless liquid (b.p. 90-91 °C) and reacts with aromatic compounds[152,153] (including benzene) sodium enolates,[152,154] neutral 1,3-dicarbonyl compounds,[154,155] olefins,[156] steroids[157] and cyanomethanephosphonates,[158] in good to excellent yields.

In 1989 Banks and Khazai prepared perfluoro-[*N*-fluoro-*N*-(4-pyridyl)-methanesulfonamide] (**28**)[159] (**Fig. 1.43**).

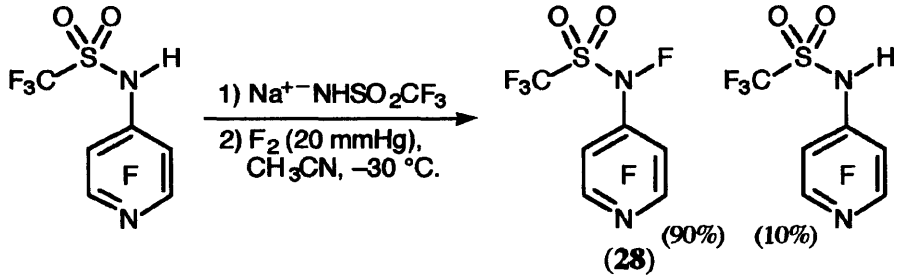


Fig. 1.43

The resulting mixture was used to effect fluorination reactions in excellent yields on sodium malonates and aromatic compounds including benzene.[160] The reactivity of **28** was found to be comparable to that of DesMarteau's reagent (**27**).

In 1991 two groups simultaneously and independently prepared fluorinating reagents based on arylsulfonylimides.

N-Fluorobis(benzenesulfonyl)imide or Accufluor™ NFSi[149] (**29**) was the reagent synthesised by Differding and Ofner[161] (**Fig. 1.44**).

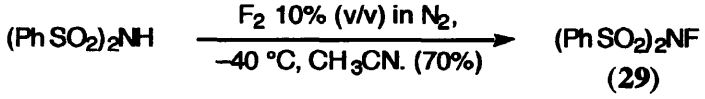


Fig. 1.44

This reagent is a stable solid [m.p.(**29**) = 114-116 °C] and gave good yields in reactions with enol ethers,[161] metal enolates,[161,162] phosphonate anions,[163] aromatic rings[161] and organometallic compounds.[161] Fluorination has also been reported γ- to a carbonyl in α,β-unsaturated ketones.[164]

In 1991 Davis and Han[165] prepared a similar reagent to that chosen by Differding and Ofner, but they combined both of the aromatic rings into one (**30**) (**Fig. 1.45**).

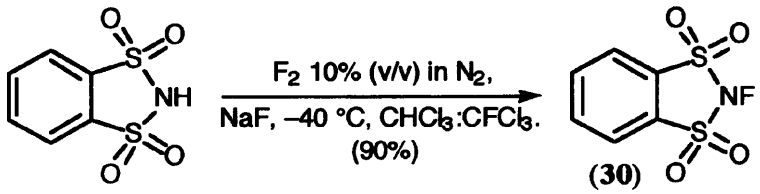


Fig. 1.45

This reagent is a stable solid [m.p.(**30**) = 139-140 °C] and gave good yields in reactions with enol ethers,[165,166] metal enolates,[165,167] including some studies using the enolates of chiral compounds[168] such as a side chain intended for the appending to the anti cancer drug Taxol.[169] Aromatic rings[165] and organometallic compounds[165,170] have also been successfully fluorinated with this reagent.

Cabrera has reported a group of N–F electrophilic fluorinating reagents which are based on oxathiazinone dioxides (**32**).[171] These are produced by the fluorination of the corresponding potassium salt, such as Acesulfam K (**31**), an artificial sweetener produced by Hoechst (Sunett®) (**Fig. 1.46**). Yields were reported as 52% to 86% for the fluorination of Grignard reagents, sodium enolates, enol acetates and activated aromatic rings.[171]

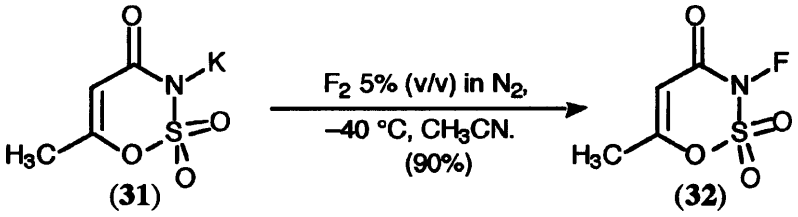


Fig. 1.46

1.6.7 *N*-Fluorosultams:

In 1988 Lang and Differding at Ciba-Geigy synthesised two camphor-derived *N*-fluorosultams.[172] These were the first enantioselective electrophilic fluorinating reagents (**Figs. 1.47** and **1.48**).

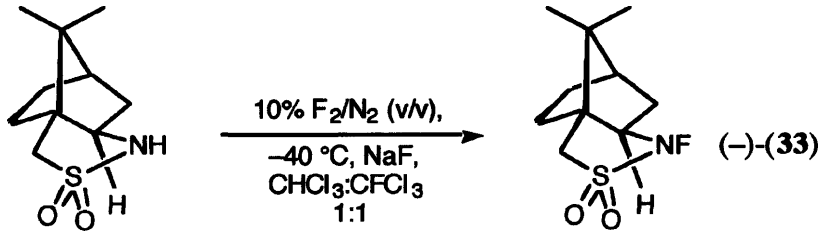


Fig. 1.47

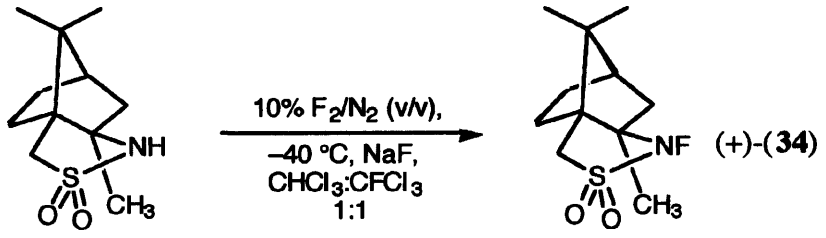


Fig. 1.48

These compounds are stable and may be stored for months without decomposition. The N–F sultam (–)-**33** reacts with metal enolates to give α-fluoroketo derivatives in reasonable to good yields. Enantiomeric excesses of ≤10% to 70% were measured for prochiral metal enolates (**Fig. 1.49**).

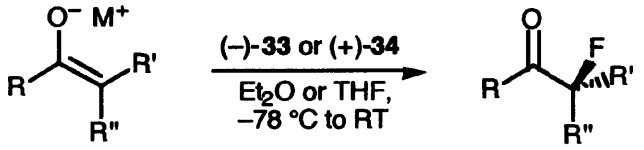


Fig. 1.49

The researchers also reported that the metal enolate was acting as a base and causing the elimination of HF (**Fig. 1.50**). They sought to eliminate this side reaction by replacing the hydrogen atom with a methyl group (+)-(**34**). However, this led to a marked decrease in the reactivity illustrated by poor (≤34%) yields, presumably due to steric crowding.

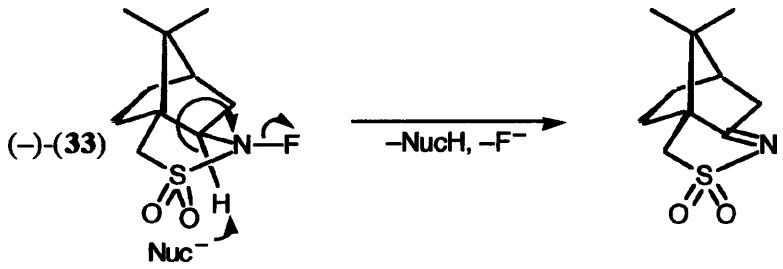


Fig. 1.50

More recently (1993) Davis has reported the synthesis and use of the dichloro-derivative of (–)-**33** as an electrophilic fluorinating reagent (**Fig. 1.51**).[173] This compound (+)-(**35**), reacts with metal enolates at –78 °C to give α-fluoroketo derivatives in good yields with enantiomeric excesses of 10% to 75% for prochiral metal enolates. The reactivity of (+)-**35** was found to be higher at –78 °C than the dihydro reagent (–)-(**33**) at room temperature. This higher reactivity at lower temperature leads to slower elimination of HF (as **Fig. 1.50**) and therefore higher yields of fluorinated products.

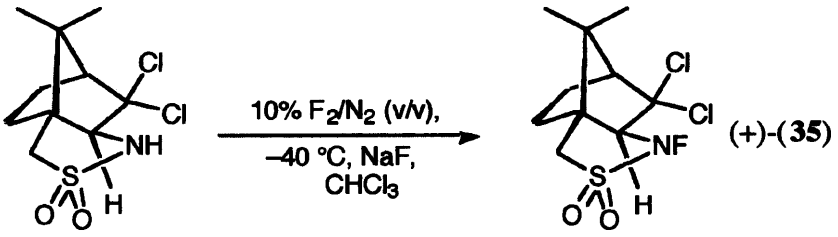


Fig. 1.51

In 1989 Lang and Differding reported a different, saccharin-derived *N*-fluorosultam[174] (**36**) (**Fig. 1.52**). This was found to be more reactive than the commercially available Barnette reagents (p 19), giving yields between 20 and 90% when reacted with metal enolates of esters and ketones.

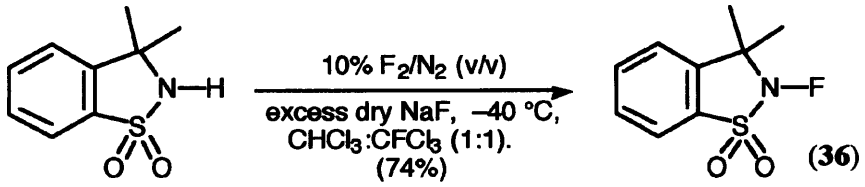


Fig. 1.52

1.6.8 *N*-Fluorolactams:

N-Fluorolactams (**Fig. 1.53**) were used by Satyamurthy[175] in 1990 as a quick and efficient way of introducing ^{18}F into organic compounds for use in positron emitting transaxial tomography[88] studies (see also acetyl hypofluorites, p 12-13).

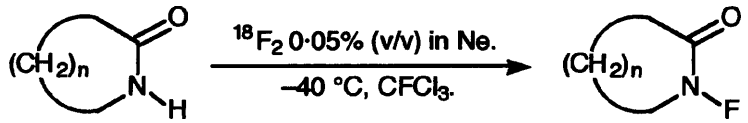


Fig. 1.53

The yields varied from 33% (n = 7) to 79% (n = 5) and radiochemical yields of 19% (n = 7) to 48% (n = 6) were achieved. The reactions with Grignard reagents proceeded in 1 to 50% yields, demonstrating that these reagents, while useful for the quick synthesis of labelled compounds, are not as synthetically useful as, for example, the perfluoro-*N*-fluorosulfonamides described above.

1.6.9 *N*-Fluorobicycloammonium salts:

The first reagent in this class was *N*-fluoroquinuclidinium fluoride (**37**). It was first synthesised in 1986 by Banks, Du Boisson, and Tsiliopoulos[176] (**Fig. 1.54**).

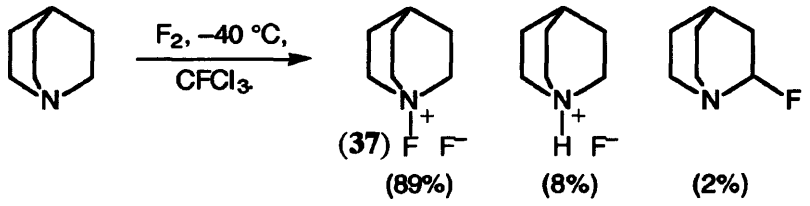


Fig. 1.54

Pure *N*-Fluoroquinuclidinium fluoride (**37**) was later isolated by the same workers[177] in 86% yield as a white, stable, non-explosive solid (m.p. = 126-128 °C).

The reagent has been used to fluorinate several types of stabilised carbanions, enamines, aromatic rings and organometallic compounds giving yields in the range of 15 to 61%.[176,177] The low yields may be attributed to one of two factors. Firstly, **37** has a poor solubility in most non-protic solvents, often leading to its use as a suspension in acetonitrile (in which it has low solubility). Secondly, it is extremely hygroscopic (see also **Section 1.3**, p 5 on the metal fluorides), increasing in weight by 10% and becoming sticky and yellow after 40 minutes in air. These properties make this reagent quite difficult to work with, so the same group developed a synthesis of the triflate salt[178] (**38**) (**Fig. 1.55**).

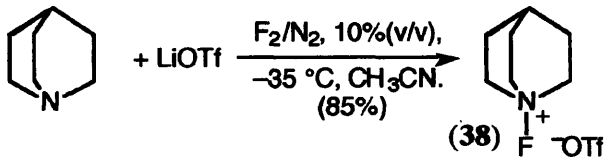


Fig. 1.55

Other salts ($CF_3CO_2^-$, $C_3F_7CO_2^-$, BF_4^-) were also prepared.[179,180] All of these salts showed a marked improvement in solubility, being significantly soluble in acetonitrile, acetone and DMSO. However, only the triflate and the tetrafluoroborate appeared to be non-hygroscopic. The increase in solubility gave rise to greatly improved yields of fluorinated products. In fact the reaction of the triflate with phenol gave a quantitative yield of fluorophenols (1:2 *o*-:*p*-).[179,180]

The second group of reagents to be developed in this class was the 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts[14,180,181] (Selectfluor™ reagents) (**Fig. 1.56**).

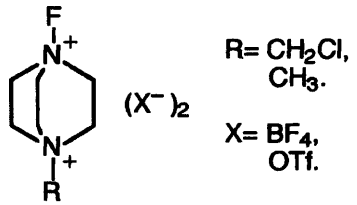
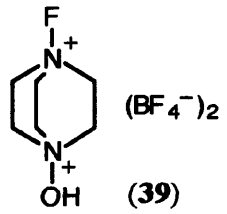


Fig. 1.56

These were developed by Banks' group at UMIST. They are stable, non-hygroscopic, non-explosive solids with a useful solubility in polar organic solvents such as acetonitrile. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (**9**) (R = CH_2Cl, X = BF_4) is now commercially available under the name of Selectfluor™ through Air Products and Chemicals Inc.[15] Since the majority of the research detailed in this thesis is related to the uses and properties of this reagent its chemistry will be outlined in greater detail in **Section 1.8.3.** (p 31).

The most recent addition to this class of electrophilic fluorinating reagents occurred in 1995 when Poss and Shia reported the synthesis of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate),[182] or Accufluor™ NFTh[149] (**39**) (**Fig. 1.57**).



(**39**)

Fig. 1.57

There are, as yet, few papers in the literature featuring this compound. The reaction with alkenes in the presence of nucleophiles has been reported[183] (**Fig. 1.58**).

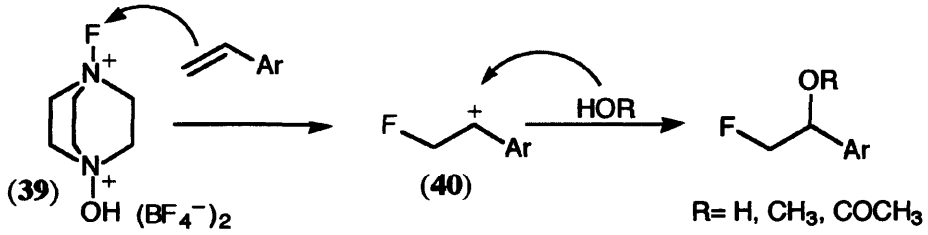


Fig. 1.58

The reaction was found to proceed with quantitative Markovnikov-type regioselectivity when carried out in acetonitrile in the presence of the hydroxy compound. The regioselectivity was dependent on the degree of stabilisation of the carbocation in species (**40**). Thus *gem*-diaryl olefins reacted with good regioselectivity, whilst *cis*- or *trans*-diaryl olefins reacted with poor regioselectivity.

The only other reference to this compound details the fluorination of hydroxy-substituted aromatic compounds (**Fig. 1.59**) and alkynes.[184]

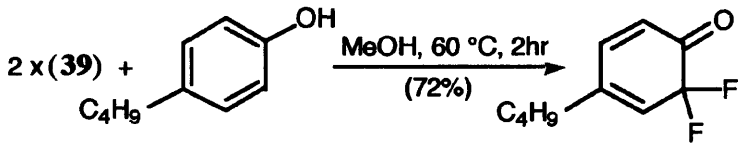


Fig. 1.59

The yields were reported to be 65-92% for the formation of the α,α-difluoroketone from 6 examples. In the same paper 4 examples of phenylalkynes were reported to form α,α-difluoroketones when refluxed with **39** in a mixture of acetonitrile and water (**Fig. 1.60**).

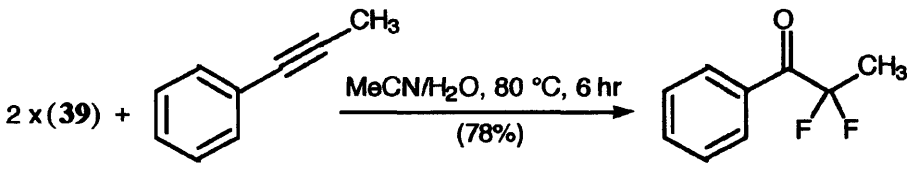


Fig. 1.60

The first step of the reaction presumably proceeds *via* a mechanism analogous to that shown in **Fig. 1.58** followed by fluorination of the resulting enol (**Fig. 1.61**). Yields of 58-78% were reported for this reaction.

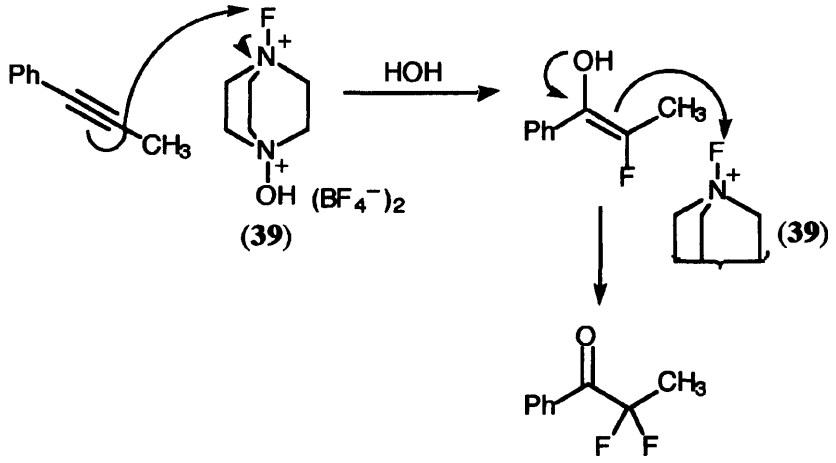
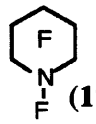
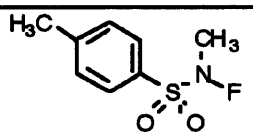
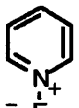
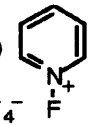
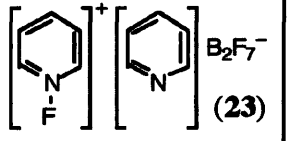
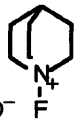
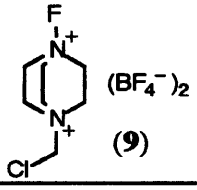
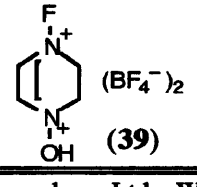


Fig. 1.61

1.7 Commercially available N–F reagents

At the time of writing there are currently nine commercially available N–F reagents. These are listed in **Table 1.1** below. The price per mole of "F+" is calculated from the price for 5 g of the reagent and is intended only as a guide. Most distributors would offer a significant reduction in price if a mole of the material was purchased. The table shows a range of £1099 /mol to £10053 /mol, with Selectfluor™ (**9**) lying third at £1275 /mol. The *N*-fluoroquinuclidinium triflate (**38**) is the most expensive whilst the two *N*-fluoropyridinium salts (**21** and **22**) are the least expensive. The reactivity of Selectfluor™ (**9**) is greater than that of the *N*-fluoropyridinium salts (**21** and **22**), so Selectfluor™ (**9**) is one of the most cost effective electrophilic fluorinating reagents currently available commercially.

Compound	Melting point Boiling point	$\delta(^{19}F)$ ppm (Solvent)	Supplier	Cost per 5g	Cost per mol "F+"
 **(17)**	b.p. 49 °C	−112·2 ($CFCl_3$)	FC[a]	£90	£5095
	m.p. 42-44 °C b.p. 90 °C/0·01Torr	−37·6 ($CDCl_3$)	ALD[b] FC PCR[c]	£64	£2601
(21) 	m.p. 185-187 °C	+48·8 (CD_3CN)	ALD FC PCR	£23	£1551
(22) 	m.p. 197-198 °C	+49·4 (CD_3CN)	ALD FC PCR	£20	£1099
 **(23)**	m.p. 196-197 °C	+48·2 (CH_3CN)	ALD AS[d] FC PCR	£24	£1593
$(PhSO_2)_2N{-}F$ **(29)**	m.p. 114-116 °C	−37·8 (N/A)	ALD AS FC PCR	£18	£1135
(38) 	m.p. 266-268 °C	+58·0 (D_2O)	FC	£180	£10053
 **(9)**	m.p. 234 °C (Dec.)	+49·0 (D_2O)	ACR[e] AP[f] ALD FC	£30 £18	 £1275
 **(39)**	m.p. 120 °C (Dec.)	+41·0 (D_2O)	AS	N/A	59.0g "F+"/kg

[a]Fluorochem Ltd., Wesley Street, Old Glossop, Derbyshire, SK13 9RY, UK; [b]Aldrich Chemical Company, 1001 West St Paul Ave, Milwaukee, WI 53233, USA; [c]PCR Inc., A Division of Harris Speciality Chemicals Inc., P.O. Box 1466, Gainesville, FL 32602, USA; [d]AlliedSignal Inc., Buffalo Research Laboratory, 20, Peabody St., Buffalo, NY 14210, USA; [e]Acros Organics, Belgium (Distributors: Fisher Scientific, 50 Fadem Road, Springfield, NJ 07081-3193, USA); [f]Air Products and Chemicals Inc., 7201, Hamilton Boulevard, Allentown, PA 18195-1501, USA.

Table 1.1
Details of the commercially available N–F reagents

1.8 Reactions of the N–F reagents

1.8.1 S_N2 versus SET

Differding has suggested that a SET, rather than S_N2 process may be taking place in the fluorination of carbanions with reagents of the N–F class. In the fluorination of a citronellic ester enolate with various N–F reagents and xenon difluoride he found that the products (**43** and **44**) expected from the radical intermediates (**41** and **42**) were only isolated when the fluorination was carried out using xenon difluoride[185] (**Fig. 1.62**).

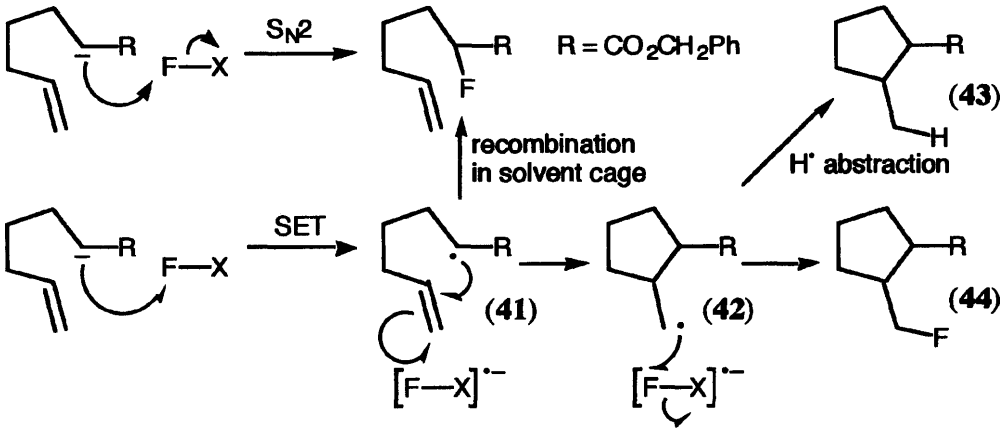


Fig. 1.62

In a subsequent publication, Differding calculated the expected rates of reaction for a series of fluorination reactions.[186] He then compared the expected rates to the experimental rates. The results suggested that SET may be occurring as a competing reaction, but that S_N2 was faster in most cases. He has also performed a study on the electrochemical reduction of the N–F bond of several of the N–F class of electrophilic fluorinating reagents.[187] The results of this study suggested that an SET pathway is indeed possible for the more oxidising members of the N–F class of fluorinating reagents.

1.8.2 N–F reagents compared:

The electrochemical reduction potential of the N–F bond has also been shown to have a good correlation with the reactivity of the reagent towards the fluorination of aromatic compounds.[188] Listed below in order of decreasing reduction potential, and hence decreasing reactivity, are the N–F compounds which were studied (**Table 1.2**).

Reagent	Section	Page	E_p (V)
N-Fluorobis[(trifluoromethyl)sulfonyl]imide (**27**)	**1.6.6**	22	+0·18
1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (**9**)	**1.6.9**	27	–0·04
1-Fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octane ditriflate	**1.6.9**	27	–0·09
N-Fluoropyridinium pyridine heptafluorodiborate (**23**)	**1.6.4**	21	–0·34
N-Fluoroquinuclidinium triflate (**38**)	**1.6.9**	26	–0·37
N-Fluoropyridinium triflate (**21**)	**1.6.4**	20	–0·47
N-Fluorobis(benzenesulfonyl)imide (**29**)	**1.6.6**	23	–0·78
N-Methyl-*N*-fluoro-*p*-toluenesulfonamide	**1.6.3**	19	–2·10
N-Propyl-*N*-fluoro-*p*-toluenesulfonamide	**1.6.3**	19	–2·20

Table 1.2
Peak reduction potentials of selected electrophilic fluorinating reagents recorded in acetonitrile against a saturated calomel electrode.

It can be seen from these results that the Selectfluor™ reagent (**9**) should be among the more reactive of the N–F reagents. However, at the start of this project, the reactivity of this new reagent had not been investigated fully, so the aim of this work was to investigate the synthetic scope and limitations of the Selectfluor™ reagent (**9**).

1.8.3 Known reactions of Selectfluor™:

The Selectfluor™ reagent is prepared in good yield over three steps from the cheap and widely available diazabicyclo[2.2.2]octane (DABCO®) (**45**) which is sometimes known as triethylene diamine (TEDA) (**Fig. 1.63**).[180,189]

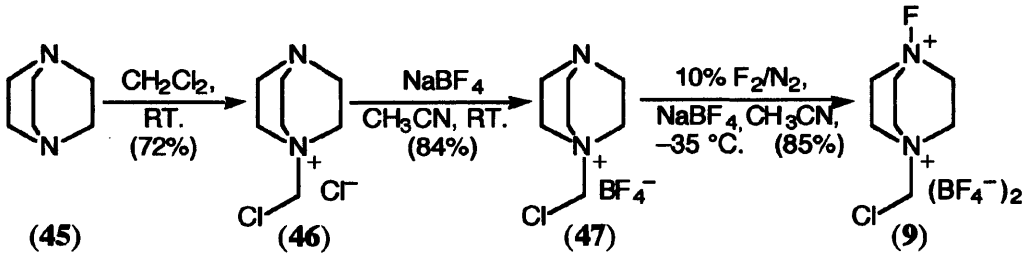


Fig. 1.63

Since the start of this project several articles have been published on the chemistry of the Selectfluor™ reagent. The earlier publications[14,181,189] gave one or two examples of the chemistry of a several classes of reactions, such as fluorination across double bonds and fluorination of enol ethers, β-diketocompounds, aromatics and organometallics. The initial findings were encouraging, so articles on the different aspects of this reagent began to appear worldwide. Zupan and co-workers have published the results of their studies on the addition of fluorine and a nucleophile across multiple bonds. The first of these detailed

the reaction with aryl substituted alkenes (**48**) in the presence of alcohols, to give *vicinal*-fluoroethers (**49** and **50**) (**Fig. 1.64**).[190] The absence of significant amounts of (**50**) where one or both R'' and R''' are alkyl demonstrated a Markovnikov-type addition, supporting the hypothesis that an α-fluorocarbocation intermediate is formed (see **Fig. 1.58**, p 27). This is attacked by the hydroxyl group to give (**49**). Yields in the region of 90% were reported.

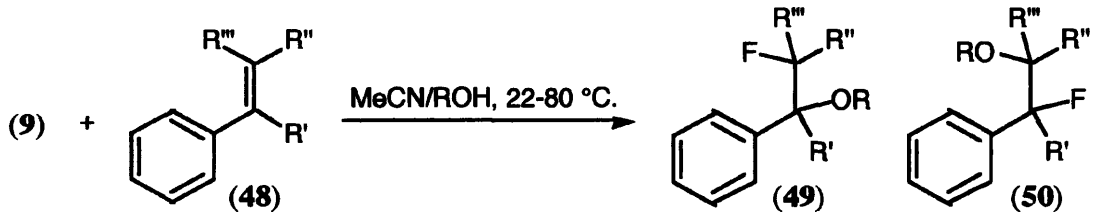


Fig. 1.64

The study of this reaction was later expanded to investigate the stereochemical aspects of the addition.[191] It was found that there is very little, if any, control over the stereochemistry, suggesting that the carbocation may react with the alcohol from either face, with no 1,2-stereocontrol from the adjacent chiral centre.

This reaction has been used by Lal and co-workers to fluorinate pyrimidines such as uracil (**51**) (*cf.* **Fig. 1.23**, p 15) and thymine (**52**) (**Fig. 1.65**).[192]

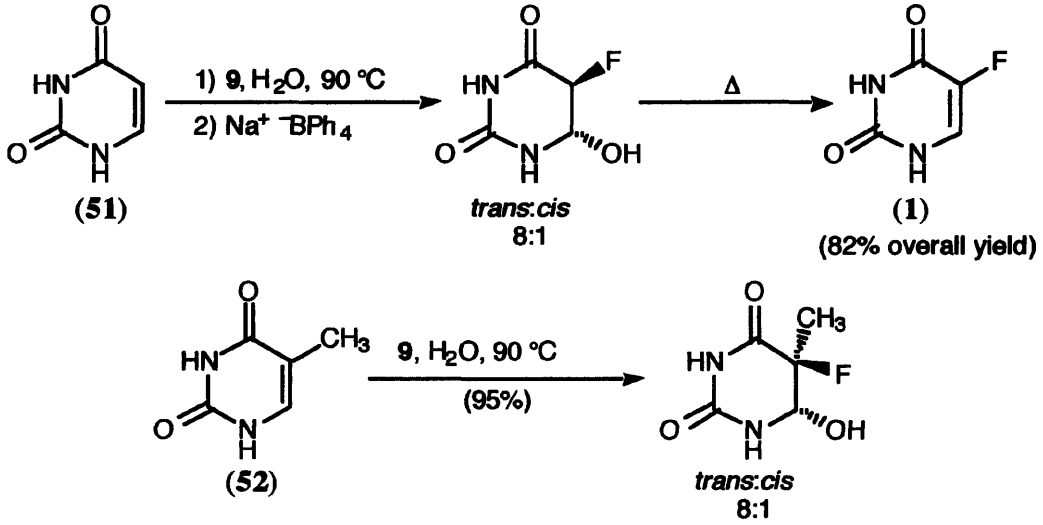


Fig. 1.65

In 1995 Zupan reported that phenylalkynes react with Selectfluor™ (**9**) in the presence of water to form α,α-difluoroketones (**Fig. 1.66**). Four examples were given with yields quoted as 36% (R = H) to 51% (R = Ph).[193] The mechanism is analogous to that proposed for the same reaction using Accufluor™ NFTh (See **Figs. 1.58** and **1.61**, p 27-28 and Ref:[184]).

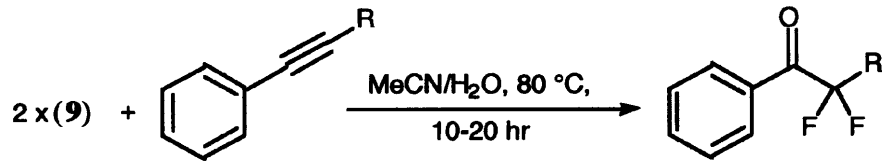


Fig. 1.66

Selectfluor has been shown by Lal to α-fluorinate sulfides.[181] This reaction has been used to introduce fluorine into the carbohydrate rings of nucleosides (**Fig. 1.67**).[12]

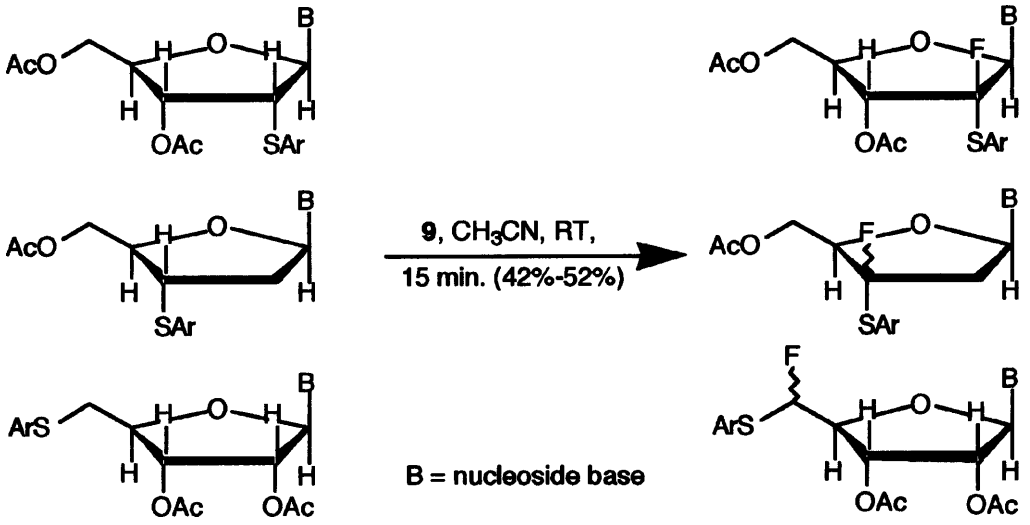


Fig. 1.67

Site-specific fluorination of aromatic compounds can be achieved by the reaction of **9** with an aryl-metal compound such as a Grignard reagent. Unactivated aromatic compounds such as benzene can be fluorinated by Selectfluor™ (66% yield of fluorobenzene),[14] but greater yields are obtained when there is an activating group on the ring (**Fig.1.68**).[181]

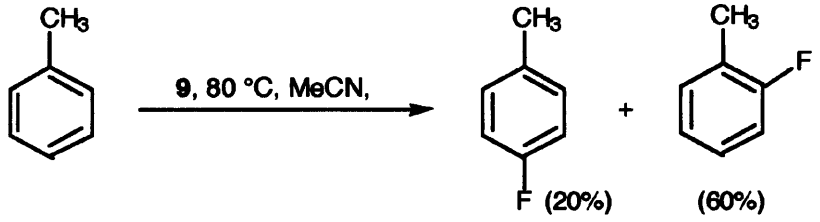


Fig. 1.68

This reactivity has been used to synthesise an analogue (**53**) of a recently introduced drug, an anthraquinone carboxylic acid, diacetyl rhein (**54**) (**Fig. 1.69**).[194] This drug (**54**) has been used for the treatment of osteoarthritis.[195] The preparation of analogues of this compound is important for the *in vitro* and *in vivo* profiling of the parent drug.

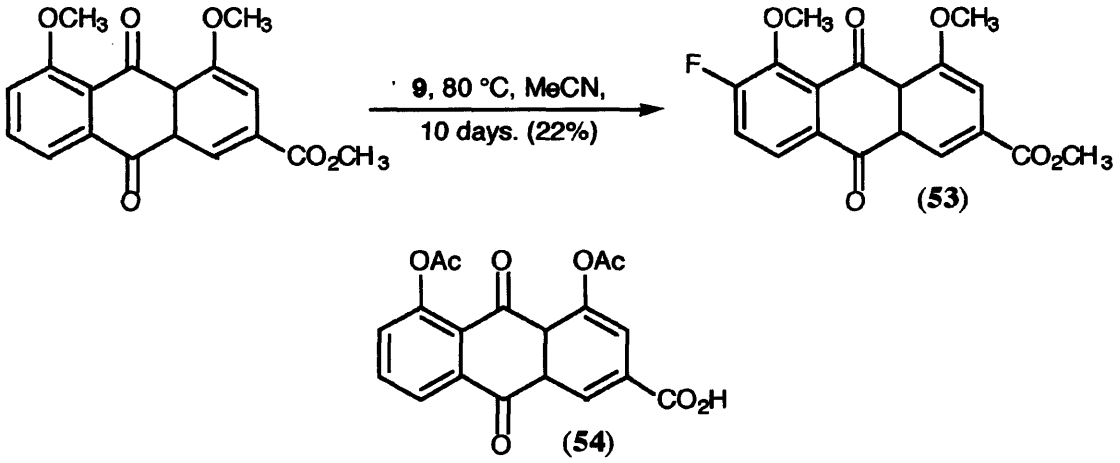


Fig. 1.69

Zupan has shown that the ease of fluorination and the resulting products can be influenced by the solvent used for the reaction.[196] Naphthalene may be fluorinated in 30% yield (to both 1- and 2-fluoronaphthalene) by Selectfluor™ in refluxing acetonitrile after 24 hours. A 75% yield was reported for the same reaction carried out in trifluoroacetic acid at 70 °C with a 4 hour reaction time. Phenanthrene also gave a 75% yield, but the reaction of anthracene produced an unexpected trifluoroacetoxylated product (**55**) (**Fig. 1.70**).

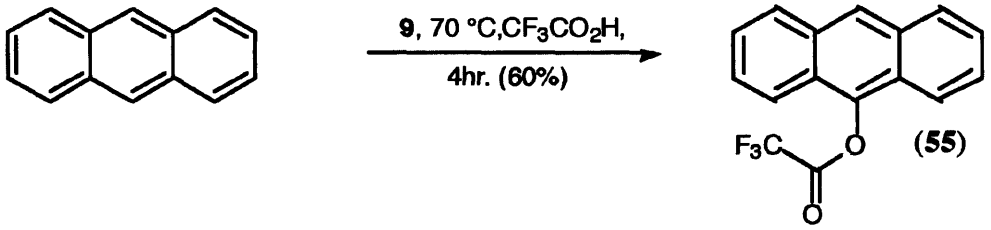


Fig. 1.70

The choice of solvent also influenced the outcome of the fluorination of 9-methoxyphenanthrene with three different products resulting from the use of three different solvents (**Fig. 1.71**). Similar results were found for the fluorination of 9-hydroxyphenanthrene, but the order of addition of the reagents as well as the solvent and stoichiometry used also determined which product was formed.

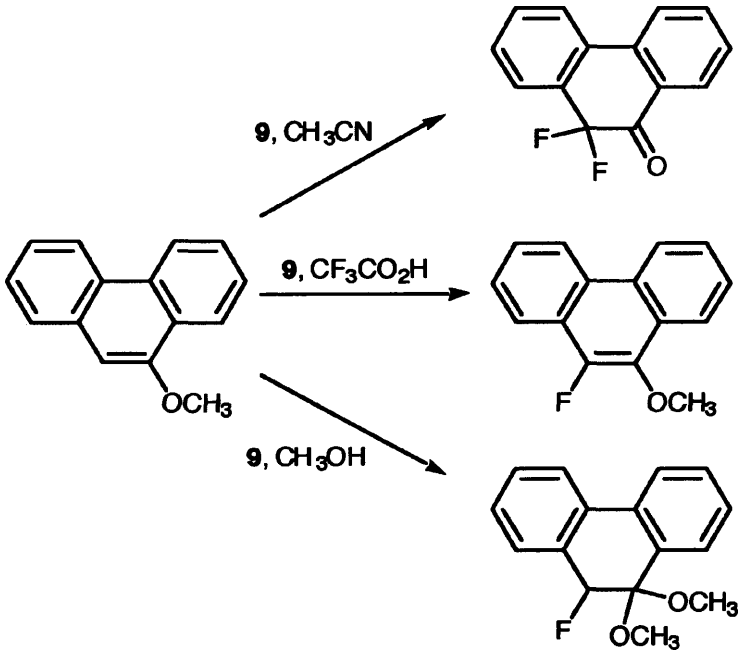


Fig. 1.71

In 1995 two separate groups reported the use of Selectfluor™ as a reagent for fluorodecarboxylation of aromatic rings. The first publication described the fluorodecarboxylation of bromofuroic acids (**56** and **59**) to form bromofluorofurans (**57** and **60**).[197] These bromofluorofurans were reported as unstable, so were derivatised *in situ* by reaction with butyl lithium and then *N*-methyl-*N*-methoxybenzamide to form the desired benzoylfluorofurans (**58** and **61**) (**Fig. 1.72**).

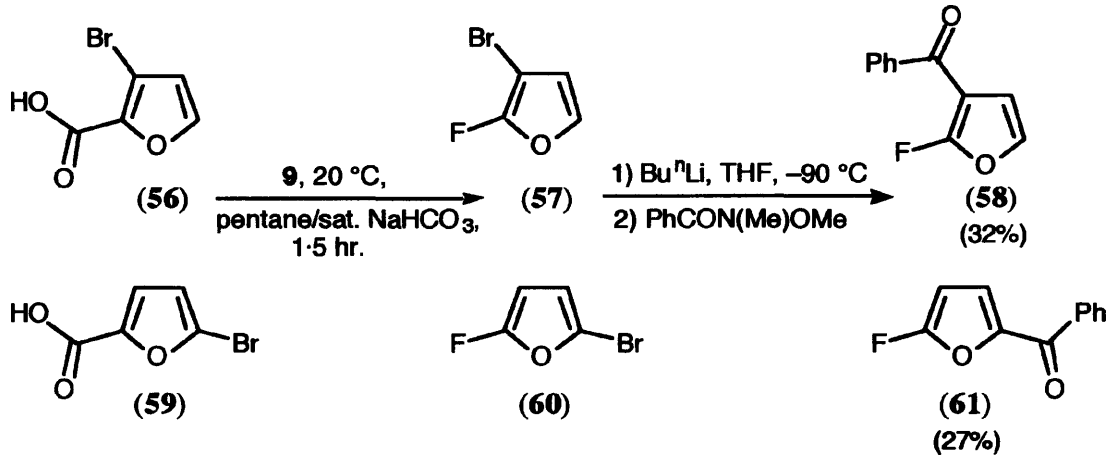


Fig. 1.72

The other fluorodecarboxylation reaction was used to introduce fluorine into a pyrrole ring.[198] Seven examples were given with yields in the range 32% to 47%. One of these examples is illustrated in **Fig. 1.73**.

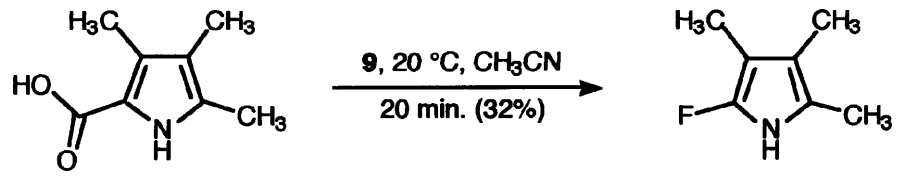


Fig. 1.73

Selectfluor™ has been shown by several research groups to react favourably with organostannanes. Such reactions have been used by McCarthy and co-workers to form vinyl fluorides from vinyl stannanes. Yields between 42% and 74% were reported.[199]

2- and 3-(Trialkylstannyl)indoles have been converted to 2- and 3-fluoroindoles by Widdowson and co-workers (**Fig. 1.74**).[200]

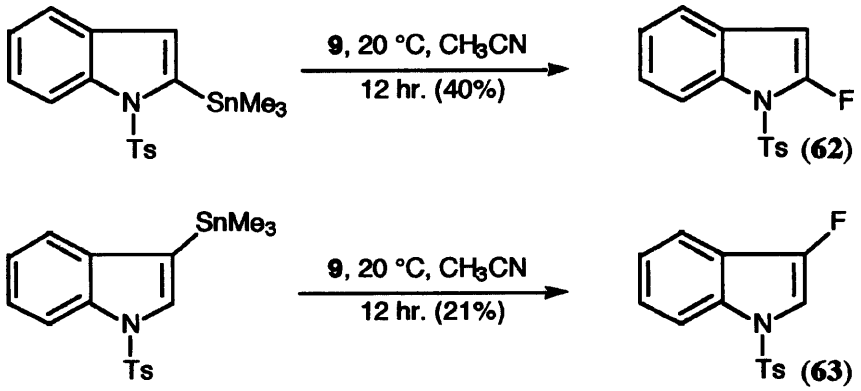


Fig. 1.74

Improved yields [61% and 72% for (**62**) and (**63**) respectively] were reported for the fluorination when caesium fluoroxysulfate was used in place of Selectfluor™. However, the serious drawbacks associated with the use of caesium fluoroxysulfate have already been emphasised. A similar result was found when the same research group used Selectfluor™ to fluorinate 4-(trimethylstannyl)steroids.[201]

5-Fluorocyclopentadiene has been synthesised from the reaction of Selectfluor™ with cyclopentadienylthallium.[202] Yields of up to 35% were reported, but the compound was unstable, so was not isolated.

2. Results and discussion

"Προαιρεισθαι τε δει αδυνατα εικοτα μαλλον η δυνατα απιθανα. "
"Probable impossibilities are to be preferred to improbable possibilities."
-Aristotle, *Poetics*.

The Selectfluor™ reagent (**9**) was synthesised in three steps from TEDA (**45**) with an overall yield of 84%. This procedure is outlined in section **2.1** below.

The properties and reactivity of the Selectfluor™ reagent (**9**) were then investigated. The results of these reactions are given in sections **2.2** to **2.7**. Conclusions are outlined in section **2.8**.

2.1 Synthesis of the Selectfluor™ reagent

This was achieved using a slight modification of the method developed by Iqbal Sharif,[180] giving an improved overall yield of **9** (78% compared to the previous 51%) (**Fig. 2.1**).

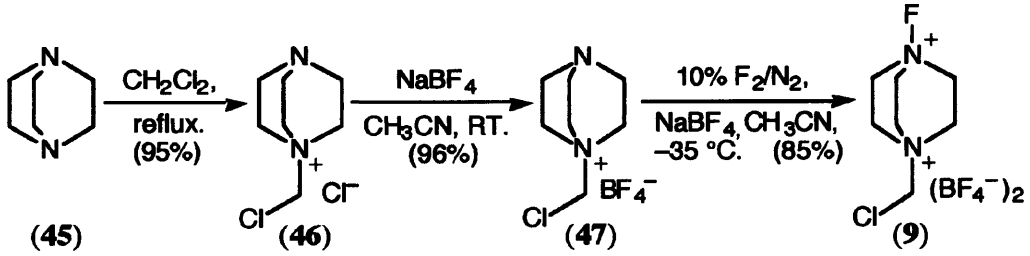


Fig. 2.1

In this procedure **45** was heated under reflux in dichloromethane for 2 hours, then the product was collected by suction filtration, and the filtrate was refluxed for a further 20 hours. This was the first departure from the method developed by Iqbal Sharif,[180] in which **45** was stirred in dichloromethane for 20 hours at room temperature to give **46** as a white crystalline solid. The yield for this step was thus improved to 95% (from 72%). It was not possible to obtain a completely satisfactory combustion analysis. This was probably due to the extremely hygroscopic nature of this compound. Other analytical data (such as m.p., mass spectrum, ^{1}H and ^{13}C NMR) were identical to those reported earlier.[180]

An improved yield was also obtained for the second step of the synthesis. This was achieved by stirring the slurry of **46** and sodium tetrafluoroborate in acetonitrile at 40 °C for 3 hours, then at room temperature for 3 days. In the original method the reaction was stirred at room temperature for 20 hours. The solution of **47** in acetonitrile was removed from the sodium chloride by suction filtration, and then used directly in the fluorination

reaction. In this way the yield was improved from the original 84% to 96%. The concentration of the solution was assayed by taking an accurately measured volume of the solution and concentrating it *in vacuo*. The solid thus obtained was dried *in vacuo* to constant weight. The total yield was calculated from this value for the concentration and the total volume of the solution obtained in the reaction. Consequently the margin for error in the quoted yield is ± 3%.

Fluorine gas for the fluorination step was generated in a medium temperature (85 °C) electrochemical cell using fused KF·2HF as the electrolyte.[177,203] This was diluted to about 10% in a nitrogen carrier and was passed into a suspension of sodium tetrafluoroborate in the diluted solution obtained in the salt exchange reaction. Fluorine was passed into the reaction mixture at –40 °C until the uptake of the fluorine had ceased. This was considered to be when fluorine was detected in appreciable quantities in the exhaust gas from the reaction mixture. The presence of fluorine was determined by the colouration of a strip of filter paper soaked in potassium iodide solution. After purging the system of fluorine the sodium fluoride formed in the reaction was removed by suction filtration. This filtration proved to be rather tricky due to the very fine nature of the precipitated sodium fluoride. The best method for performing the filtration was to allow the suspension to settle overnight and then carefully decant off the supernatant fluid. This cloudy solution could then be filtered through Celite® without excessive difficulty. The remaining solid was then stirred with dry, warm acetonitrile to leech out any remaining product. This suspension was then filtered through the pad used earlier. The filtrate was concentrated *in vacuo* to give a suspension from which the first crop of **9** was collected by suction filtration and dried. The process was repeated on the filtrate thus obtained to obtain a second and third crop. It can be seen from **Table 2.1** that the total yield of **9** obtained was 89%, but that the material only had an average purity of 95%, thus giving an effective yield of 85%. The molar percentage of each of the components in the product was calculated by ^{1}H NMR (200 MHz, deuterium oxide).

Crop	Yield (g)	Yield if crop was pure (%)	% N–F (**9**)		% N–H (**64**)		% N (**47**)		Corrected Yield (%)
			molar	mass	molar	mass	molar	mass	
1	110·2	78	95	96	3	3	2	1	75
2+3	15·7	11	87	88	10	9	3	2	10
Total	125·9	89	Ave:	95	Ave:	4	Ave:	1	85

Table 2.1

It can be seen from **Table 2.1** that a protonated species (**64**) was generated in the reaction. This possibly occurs when traces of water present in the reaction mixture are oxidised to oxygen difluoride and hydrogen fluoride and/or oxygen by elemental fluorine (**Fig. 2.2**).

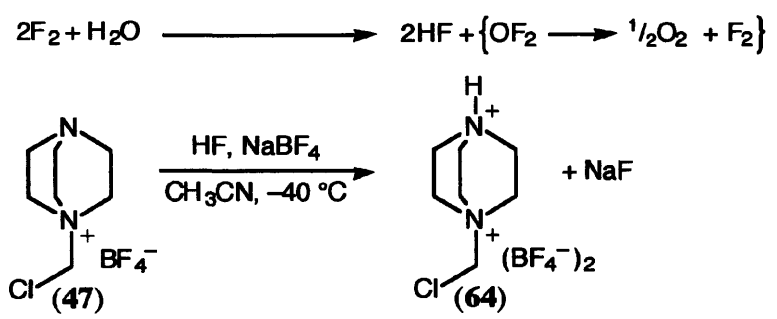


Fig. 2.2

The material obtained from the reaction was found to have a similar purity and impurity profile to that obtained commercially. Reactions were therefore performed using the crude material and assuming a 95% (w/w) content of active fluorinating reagent (**9**).

2.2 Thermal stability of Selectfluor™

To test the thermal stability of Selectfluor™ the reagent was heated at different temperatures in acetonitrile. A substrate [dibenzoylmethane (**65**), 1.0 equivalents] was then fluorinated using the resulting solution (**Fig. 2.3**). The yields were then compared to that obtained from an unheated solution of the reagent (**Table 2.2**). The substrate (**65**) was chosen because it gives a quantitative crude yield of monofluorinated product (**66**) when reacted with Selectfluor™ (see **Section 2.3.1**).

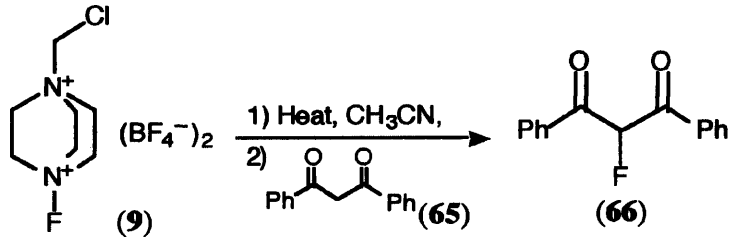


Fig. 2.3

Entry	Temperature (°C)	Heating time (hr)	Crude yield[a] of **66** (%)
1	20	0	100
2	20	24	98
3	40	24	94
4	82	24	93

a. Calculated from ^{1}H NMR analysis and mass return of the isolated crude product

Table 2.2

It may be seen from the data that the loss of reactivity over a 24 hour period is negligible at room temperature, but becomes significant when Selectfluor™ is heated at 40 °C for 24

hours. However, the decomposition is not much greater when the temperature is increased to 82 °C (the boiling point of acetonitrile). This implies that, at elevated temperatures, the activity quickly falls to a certain point and then the decomposition slows to a much lower rate. The 1% difference in the yields between the 40 °C and 82 °C reactions is within experimental error, so may not even represent any further decomposition of the reagent.

The near constant loss of activity at elevated temperature could be explained if the N–F group was reacting stoichiometrically with an impurity in the Selectfluor™ or solvent. Once this impurity had been consumed the rate of decomposition would be drastically reduced. Such an impurity could be water. At the elevated temperatures used for the decomposition stage, water may be nucleophilic enough to react with the N–F group to give the unstable HOF and **64** (**Fig. 2.4**) in a reaction similar to that suggested for the formation of **64** in the synthesis of Selectfluor™ (**Fig. 2.2**).

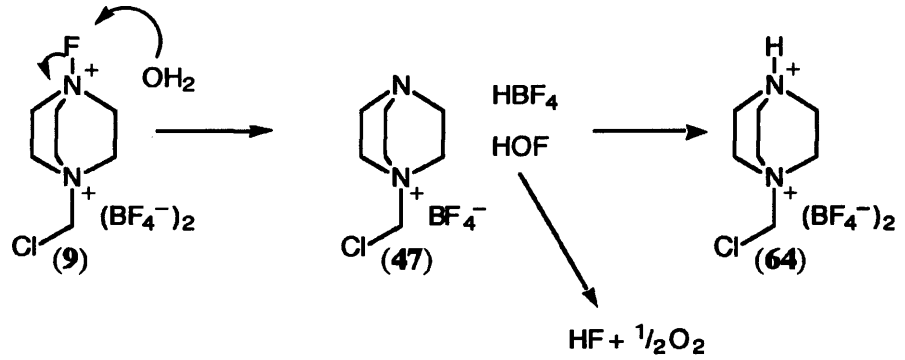


Fig. 2.4

The HF is then consumed by reaction with the glass walls of the reaction vessel. If this is the route of decomposition, then it seems that, at 40 °C, this reaction is fast enough to consume the water in the solvent and Selectfluor™. The reaction was carried out on a 5·0 mmole scale, so 6% of Selectfluor™ reagent consumed corresponds to 0·3 mmole. This much water would weigh 5·4 mg. 50 ml of HPLC grade acetonitrile was used as solvent, so the water content would have to be 10·8 mg per 100ml or 0·011% (w/v). The supplier of the solvent used (Aldrich) specifies a water content of <0·02%. Acetonitrile is quite hygroscopic, so the water content could easily explain the loss of fluorinating power of Selectfluor™. In real use the Selectfluor™ reagent would not be heated in the absence of a substrate. Consequently, decomposition of the reagent would not be so pronounced as seen in this experiment unless a very weak nucleophile was used as the substrate.

2.3 Fluorination using Selectfluor™

2.3.1 Fluorination of 1,3-dicarbonyl compounds[204]

At the start of this research project Banks[14] and Lal[181] had reported the reaction of Selectfluor™ with silyl enol ethers and enol acetates (**Fig. 2.5**) as well as the sodium salts of a number of malonates (**Fig. 2.6**).

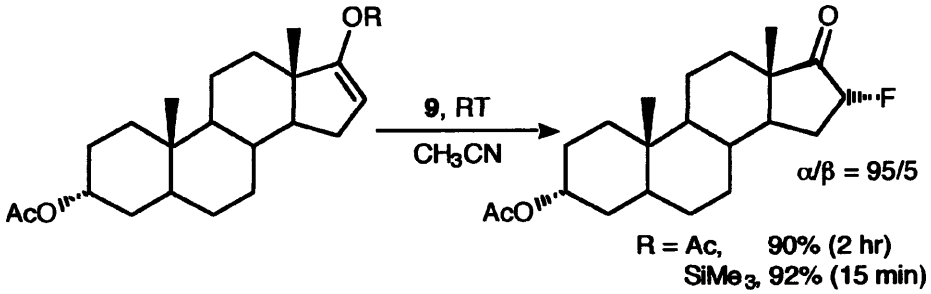


Fig. 2.5

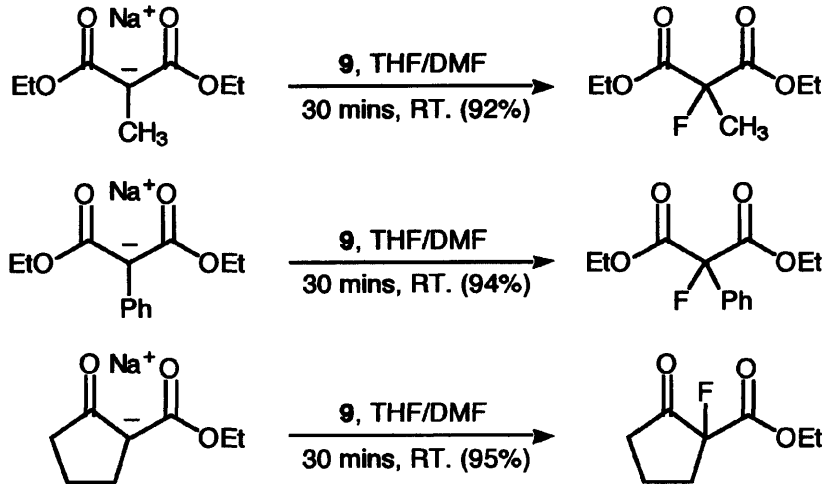


Fig. 2.6

A systematic study on the fluorination of neutral 1,3-dicarbonyl compounds had not been published. The following work was carried out to demonstrate the synthetic usefulness of Selectfluor™ for this purpose. Reactions were carried out on neutral compounds with activated α-protons and on carbanions of compounds with less active α-protons. Most of the keto compounds investigated were available from chemical suppliers at a reasonable cost, but two were either not available or were too expensive to purchase, and so had to be synthesised. *N*,*N*-Dimethylbenzoylacetamide (**67**) was prepared by a Claisen condensation (**Fig. 2.7**).

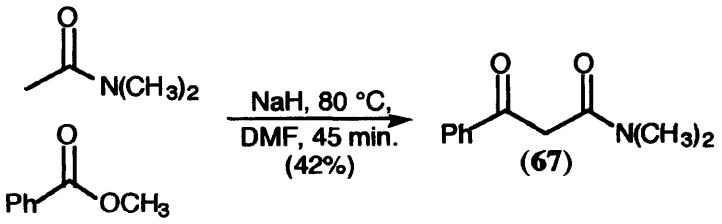


Fig. 2.7

After the reaction was complete (as judged by TLC) the suspension was cooled to room temperature and the sodium salt of **67** was acidified with aqueous hydrochloric acid. Neutral **67** could then be extracted into an organic solvent and purified by chromatography. The resulting tacky solid was then recrystallised to give pure **67**. ^{1}H NMR (200 MHz, $CDCl_3$) showed [by integration of signals at δ4·11 (keto: $COCH_2CO$) and δ5·79 (enol: $C{=}CHCO$)] that the keto and enol forms of **67** actually exist in equilibrium (ratio ≈ 2:1 keto:enol) at room temperature (**Fig. 2.8**).

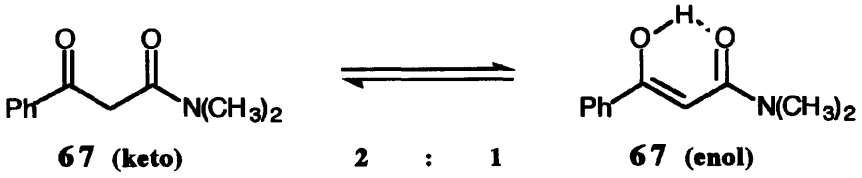


Fig. 2.8

The two methyl groups appeared at the same chemical shift, indicating that rotation about the amide bond was unhindered.

(±)-*N*-Methyl-*N*-(1-phenylethyl)-2-benzoylacetamide (**70**) was prepared in three steps from simple starting materials with an overall yield of 36% (**Fig. 2.9**).

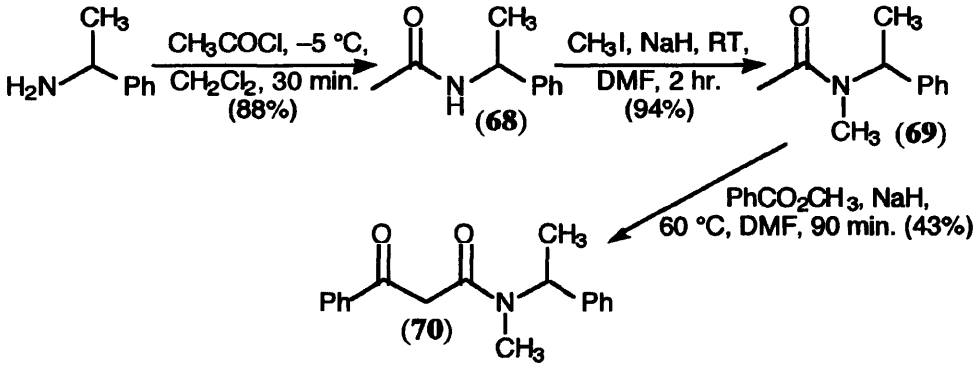
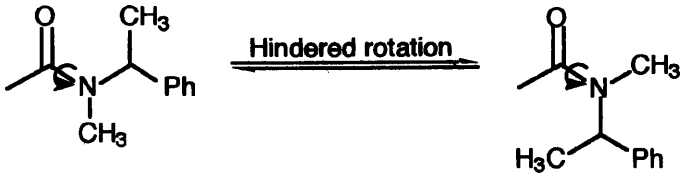


Fig. 2.9

The first reaction is a simple condensation of an acid chloride with a (racemic) chiral amine. Two equivalents of the amine were used as 1 mole of hydrogen chloride is produced in the reaction. The amine hydrochloride produced was washed out with dilute hydrochloric acid. The dried organic solution was then concentrated *in vacuo* and the resulting oil was crystallised to give pure **68** as a white powder.

This was then subjected to methylation in DMF and methyl iodide using sodium hydride as a base. This reaction gave what appeared to be a quantitative yield of **69**, but ^{1}H NMR

(200 MHz, $CDCl_3$) analysis showed that the oil contained about 6% unreacted starting material (**68**). The NMR analysis also showed that there was hindered rotation about the amide bond, giving rise to separate spectra for the two rotamers (ratio ≈ 2:1 major:minor at room temperature) (**Fig. 2.10**).



69 (major) **2 : 1** **69 (minor)**

Fig. 2.10

The third step in this synthesis is a Claisen condensation, similar to that used in the synthesis of *N*,*N*-Dimethylbenzoylacetamide (**67**). This reaction was performed on the unpurified **69**. As with compound **67** the keto and enol forms of **70** exist in equilibrium (ratio ≈ 2·4:1 keto:enol) at room temperature [by integration of signals at δ4·23 (keto: $COC\underline{H}_2CO$) and δ5·82 (enol: $C{=}C\underline{H}CO$)]. This makes for a rather complicated ^1H NMR (200 MHz, $CDCl_3$) spectrum, as the rotation about the amide bond is hindered in the keto form giving rise to separate spectra for the two rotamers (ratio ≈ 2·3:1 major:minor) at room temperature [by integration of signals at δ4·23 (keto, major: $COC\underline{H}_2CO$) and δ4·32 (keto, minor: $COC\underline{H}_2CO$)](**Fig. 2.11**).

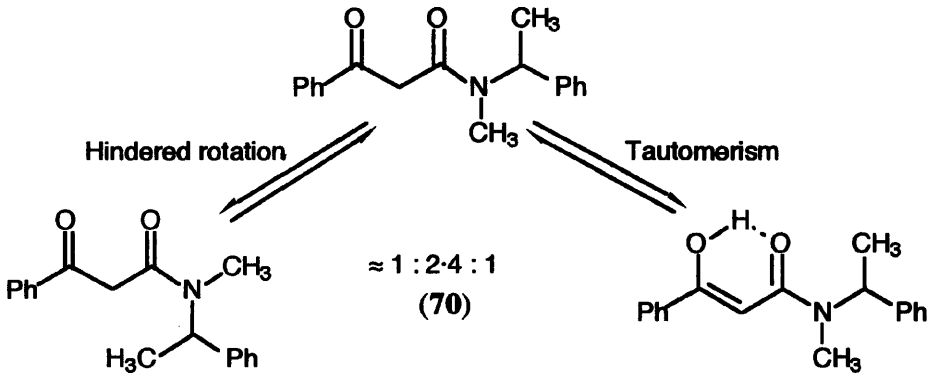


Fig. 2.11

In discussing the reactions of nucleophiles with **9** it should be noted that the mechanism of fluorination is, as yet, uncertain (see p 30). The evidence so far seems to consistent with an S_N2 mechanism.[185,186,187] Mechanisms for the following reactions of **9** with electrophiles were explained on the basis of the S_N2 mechanism. However, throughout this project the author has been looking for evidence of reaction *via* the SET mechanism.

In the first series of reactions **9** was used to monofluorinate 1,3-dicarbonyl compounds. All but the reaction with diethyl phenylmalonate proceeded under neutral conditions. The reactions performed are summarised in **Fig. 2.12** and **Table 2.3**.

In a typical reaction under neutral conditions, the substrate was dissolved in acetonitrile at room temperature. The Selectfluor™ reagent (**9**) was then added and the resulting

suspension was stirred until the reaction was judged to be complete by TLC analysis in an appropriate solvent system. In most cases the course of the reaction could be estimated by the dissolution of **9** followed by the precipitation of **64**. On completion of the reaction the acetonitrile was removed *in vacuo* and the resulting solid/semi-solid was partitioned between water and dichloromethane. The layers were then separated, the organic layer washed twice with water, dried, and concentrated *in vacuo*. The resulting material was then purified as indicated.

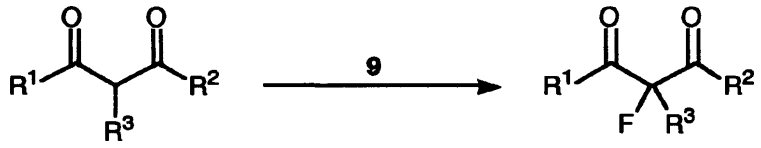
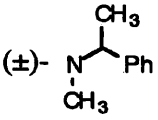


Fig. 2.12

Entry	R^1	R^2	R^3	Method [Note1]	Eq. **9**	Temp (°C)	Time (hr)	Crude Yield [Note2]	Purif. Method [Note3]	Pure Yield	Prod. no.
1	$-(CH_2)_3-$		CH_3	n	1·1	RT	19	–	tritur.	84%	**71**
2	Ph	Ph	H	n	1·0	RT	5	100%	recryst.	84%	**66**
3	Ph	$N(CH_3)_2$	H	n	1·0	RT	3	96%	recryst.	87%	**72**
4	Ph	(±)- 	H	n	1·0	RT	67	87%	chrom.	80%	**73** and **74**
5	Ph	OEt	H	n	1·0	RT	54	88%	chrom.	22%	**75**
6	CH_3	OEt	H	n	1·0	RT	120	57%	–	–	**76**
7	OEt	OEt	Ph	b	1·0	RT	20	96%	chrom.	93%	**77**

[1] n = neutral conditions, b = basic conditions (see text).
[2] The crude yield is calculated from the amount of crude material obtained in the reaction adjusted according to its purity by ^1H NMR.
[3] recryst. = recrystallisation, chrom. = flash or dry flash chromatography, tritur. = trituration (see text).

Table 2.3

In the case of **Entry 1** the product [2-fluoro-2-methylcyclohexane-1,3-dione (**71**)] was found to be hygroscopic and extremely soluble in water. Consequently the usual work-up was not suitable for this reaction. Instead, the acetonitrile was removed *in vacuo*, then the crude reaction concentrate was triturated with three portions of dichloromethane. The combined extracts were concentrated *in vacuo* and the resulting solid was extracted into boiling petrol six times. The cooled petrol extracts were concentrated *in vacuo* to form a slush which was cooled, then filtered. The resulting solid was washed with cold petrol, and then dried *in vacuo*. It was not possible to obtain a satisfactory combustion analysis on this material due to its affinity for water. The results obtained were consistent with a water content of 3%.

In the case of **Entry 5** some difluorination occurred, giving rise to a mixture of (±)-ethyl 2-fluorobenzoylacetate (**75**) (92 mol%), ethyl 2,2-difluorobenzoylacetate (**78**) (4 mol%), and starting material (4 mol%) (**Fig. 2.13**). The compounds **75** and **78** have very similar R_f values in wide range of solvents, so very careful chromatography is required to separate them. The low isolated yield of this material could probably be improved by using HPLC, or repeated chromatography.

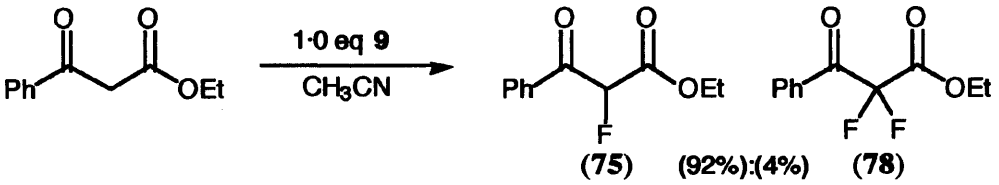


Fig. 2.13

Ethyl 2-fluoroacetoacetate (**76**) proved difficult to isolate due to co-distillation with the acetonitrile solvent [b.p. (**76**) = 52-55 °C @ 3 mmHg].[105] The small amount of material which was recovered was contaminated with about 15% ethyl acetoacetate, and was not purified any further.

In the reactions under neutral conditions **9** reacts with the enolic form of the substrate (**Fig 2.14**).

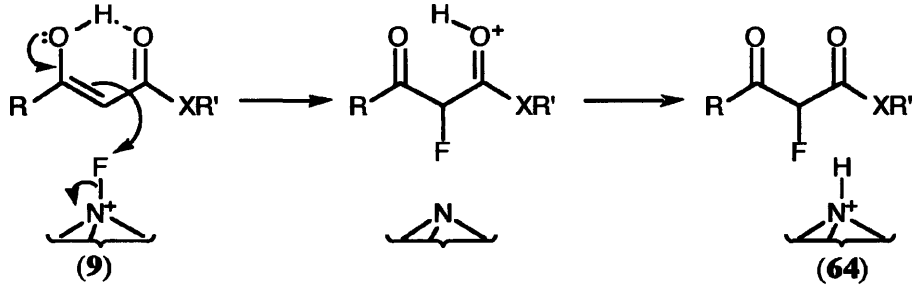


Fig 2.14

This is supported by the very short reaction times of substrates with a high enolic content such as dibenzoylmethane and *N*,*N*-dimethylbenzoylacetamide (**65**).

As mentioned earlier the diethyl phenylmalonate had to be reacted under basic conditions to form diethyl 2-fluoro-2-phenylmalonate (**77**). A reaction was performed under neutral conditions, but diethyl phenylmalonate was recovered unchanged after 55 days of stirring at room temperature in acetonitrile with **9**. A positive sodium iodide test after this time showed that the Selectfluor™ reagent had not been consumed. Under basic conditions the carbanion attacks **9** at fluorine performing a simple S_N2 reaction (**Fig. 2.15**).

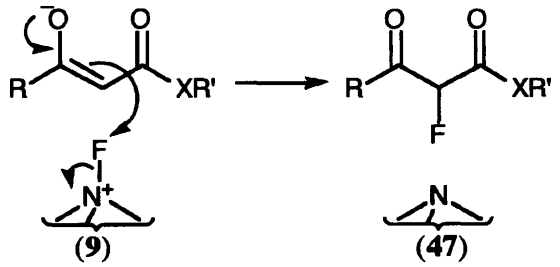
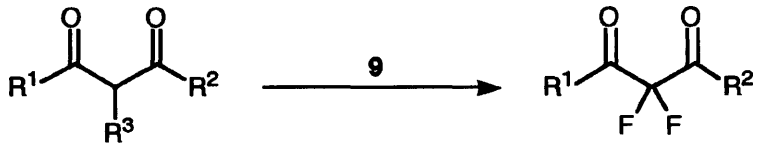


Fig. 2.15

In a typical reaction under basic conditions, the substrate was dissolved in THF and added to an oil free suspension of sodium hydride in THF. The resulting suspension (or solution) was stirred at room temperature until no more hydrogen was evolved. The Selectfluor™ reagent (**9**) was then added and the suspension was stirred at room temperature after breaking up any lumps of **9**. When the reaction was judged to be complete by TLC analysis the THF was removed *in vacuo* and the resulting material was partitioned between water and dichloromethane. The layers were then separated, the organic layer washed twice with water, dried, then concentrated *in vacuo*. The resulting material was purified as indicated.

In the next series of reactions some difluoro compounds were synthesised, from both dihydro and monofluoro starting materials. The results of these experiments are shown below in **Fig. 2.16** and **Table 2.4**.



Scheme 2.16

Entry	R^1	R^2	R^3	Method [Note1]	Eq. **9**	Temp (°C)	Time (hr)	Crude Yield [Note2]	Purif. Method [Note3]	Pure Yield	Prod. no.
1	Ph	Ph	H	n	2·1	RT	192	96%	recryst.	78%	**79**
2	Ph	$N(CH_3)_2$	H	n	3·2	40	647	93%	chrom.	91%	**80**
3	Ph	$N(CH_3)_2$	F	b	1·2	RT	27	84%	chrom.	73%	**80**
4	Ph	OEt	F	b	1·1	RT	24	95%	–	95%	**78**

[1] n = neutral conditions, b = basic conditions (see text).
[2] The crude yield is calculated from the amount of crude material obtained in the reaction adjusted according to its purity by ^1H NMR.
[3] recryst. = recrystallisation, chrom. = flash or dry flash chromatography.

Table 2.4

It can be seen from the above results that fluorination of the neutral monofluoro compounds (**Entries 1** and **2**) is much slower than for the equivalent unfluorinated compound (**Entries 2** and **3** in **Table 2.3**). This is due to the fact that the fluorinated compounds have a lower equilibrium amount of the enolic form. This is clearly

demonstrated by compounds **67** and **72**. As mentioned earlier (p 42), the ^1H NMR spectrum of the dihydro compound (**67**) shows a significant amount of the enol tautomer, whereas the NMR spectrum of the monofluoro compound (**72**) showed no contribution from the enol tautomer. The monofluoro ketones have a lower enolic character due to the lone pairs of electrons of the fluorine atom repelling the Π-electrons of the enolic double bond, thus destabilising the enol relative to the ketone.

The isolated yield of ethyl 2,2-difluorobenzoylacetate (**78**) was much better than that for the monofluoro analogue (**75**). This was due to the fact that, unlike the monofluoro analogue (**75**), **78** was produced as a pure compound rather than a mixture. In fact **78** was pure enough following the usual work-up procedure that no further purification was required.

The fluorination of *N*,*N*-dimethyl-2-benzoyl-2-fluoroacetamide (**72**) was carried out under both neutral and basic conditions (**Entries 2** and **3** respectively). In the neutral experiment the dihydro compound was used, but the first fluorination proceeds in about 3 hours, so **72** was effectively generated *in situ*. It can be seen from **Table 2.4** that the better yield was obtained in the reaction under neutral conditions, but the reaction was extremely slow, taking nearly a month to go to completion.

2.3.2 Stereoselective fluorination

With the recent interest in the development of fluorinated bio-active compounds has come the need for stereoselective fluorinations. Where a compound is intended for use in a biological system it is important that the stereochemistry of the molecule in the final product is carefully controlled.[205] Indeed, the United States of America's Food and Drug Administration authority guidelines state that enantiomers must be considered as separate compounds and that activity and safety data must be produced for each stereoisomer.[206]

It is shown elsewhere in this thesis that Selectfluor™ is a suitable reagent for the site selective fluorination of a variety of organic substrates. In addition, the reaction of **70** with Selectfluor™ (**9**) (**Entry 4, Table 2.3**) gave rise to the two monofluoro diastereoisomers (**73** and **74**) (**Fig. 2.17**).

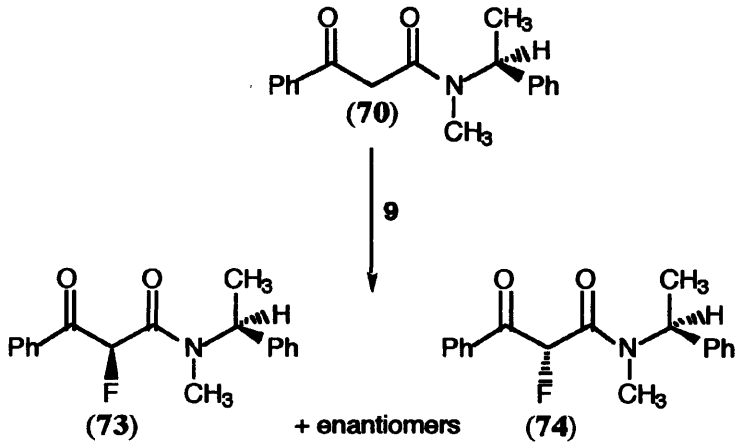


Fig. 2.17

^{1}H NMR (200 MHz, $CDCl_3$) showed the presence of two rotamers (ratio ≈ 1·6:1) and two diastereoisomers. The d.e. in this reaction was judged to be about 6% by ^{19}F NMR (188 MHz, $CDCl_3$). Interestingly, the diastereoisomers had the same fluorine chemical shift in the major rotamer, but showed a Δδ of 1·27 ppm (188 MHz, $CDCl_3$) in the minor rotamer.

In an attempt to increase the d.e. of the fluorination the chiral enamine **81** was synthesised as shown in **Fig. 2.18**. It was not considered necessary to synthesise the enantiomerically pure isomer of **81** in this reaction because fluorination of the racemate would produce a racemic mixture of the two diastereomers of **82**. ^{1}H and ^{19}F NMR of the crude reaction mixture would then have yielded the value for the diastereomeric excess of the reaction. Therefore, racemic α-methylbenzylamine was used.

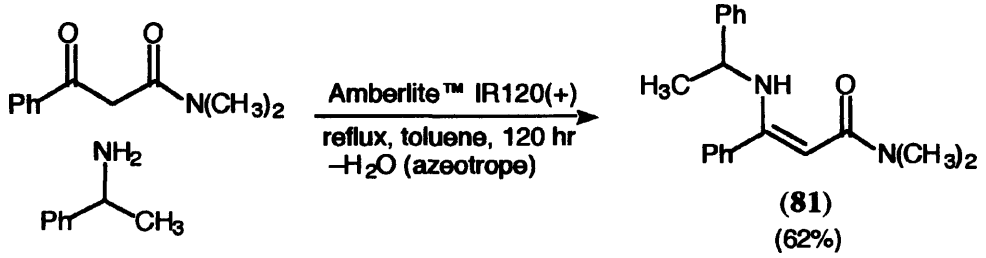


Fig. 2.18

This compound was then reacted with Selectfluor™. Unfortunately, the ^{1}H NMR (200 MHz, $CDCl_3$) of the crude material from this reaction showed no signal which could be attributed to the CHF group and the ^{19}F NMR (188 MHz, $CDCl_3$) showed the presence of a C=CF group at δ–60.33 ppm (CHF usually appears at around δ–110 ppm). This suggests that the fluorinated product (**82**) had tautomerised to the enamine form (**83**), so any stereochemistry at the C–F bond was lost (**Fig. 2.19**).

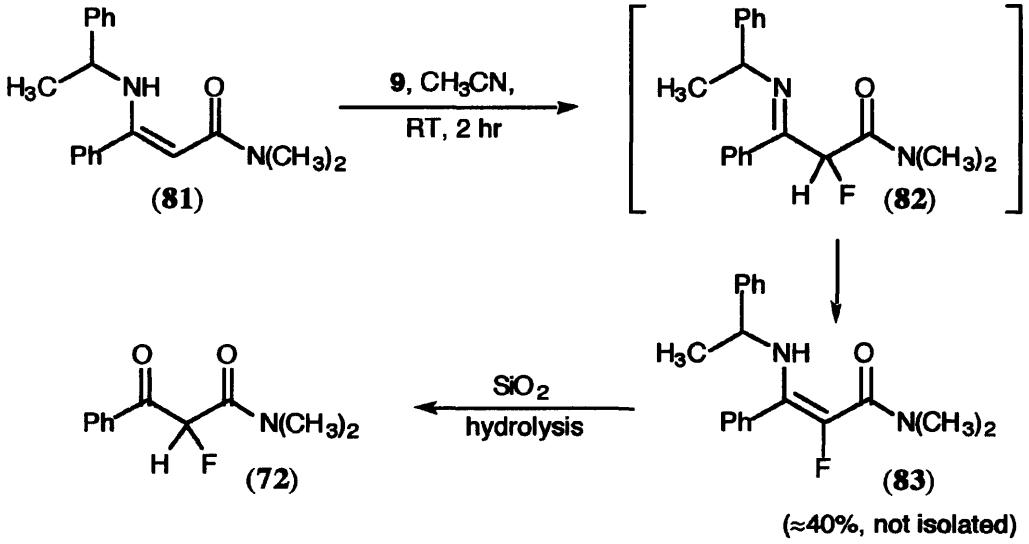


Fig. 2.19

Compound **83** also proved impossible to purify due to hydrolysis when in contact with silica. The hydrolysis of **83** to give **72** may have been diastereoselective, but the use of racemic **81** could only result in racemic **72** even if the hydrolysis of **83** proceeded with 100% enantiomeric excess.

2.3.3 A new route to an existing chiral derivatising reagent

Chiral derivatising reagents are used to determine the enantiomeric excess of a stereogenic reaction as shown in **Fig. 2.20**.

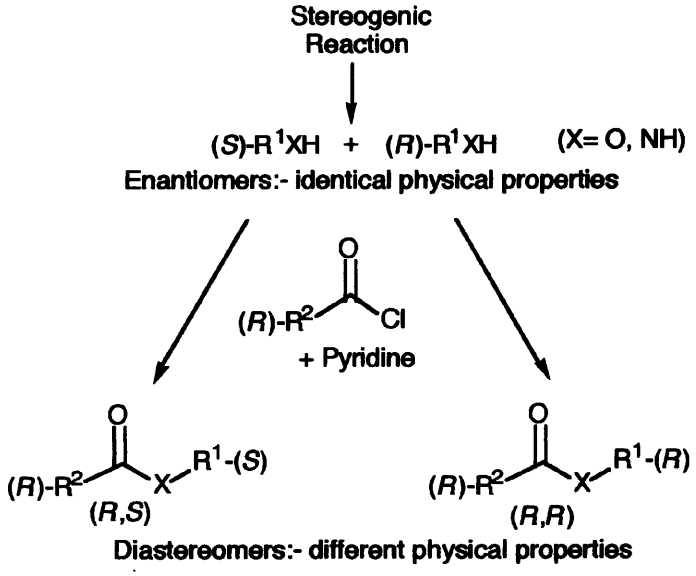
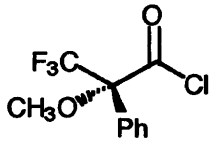


Fig. 2.20

The derivatised enantiomers become diastereoisomers with different properties, including potential differences in NMR chemical shifts. Probably the best known of these reagents is Mosher's acid chloride[207] (**84**):

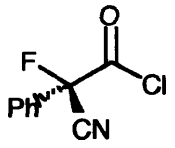


R-(–)-**84**

Reagents chosen for this task must be reactive enough to prevent possible kinetic resolution in the derivatisation. They must also have large enough $\Delta\delta$ values when incorporated into a chiral molecule to allow accurate NMR integration. Mosher's acid chloride (**84**), although widely available, is quite expensive (£90·00 for 1 g).[208] For this reason the acid chloride is usually prepared in the laboratory from the acid (£44·00 for 1 g).[209] Derivatives sometimes have $\Delta\delta$ values too small to allow accurate integration, especially when the chiral centre is far from the derivatised end of the molecule. The steric crowding around the α-carbon also results in a lack of reactivity towards some secondary

alcohols. This can sometimes lead to misleading results if the acid chloride reacts more quickly with one enantiomer than the other.

With these requirements in mind a Japanese group working with Takeuchi have developed a suitable alternative to Mosher's acid chloride (**85**).[210]



R-(+)-**85**

This compound has a fluorine atom attached directly to the α-carbon atom, thus leading to a less sterically hindered molecule. They also incorporated a nitrile group on the α-carbon. The fluorine and nitrile act as strong electron withdrawing groups, leading to a decrease of electron density at the carbonyl group, thus increasing the reactivity of the acid chloride. The three groups attached to the α-carbon also have marked differences in steric bulk, leading to a lower degree of free rotation and thus larger Δδ values in diastereoisomers of derivatives. Diastereoisomeric derivatives of this compound have been shown to compare favourably with those of Mosher's acid.[211]

Takeuchi reported that the most effective way to synthesise optically pure samples of the reagent was to separate the amide diastereoisomers (**86** and **87**) of the compound by fractional crystallisation . The amides could then be converted to the optically pure acid chlorides *via* the acid (**Fig. 2.21**, overleaf). This synthesis is somewhat hazardous as it involves the volatile and toxic DAST[41] (p 7). If a synthesis could be formulated which avoids the use of this reagent, then the preparation of the Takeuchi reagent would become more attractive for researchers desiring small quantities of the material.

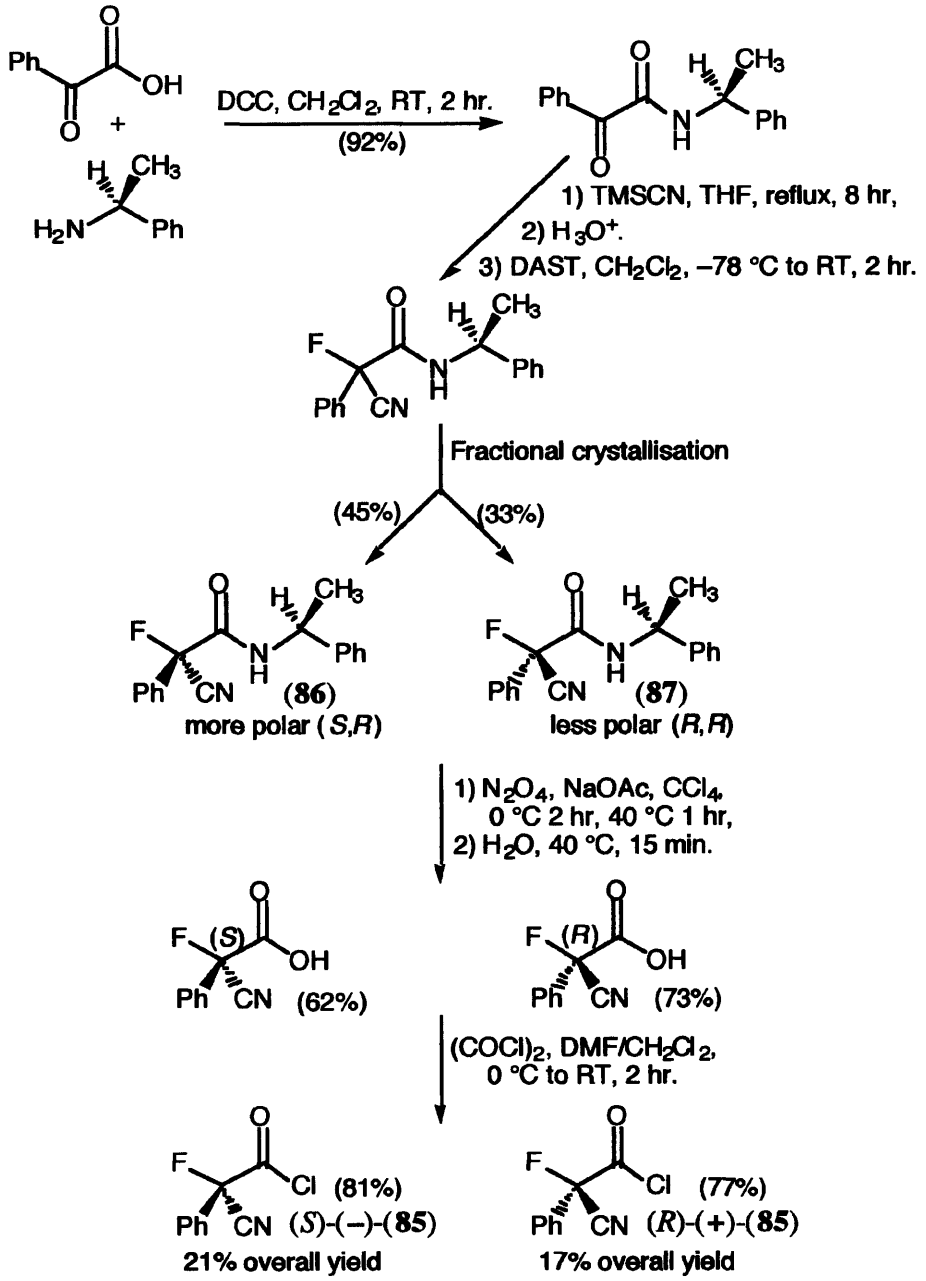


Fig. 2.21

Ethyl (±)-phenylcyanoacetate was efficiently converted to the diastereomeric amides (**88** and **89**) using titanium tetraisopropoxide as a catalyst as shown in **Fig. 2.22.**

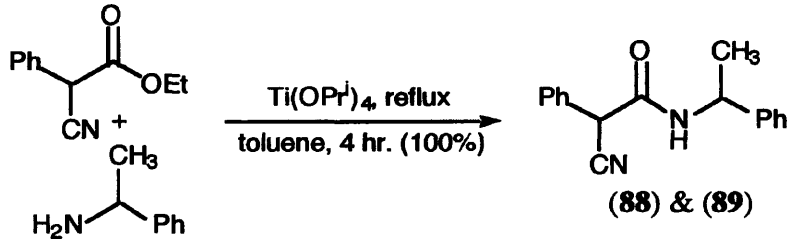
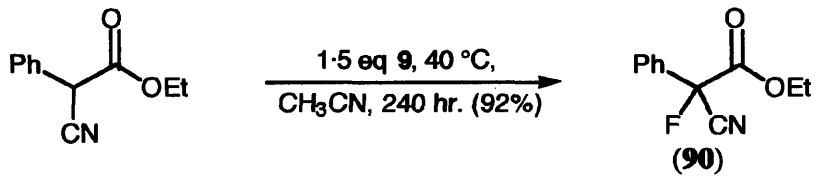


Fig. 2.22

However, it was not possible to fluorinate these compounds using Selectfluor™ under neutral conditions. It was, however, possible to fluorinate the ester directly to give ethyl (±)-cyanofluorophenylacetate (**90**) in excellent yield (**Fig. 2.23**).



(**90**)

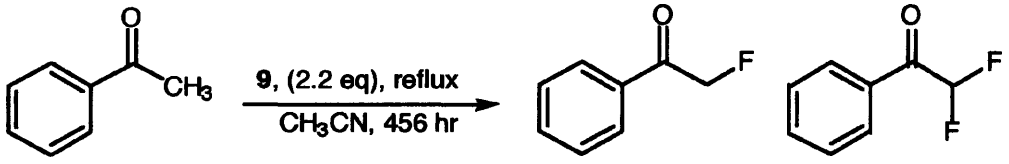
Fig. 2.23

This compound could then be converted to the amides (**86** and **87**) using the titanium tetraisopropoxide method described for amides (**88** and **89**). The Japanese workers have carried out this reaction successfully giving a unoptimised yield of 31% of **86** and **87**.[210] These can then be converted to *S*-(–)-**85** and *R*-(+)-**85** in 50% and 56% yields (respectively) using the method described by Takeuchi (**Fig. 2.21**). This would give an overall yield of 15% and 17% respectively.

These unoptimised yields are similar to those obtained by the Japanese workers with the same number of steps in the synthesis. The reagents used in the proposed new synthesis are about the same price as those used in the original route, but the advantage lies in the use of Selectfluor™ rather than DAST to introduce the fluorine atom into the molecule. Selectfluor™, unlike DAST, does not require any special handling techniques, so the reagents [*S*-(–)-**85** and *R*-(+)-**85**] can now be prepared safely and on a large scale if required.

2.3.4 Fluorination of acetophenone

As mentioned previously, there is some debate as to whether fluorination by the N–F class of reagents occurs *via* an S_N2 (**Fig. 2.15**, p 46) or SET pathway. In an effort to promote Selectfluor™ into performing fluorination *via* an SET mechanism, acetophenone was reacted with Selectfluor™ under reflux in acetonitrile (**Fig. 2.24**).



(**91**) (61%) (**92**) (trace)

Fig. 2.24

Acetophenone has a negligible enol content, so the S_N2 reaction would be very slow for this substrate. This slow rate of S_N2 reaction could allow the SET mechanism (**Fig. 2.25**) to compete for the fluorination. The experiment confirmed that the reaction was slow, with only 61% conversion to the monofluoro derivative (**91**) after 19 days at reflux. Selectfluor™ was added to the reaction mixture at regular intervals to maintain the

concentration of active fluorinating reagent. A trace of the difluorinated compound (**92**) was also detected in the ^1H NMR (200 MHz, $CDCl_3$) of the crude reaction mixture.

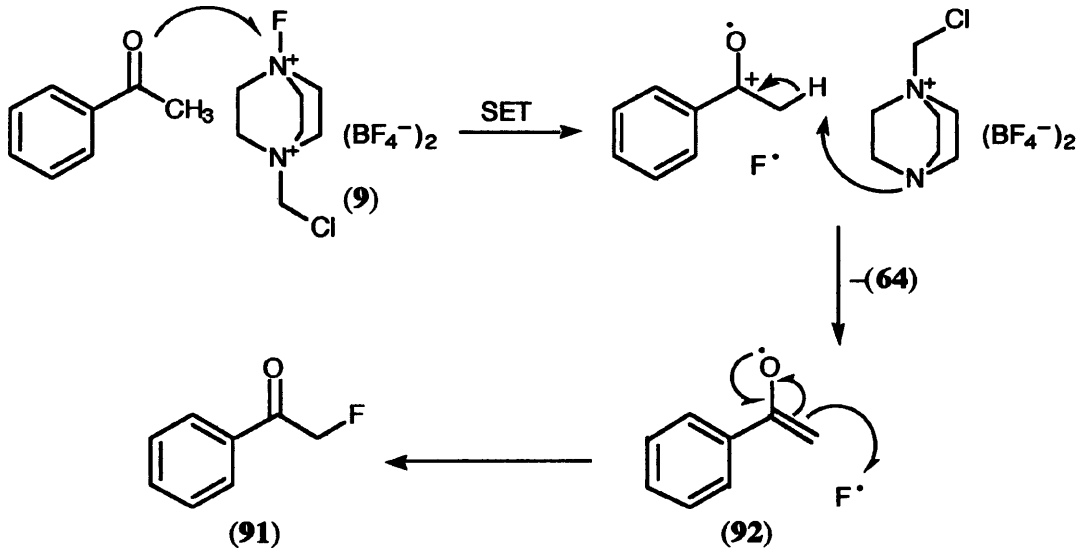


Fig. 2.25

In an attempt to encourage the fluorination to proceed *via* a radical chain pathway, the reaction was repeated with the addition of AIBN to the refluxing reaction mixture.

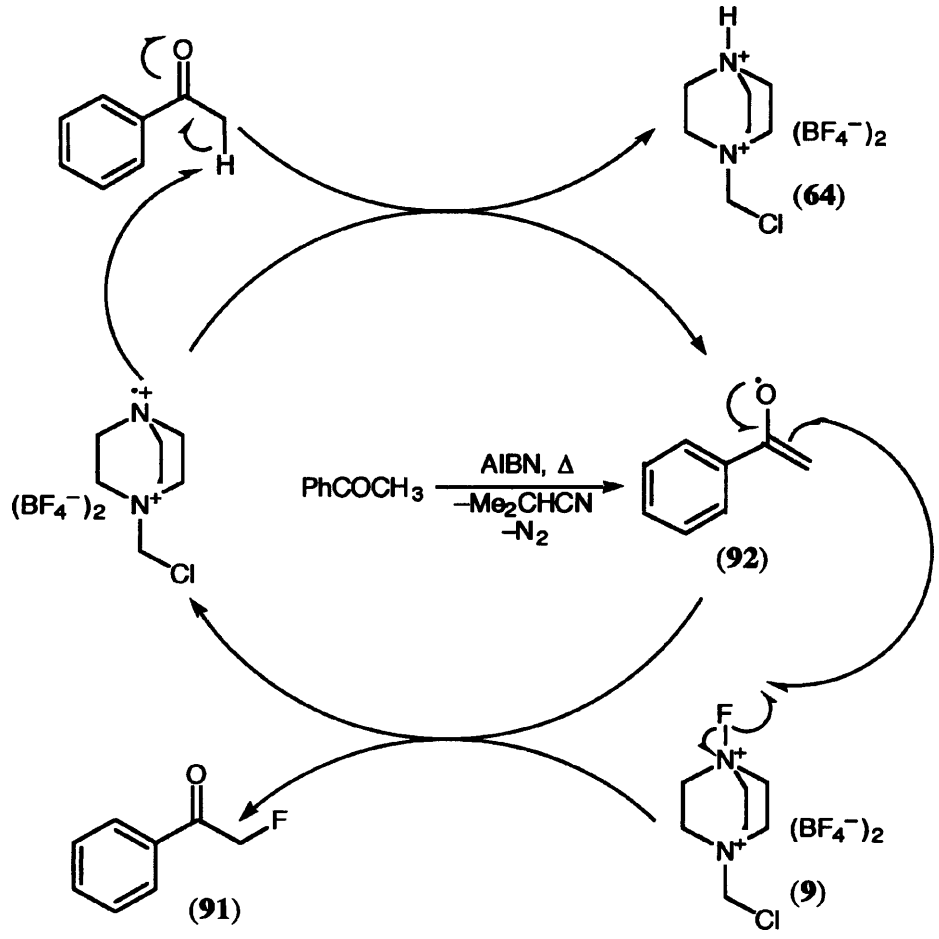


Fig. 2.26

If the SET mechanism was in operation it would be expected that AIBN would be able to generate **92** which could then start a radical chain reaction (**Fig. 2.26**). However, the addition of AIBN to the reaction mixture did not significantly increase the rate of formation of **91** but many by-products were observed in the reaction mixture. This suggests that the fluorination is not being achieved by a radical process, but rather an S_N2 mechanism. The sluggish nature of the reaction being due to the very low enol content of acetophenone.

2.4 Selectfluor™ as an oxidising agent[212]

2.4.1 Oxidation of benzyl alcohols

It is inevitable that compounds which act as sources of "F+" are also capable of acting as oxidising agents. This is due to the great thermodynamic drive for fluorine to exist as F⁻ (**Fig. 2.27**).

$$F^{\bullet}_{(g)} + e^- \longrightarrow F^-_{(g)} \qquad \Delta H = -328\ kJmol^{-1}$$

Fig. 2.27

To investigate the synthetic usefulness of Selectfluor™ as an oxidising agent some benzylic alcohols were treated with Selectfluor™ (**9**) in refluxing acetonitrile. It was found that the benzylic alcohols were slowly oxidised to benzaldehydes (**Fig. 2.28**). The results for the various substrates are shown in **Table 2.5**.

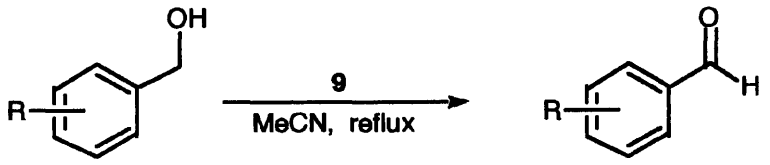


Fig. 2.28

Entry	R	Molar Ratio **9** : $ArCH_2OH$	Time (hr)	Pure, isolated yield of ArCHO (%)	Product
1	H	1·05	18	43	**93**
2	2-Cl	2·00	45	42	**94**
3	4-Cl	1·50	15	37	**95**
4	2-NO_2	1·10	435	56	**96**
5	4-NO_2	1·10	65	62	**97**

Table 2.5

In a typical reaction the substrate (5·0 mmol) was heated with Selectfluor™ (**9**) in boiling acetonitrile under nitrogen until oxidation was complete (as judged by TLC). The reaction solution was then concentrated *in vacuo*, and the residue was partitioned between

water and dichloromethane. The organic layer was washed twice with water, dried then concentrated *in vacuo* and the residue purified by recrystallisation or chromatography.

A nitro group, especially when positioned *ortho* to the hydroxymethyl function, retards the oxidation process (**Entries 4 and 5**). This is also the case when there is a chlorine atom *ortho-* to the hydroxymethyl group (**Entry 2**). It is likely that an SET–initiated radical-mode benzylic hydrogen abstraction is responsible for this oxidation process (**Fig. 2.29**), although this has not been proved.

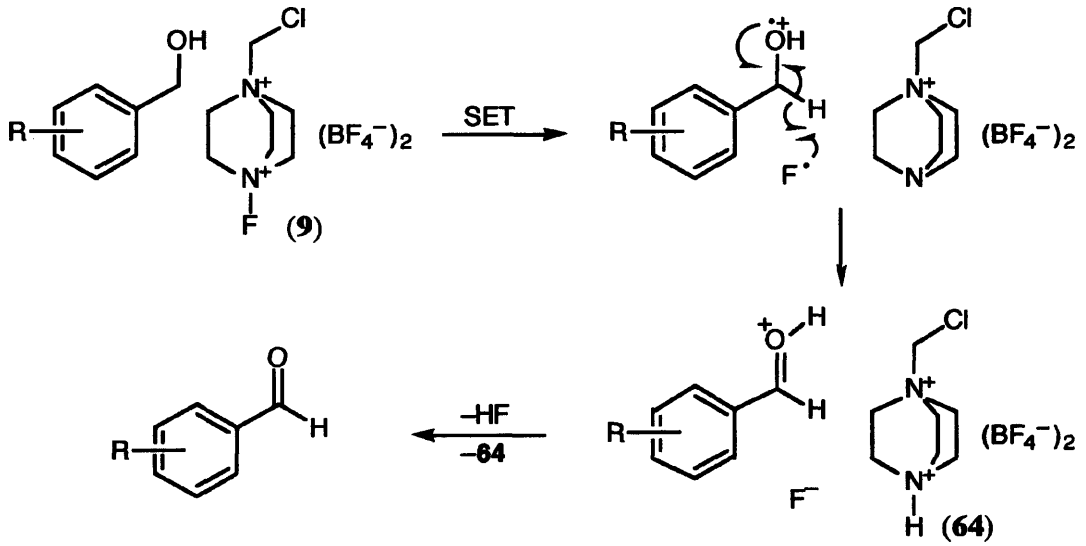


Fig. 2.29

Oxidation reactions of this type have been reported for *N*-halosuccinimides.[213] In the case of *N*-iodosuccinimide the suggested mechanism proceeds *via* iodination of the hydroxyl oxygen atom followed by homolytic fission of the O–I bond to form a radical pair (**Fig. 2.30**).[214] The benzyloxy radical (**99**) then abstracts a benzylic hydrogen atom from benzyl alcohol or benzyl hypoiodite (**98**).

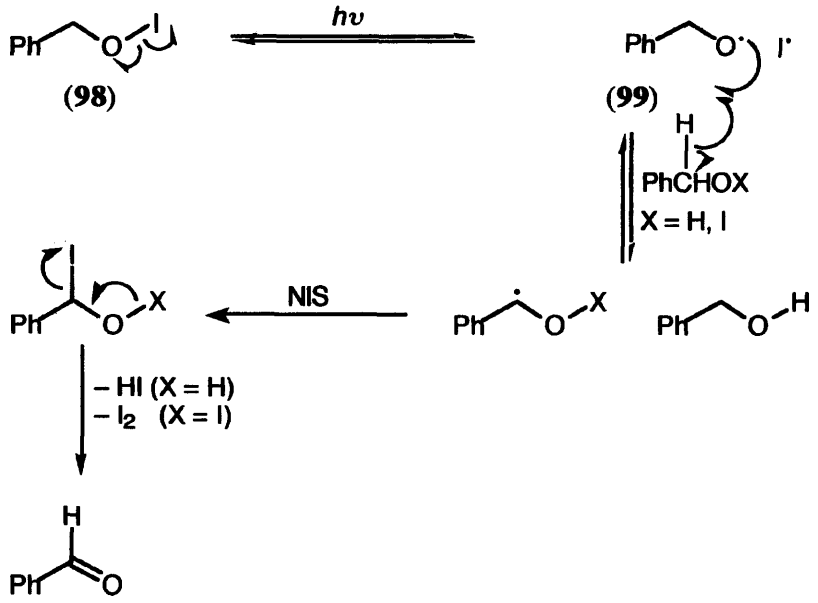


Fig. 2.30

Use of a 50–100% excess of the oxidant **9** in all of the reactions featured in **Table 2.5** produced small but detectable (<10%) quantities of a benzoic acid except in the case of the *ortho* nitro-substrate. By contrast, benzoic acid itself was isolated in 87% yield following treatment of benzyl alcohol with 2·2 equivalents of **9** at 82 °C for 48 hours in acetonitrile.

2.4.2 Oxidation of benzaldehydes

Separate oxidation of benzaldehyde and some of its *para*–substituted derivatives with a 1·2–1·4 molar proportion of **9**, followed by treatment with water provided the corresponding benzoic acids in fair-to-excellent yields (**Fig. 2.31** and **Table 2.6**).

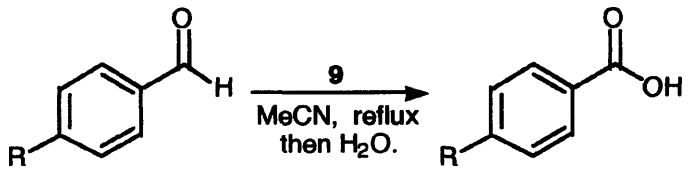


Fig. 2.31

Entry	R	Molar Ratio **9** : ArCHO	Time (hr)	Pure, isolated yield of $ArCO_2H$ (%)	Product
1	H	1·20	31	46	**100**
2	Cl	1·40	66	93	**101**
3	NO_2	1·20	384	50[a]	**102**
4	CN	1·20	80	87	**103**

a. Determined by ^1H NMR analysis, which revealed the presence of *ca.* 50% unchanged aldehyde.

Table 2.6

2.4.3 Reactions involving 4-chlorobenzoyl fluoride

It was established by ^{19}F NMR analysis of reaction mixtures that the oxidation of the benzaldehydes proceed *via* benzoyl fluorides. This was further confirmed by one-pot derivatisation reactions involving dimethylamine or methanol (**Fig. 2.32**). The related direct transformations of an aldehyde to an acid chloride or bromide appear to be quite rare.[215] Isolation of the benzoyl fluorides proved troublesome owing to inadvertent hydrolysis and attack on glass, but was achieved in the case of *p*–chlorobenzoyl fluoride using Teflon® FEP apparatus.

Selectfluor™ is only one of numerous electrophilic fluorinating reagents, including N–F compounds,[216] that are known to be strong oxidising agents. Caesium fluoroxysulfate rapidly oxidises both aromatic and aliphatic aldehydes to the corresponding acid fluorides[217] *via* a mechanism analogous to the SET-initiated radical-type process proposed in **Fig. 2.29**. Nevertheless, Selectfluor™ is the more suitable reagent for this process since $CsSO_4F$ is not commercially available and its use is hazardous.[218] The synthesis of acyl fluorides using BrF_3 has also been reported[219] although, being volatile

(b.p. 127 °C)[220] and toxic, this reagent is not much more user-friendly than caesium fluoroxysulfate.

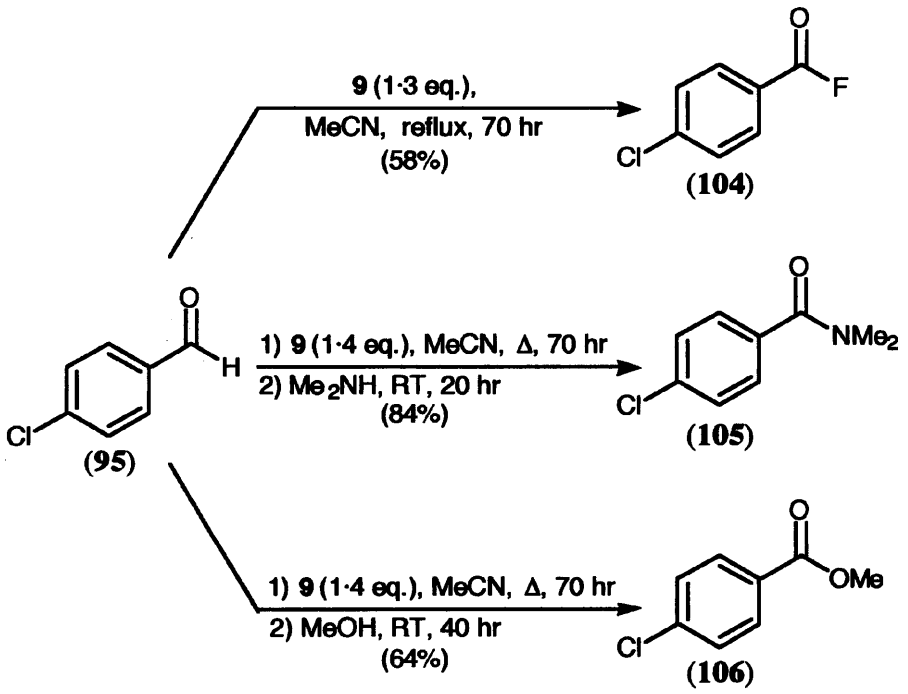


Fig. 2.32

Acyl fluorides are not as reactive towards nucleophiles as acyl chlorides or acyl bromides. This has led to their use in the field of peptide synthesis.[221] *N*-FMOC amino acids were reacted with cyanuric fluoride to give the corresponding acyl fluorides (**Fig. 2.33**).

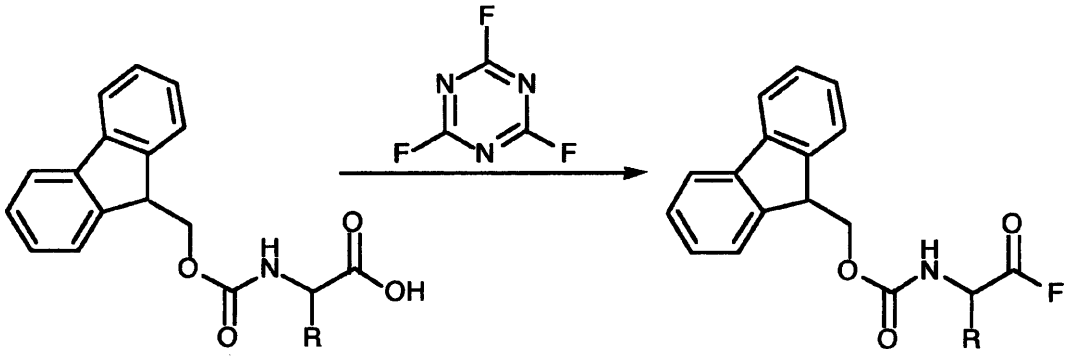


Fig. 2.33

These reagents are stable enough to have a long shelf-life when compared to the corresponding acid chlorides. This stability comes at the cost of reactivity, but they have been shown to be reactive enough to be used in the variety of procedures required in the synthesis of peptides. For example, nonapeptides have been prepared in useful yields from acyl fluorides using automated, solid-phase methods.[221]

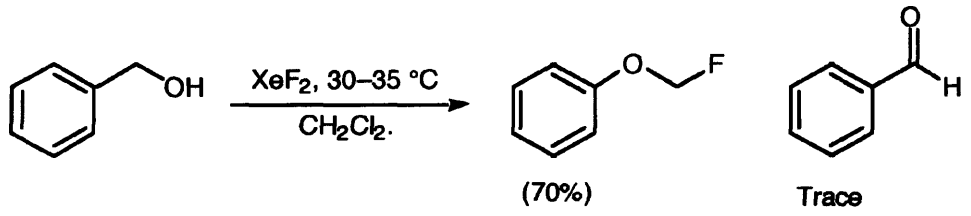


Fig. 2.34

Interestingly, the well-known commercial electrophilic fluorinating reagent xenon difluoride reacts with benzylic alcohols in a very different manner from **9** to give fluoromethoxy-benzenes as the major product. Traces of benzaldehydes were also observed (**Fig. 2.34**).[222] No mechanism was proposed for the reaction.

2.5 Reactions between (–)-menthol and Selectfluor™[223]

In an attempt to provide an example of the oxidation of an alkyl alcohol by Selectfluor™, (–)-menthol (**107**) was heated under refluxing acetonitrile with 2·2 equivalents of Selectfluor™. When TLC analysis (SiO_2, 67% ethyl acetate in petrol) indicated that all of the (–)-menthol had been consumed the reaction mixture was cooled and partitioned between dichloromethane and water. The organic layer was dried and concentrated *in vacuo* to give a tacky orange solid. It was apparent from the ^1H NMR (200 MHz, $CDCl_3$) of the crude material that no menthone (**108**) had been produced in the reaction (**Fig. 2.35**). The crude material was crystallised from ethyl acetate and petrol to yield a free-flowing, white powder.

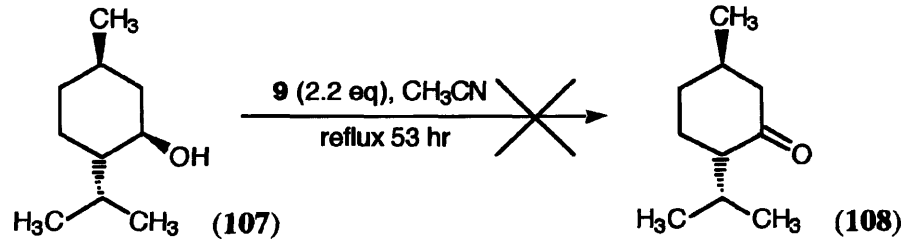
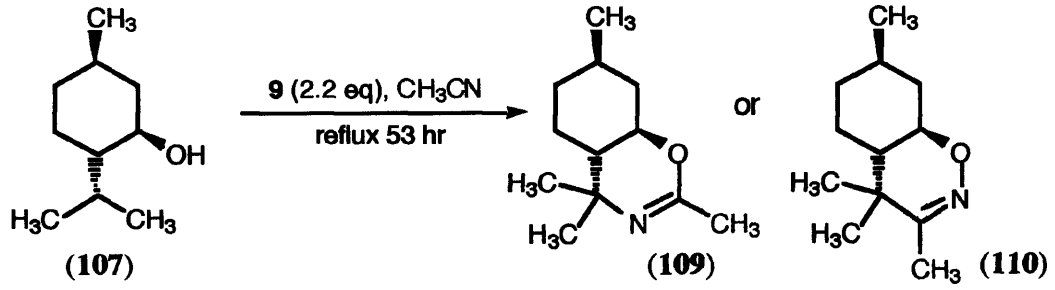


Fig. 2.35

The ^1H NMR (200 MHz, $CDCl_3$) of this material showed remarkable similarities to the starting material, (–)-menthol (**107**). The most notable of these was the appearance of a triplet of doublets at δ4·30 ppm (J = 11·0 and 4·5 Hz). The coupling pattern of this signal coincides fairly closely with the signal observed for the Pr^{i}CH–CHOH cyclohexyl ring hydrogen atom in (–)-menthol itself (δ3·39 ppm, J = 10·5 and 5·0 Hz), thus suggesting that the ring and the relative stereochemical arrangement of the isopropyl and hydroxy groups had been retained. The difference of nearly 1 ppm in the shift suggested that the hydroxyl group had been modified by the reaction. The methyl groups of the isopropyl fragment of the new molecule showed as singlets (at δ1·34 and 1·49 ppm) whilst those of (–)-menthol are present as doublets (δ0·89 and 0·91 ppm, J = 3·5 and 3·5 Hz). This

indicated that the hydrogen atom of the isopropyl group had been replaced with a group which does not couple to the two methyl groups.

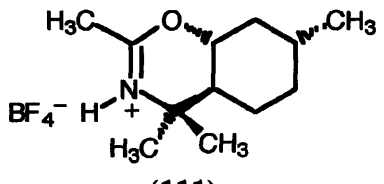
In addition to the (–)-menthol-like features of the spectrum was a singlet at δ1·49 ppm suggesting the presence of an extra, non-coupled methyl group. Elemental microanalysis showed the presence of nitrogen (5% by mass) in the compound. These two clues together suggested that the (–)-menthol had reacted in such a way as to incorporate a molecule of the acetonitrile solvent. The mass spectrum (Ar FAB$^+$) of the product showed a base peak at 196 which was close to the combined masses of acetonitrile (M = 41) and (–)-menthol (M = 156). The NMR evidence mentioned earlier suggested that the hydroxyl and the isopropyl groups of the (–)-menthol molecule had been modified by the reaction. This, with the mass spectrum led to the hypothesis that a molecule of acetonitrile had been inserted between these two groups (**Fig. 2.36**).



(**107**) (**109**) (**110**)

Fig. 2.36

However, the TLC R_f (0·06 in 67% ethyl acetate in petrol) and microanalysis data (Found: C, 51·1; H, 7·7; N, 5·0%) was incongruent with either of these two structures ($C_{12}H_{21}NO$ requires C, 73·8; H, 10·8; N, 7·2%). The final piece of evidence came with the ^{19}F NMR (188 MHz, $CDCl_3$), which showed a singlet at δ–71·8 ppm. This was indicative of a tetrafluoroborate group. If either **109** or **110** were protonated on the nitrogen atom with HBF_4 the molecular formula would be $C_{12}H_{21}NO{\cdot}HBF_4$, requiring C, 50·9; H, 7·8; N, 5·0%. This closely matched the results obtained, so candidates for the structure of the compound had been narrowed down to two possibilities. At this point x-ray crystallographic analysis of the compound (**Appendix A**) showed that the imino methyl group was adjacent to the oxygen atom rather than the isopropyl group (**Fig. 2.37**). This is the first reported crystal structure of a *trans*-4a,5,6,7,8,8a-hexahydro-4*H*-benzo[1,3]oxazine ring nucleus.



(**111**)

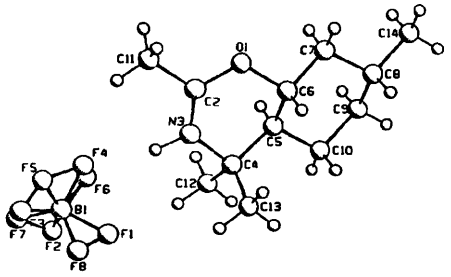


Fig. 2.37

The reaction was repeated using propionitrile and butyronitrile as solvents for the Selectfluor™ and (–)-menthol. It was found that these nitriles also formed the oxazine ring system in varying yields (**Fig. 2.38** and **Table 2.7**).

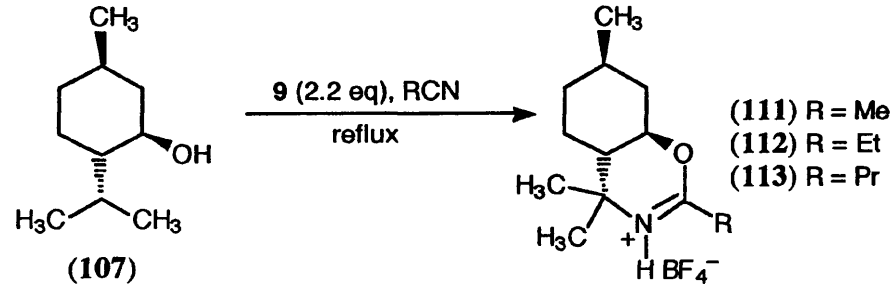


Fig. 2.38

Entry	R	Time (hr)	Pure, isolated yield of product (%)	Product
1	Me	53	50	111
2	Et	64	31	112
3	Pr	68	21	113

Table 2.7

4-methylpentan-2-ol (**114**) and (+)-isomenthol (**116**) also formed oxazinium salts with Selectfluor™ in refluxing acetonitrile (**Fig. 2.39**).

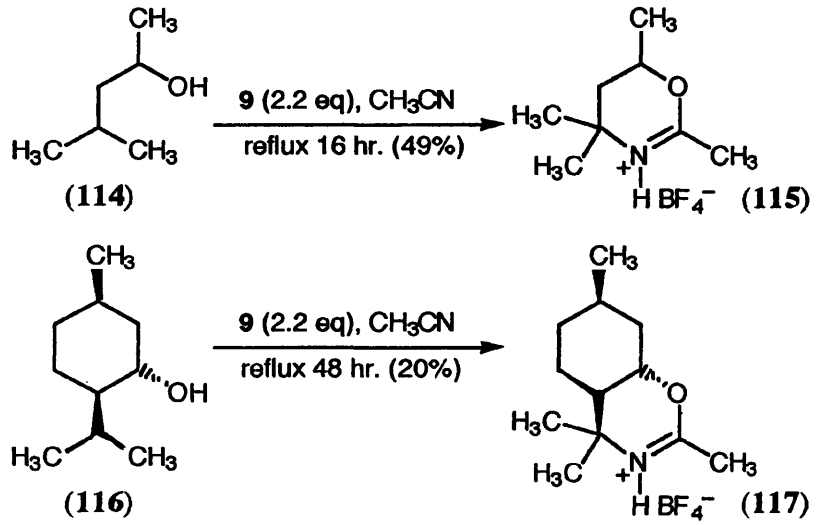


Fig. 2.39

The poor yields of these reactions are believed to stem, in part, from the hydrolysis of the oxazinium salts and conversion of the alcohol to a mixture of side products which proved impossible to isolate. Small amounts of the alcohol were observed in the crude NMR spectra of some reactions, but attempts to increase the yield by using a further excess of Selectfluor™ were unsuccessful. A 49% yield of the oxazinium salt (**111**) was obtained when four equivalents of Selectfluor™ were heated with (–)-menthol under refluxing acetonitrile for 69 hours. A sodium iodide test of the reaction mixture failed to

show the presence of any oxidising material after this time indicating that all of the Selectfluor™ had been consumed.

Improved yields were obtained when the crude reaction product (**111**) from (–)-menthol, Selectfluor™ and acetonitrile was treated with 10% aqueous sodium hydroxide at room temperature for 16 hours. This resulted in the production of the hydroxy amide (**118**) in 83% isolated yield. The crude amide could be hydrolysed further to the hydroxyamine in 51% isolated yield as the maleate salt monohydrate (**119**) (**Fig. 2.40**).

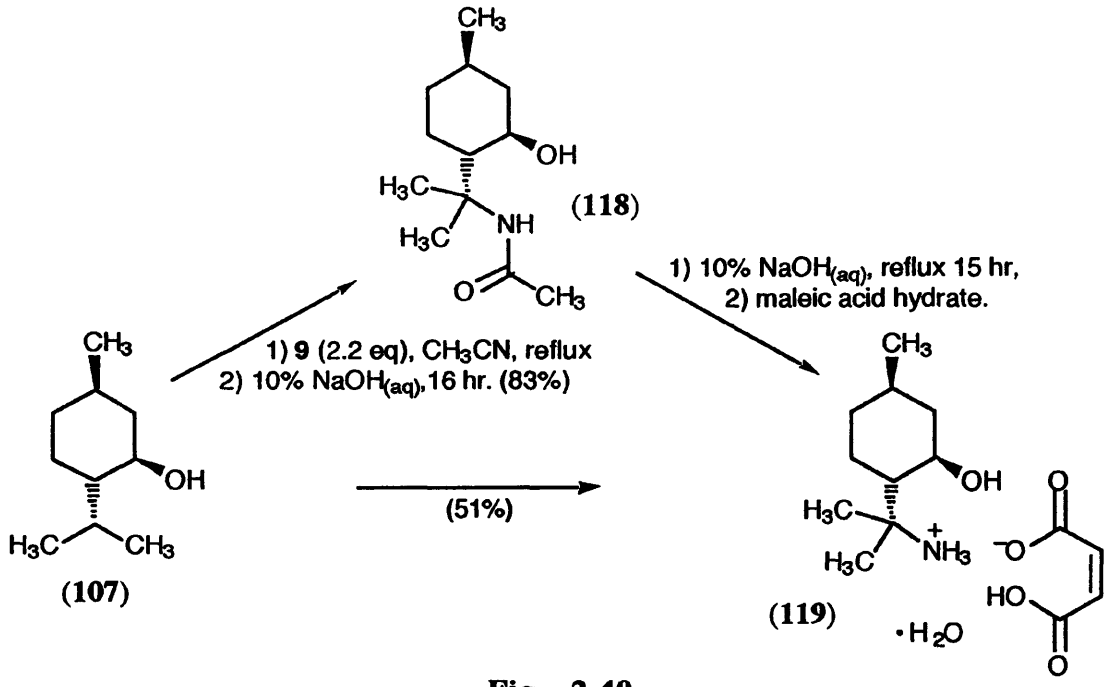


Fig. 2.40

The mechanism suggested for the formation of the oxazine ring initially involves the formation of a radical on the oxygen atom. This could be effected either by SET or by the decomposition of an alkyl hypofluorite formed by the nucleophilic attack of the hydroxyl group on Selectfluor™ (**Fig. 2.41**).

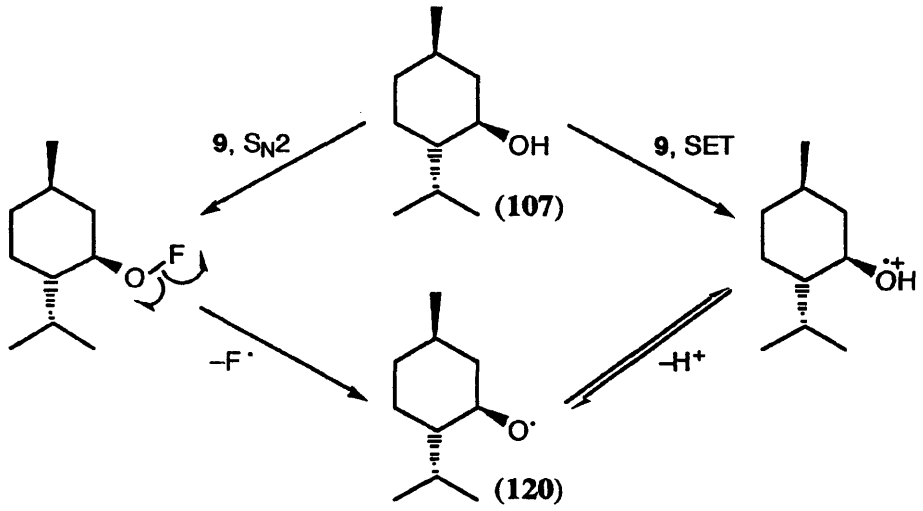


Fig. 2.41

The radical thus formed (**120**) is in the correct position to abstract a hydrogen atom from the isopropyl group. The resulting tertiary alkyl radical is then oxidised by Selectfluor™ in a SET reaction to form a tertiary carbenium ion which is then trapped by the acetonitrile solvent in a Ritter-like reaction.[224] The lone pair on the oxygen atom then attacks the carbon atom of the acetonitrile fragment. Deprotonation of the oxygen atom followed by protonation of the imine results in the formation of **111** (**Fig. 2.42**).

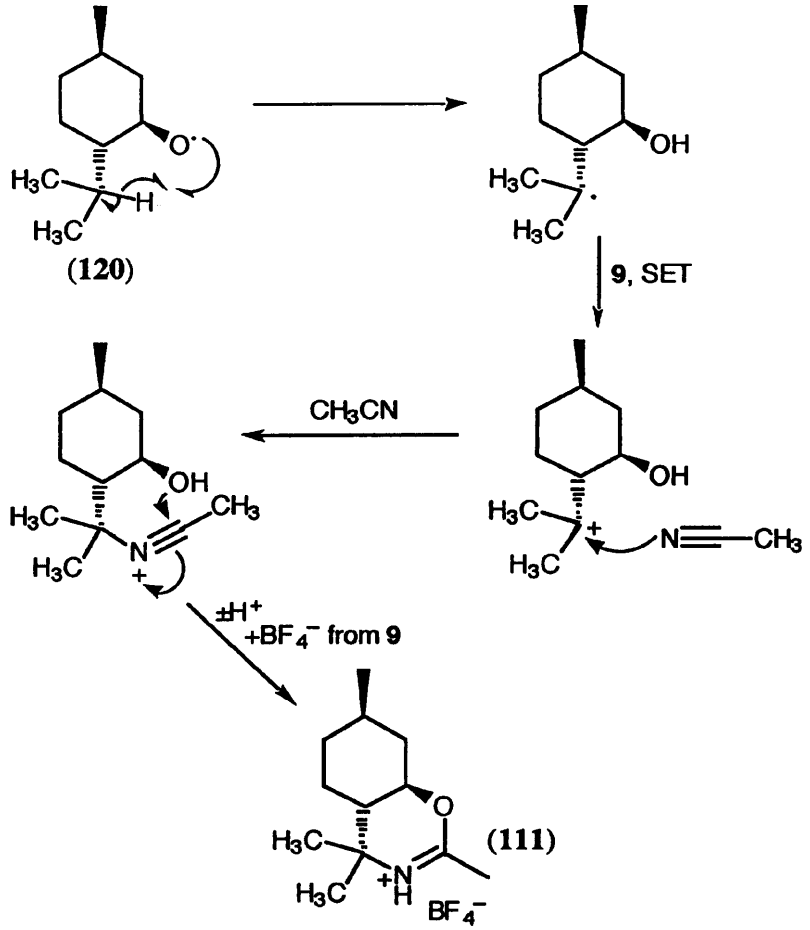


Fig. 2.42

Other substrates (2-methybutan-1-ol, pentan-2-ol and 4-phenylbutan-2-ol) were reacted with Selectfluor™ in acetonitrile under conditions identical to those which resulted in the formation of **111**, but it was not possible to isolate or identify the products present in the thick, black oils which resulted from these reactions. This supports proposed mechanism involving the formation of a tertiary carbenium ion. To undergo an analogous reaction these substrates would have to form much less stable primary or secondary carbenium ions. It is suggested by the nature and ^1H NMR spectrum (200 MHz, $CDCl_3$) that the reactions resulted in molecular fragmentation and polymerisation possibly due to the formation of these high-energy carbenium intermediates.

This reaction is an example of remote functionalisation, a particularly difficult process to effect. A search of the literature revealed two other cases where a nitrile is incorporated into a substrate in the presence of an electrophilic halogenating agent. The first describes

the reaction between alkenes and Selectfluor™ in nitrile solvents.[225] In this case the Selectfluor™ fluorinates the alkene to form an α-fluorocarbenium compound which reacts with solvent and is hydrolysed to the corresponding amide (**Fig. 2.43**).

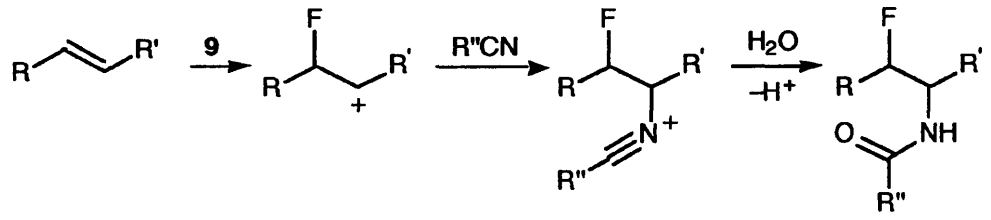


Fig. 2.43

The second example involves the reaction between an allylic alcohol and trichloroacetonitrile to form a trichloroacetimidate.[226] This is then reacted with iodonium dicollidinium perchlorate (which acts as a source of "I+"). The delivery of the iodonium ion to the double bond facilitates nucleophilic attack by the nitrogen atom at the other olefinic carbon atom thus closing the 5-membered ring to form a 4,5-dihydrooxazole (**Fig. 2.44**). Delivery of the nitrogen atom was found to be stereoselective, with attack occurring *syn*- to the allylic oxygen atom, giving only the *cis*-substituted product.

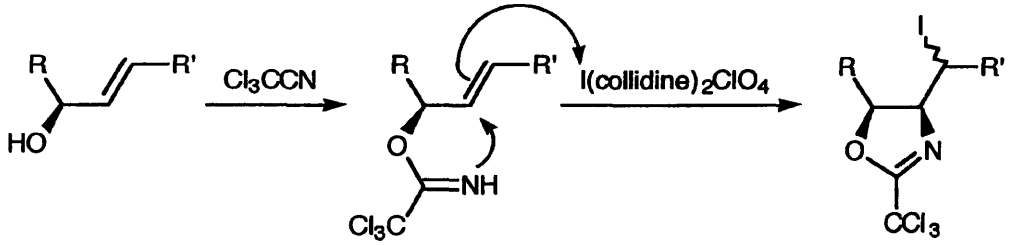
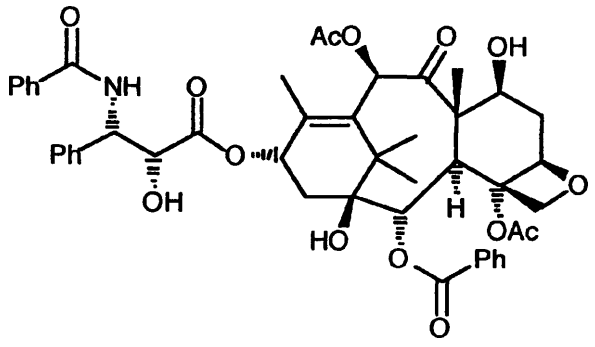


Fig. 2.44

2.6 Attempted reductive amination of a difluorobenzoylacetate

There has recently been much interest in the area of taxanes and their use as cancer chemotherapeutic agents. One of these substituted taxanes, paclitaxel (Taxol®,[227] **121**) is present in the bark of the Pacific yew tree, *Taxus brevifolia*. It has proved to be particularly effective in the treatment of ovarian and breast tumours.[228]



Paclitaxel (Taxol®, **121**)

Paclitaxel owes its anti-cancer properties to the fact that it binds strongly to tubulin, preventing the disassembly of microtubules, a process which is essential for cell division. Originally the Pacific yew was the only source of the drug, but the bark from six 100-year old trees yields only enough paclitaxel to treat one patient. Much work has gone into the development of semi-synthetic routes for the production of this and analogous compounds.[229]

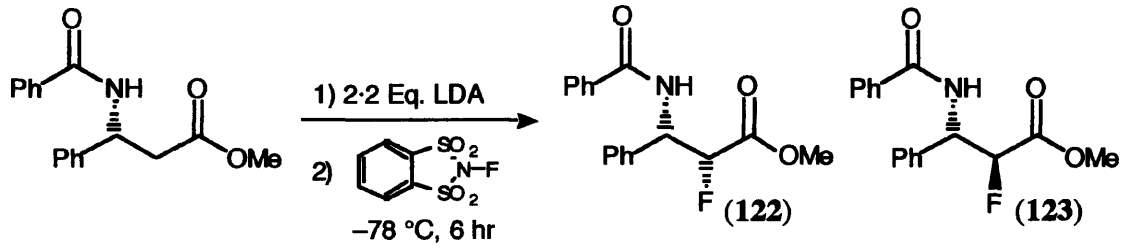


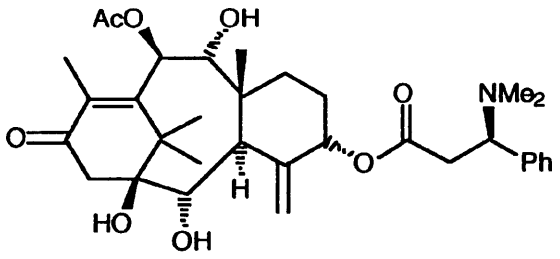
Fig. 2.45

It has been suggested by Swindell and co-workers that intramolecular hydrogen bonding between the hydroxy group of the C-13 side chain and the adjacent ester and amide groups is responsible for holding the side-chain in the correct conformation for receptor binding.[230] In order to probe this possibility Davis and co-workers have synthesised the fluoro-analogue of the C-13 side chain (**122**, **Fig. 2.45**).[169] The increased electronegativity of the fluorine atom over the hydroxyl group should enhance any hydrogen bonding with the amide group, but hydrogen bonding to the ester group is no longer possible due to the absence of a hydrogen atom for donation (**Fig. 2.46**). The steric effect of replacing the hydroxyl group with a fluorine atom should be small because of the similarity of the typical C–F and C–O bond lengths (1·39 and 1·43 Å respectively).[1]

(**121**) (**122**)

Fig. 2.46

Taxine B (**124**) is a compound found in *Taxus baccata*, the European or English yew tree. This is one of the compounds primarily responsible for the toxicity of the English yew. Taxine B itself is not useful as an anti-cancer drug because it exhibits broad spectrum toxicity, showing little selectivity towards tumour cells. The compound exhibits an LD_{50} in mice of 13 mg/kg, causing convulsions, reduction in blood pressure and cardiac arrest in diastole.[231] It is thought that this toxicity is due to its action as a calcium ion antagonist,[232] thus interfering with the mechanism of muscle contraction.



Taxine B (**124**)

The propanoic acid group which forms the C-5 side chain of taxine B is the taxane ester of the compound known as Winterstein's Acid after its discoverer.[233] At physiological pH it is prone to the elimination of dimethylamine, forming the more stable cinnamate (**125**) and rendering the molecule virtually inactive (**Fig. 2.47**).

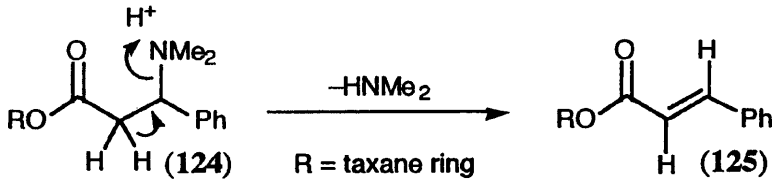


Fig. 2.47

The group working with Dr. Nick Lawrence at UMIST were interested in acquiring a sample of the 2,2-difluorinated ethyl ester of Winterstein's Acid (**126**, **Fig. 2.48**). The aim was to replace the C-5 side-chain in naturally occurring Taxine B with this group, thus removing the possibility of elimination of dimethylamine. Loss of the dimethyamino group would now require a stable C–F bond to be broken, making the process energetically unfavourable. In an attempt to synthesise compound **126**, ethyl 2-benzoyl-2,2-difluoroacetate (**78**) was subjected to reductive amination using dimethylamine and sodium cyanoborohydride.

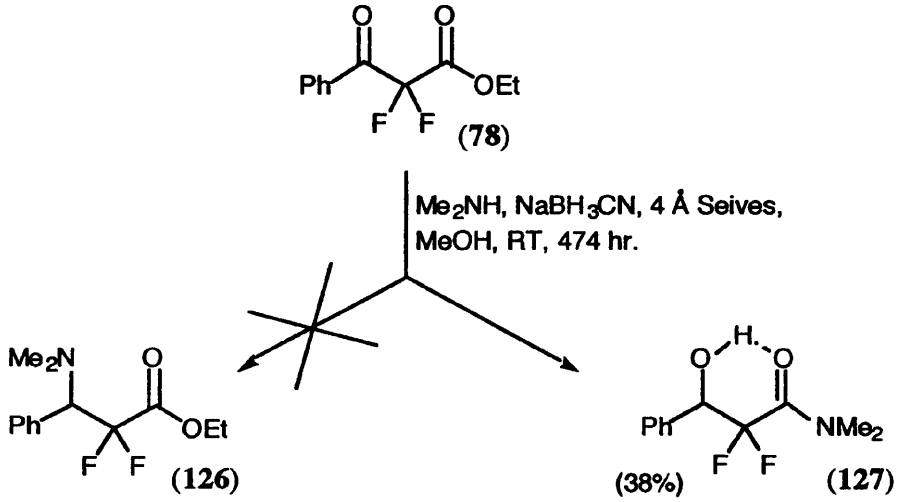


Fig. 2.48

The dimethylamine (added before the sodium cyanoborohydride) produced a noticeable exotherm when added to the reaction mixture. This was caused by the dimethylamine

reacting with the ethyl ester to form an amide. Qualitatively, the reactivity of the ester towards the dimethylamine was approximately that which would be expected for an acid chloride. This increased susceptibility to nucleophilic attack at the carbonyl group is caused by the electron withdrawing effect of the two α-fluorine atoms. This enhanced reactivity of α-difluoroesters towards nucleophilic substitution has been used to good effect by Tsukamoto and Coward. They have used benzylamine to selectively displace *tert*-butanol from an α-difluoro ester in the presence of another *tert*-butyl ester (**Fig. 2.49**).[234]

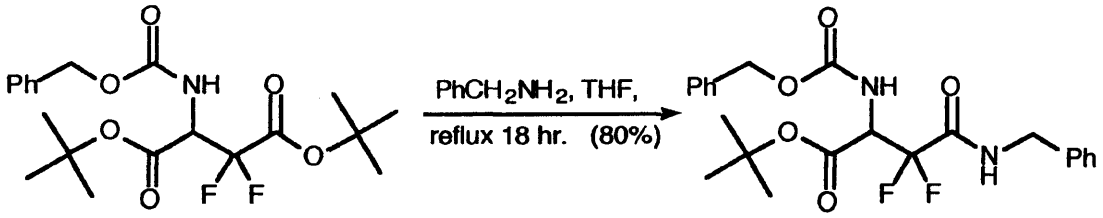


Fig. 2.49

Although the reduction of the ketone by sodium cyanoborohydride is very slow (much slower than with sodium borohydride), the formation of the imine is much slower, so no amine was produced in the reaction. The structure of the product was confirmed by comparison to an authentic sample of **127** synthesised by reduction of **80** (**Fig. 2.50**).

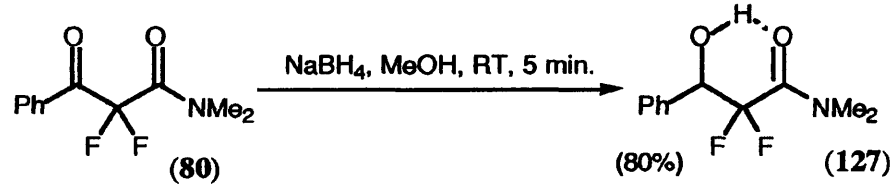


Fig. 2.50

The ^{1}H and ^{19}F NMR data of **127** show that one of the fluorine atoms is not coupled to the hydrogen atom on the adjacent carbon atom. This suggests that the molecule is held in a fixed conformation such that the dihedral angle between this fluorine atom and the hydrogen atom is close to 90 degrees (Karplus equation) (**Fig. 2.51**).

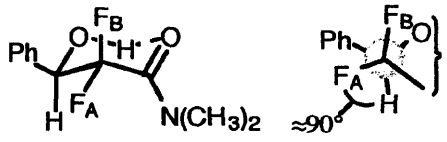
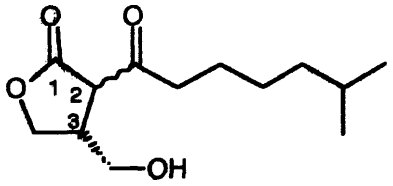


Fig. 2.51

The synthesis of **126** could possibly be achieved by displacement of the tosylate of **127** using dimethylamine. This amide could then be carefully converted to the required taxane ester using titanium tetraisopropoxide and the protected hydroxy taxane in toluene.

2.7 Synthesis of 2-Fluoro-A-factor

(3*R*)-(–)-A-Factor (**128**) is an inducer of cytodifferentiation in many streptomycetes. In *Streptomyces griseus*, it can induce the biosynthesis of streptomycin in inactive mutants and bring about the formation of spores in asporophological modifications.[235] The full stereostructure of A-factor was determined as (3*R*) (with rapid epimerisation at C-2) in 1983 by Mori,[236] although the substance was first isolated from *S. griseus* by Khoklov in 1976.[237]



(3*R*)-(–)-A-Factor (*R*)-(**128**)

Following the earlier research on the fluorination of 1,3-dicarbonyl compounds, this compound looked like an ideal candidate for fluorination at the 2-position using Selectfluor™. A search of the literature revealed several methods for the synthesis of A-factor, as the (3*R*), (3*S*) or (3*RS*) stereoisomers. The earliest of these, published in 1982 by Mori and Yamane, describes the synthesis of both the (3*R*) and (3*S*) stereoisomers.[238] The publication describes the resolution of (±)-paraconic acid (**129**) with (*R*)-α-phenethylamine, followed by reduction using borane-dimethylsulfide to form the butanolide (**130**) (**Fig. 2.52**).

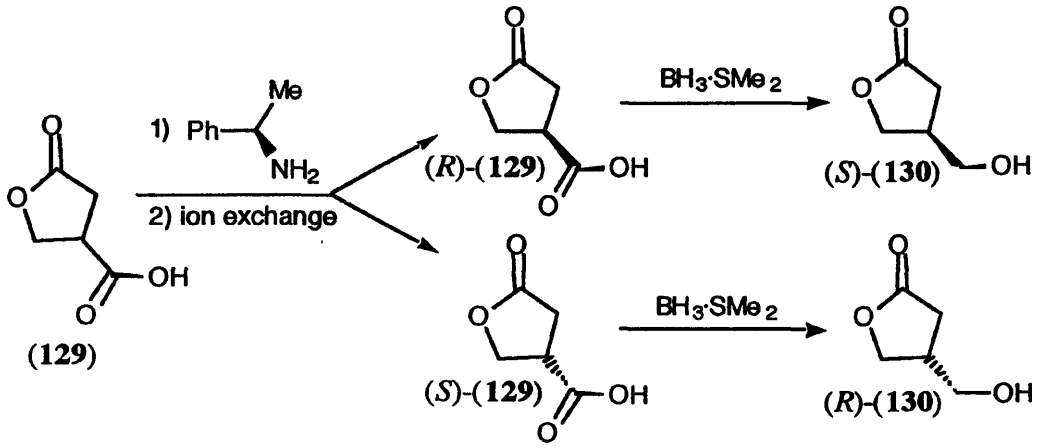
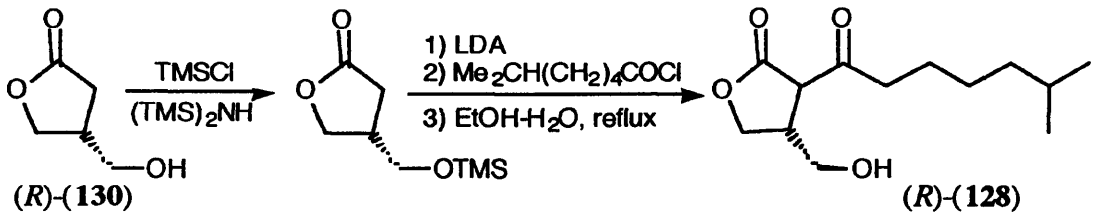


Fig. 2.52

The enantiomeric lactones were then protected as the trimethylsilyl ethers, deprotonated and acylated with 6-methylheptanoyl chloride at –78 °C to form the two (3*R* and 3*S*) stereoisomers of silylated A-factor. The crude, protected products were treated with a refluxing solution of ethanol-water to remove the trimethylsilyl groups (**Fig. 2.53**).

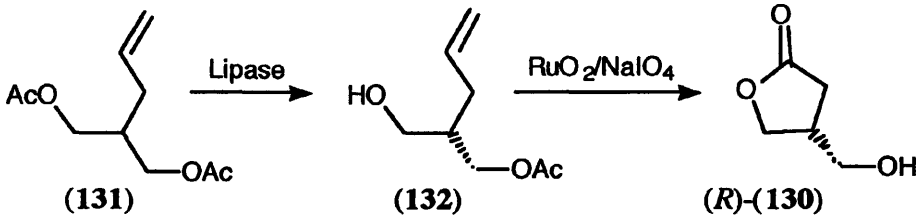


(*R*)-(**130**) (*R*)-(**128**)

Fig. 2.53

A more recent publication on the synthesis of A-factor describes the use of pig pancreatic lipase to effect a stereoselective hydrolysis of a symmetrical diester and hence obtain **128** in a stereoisomerically pure form (**Fig. 2.53**).[239] Other work has been published on the use of selectively stereogenic reactions using chiral auxiliaries.[240,241] A synthesis of racemic **128** *via* the reduction of a 2-ethoxyfuran has also been described.[242]

In the synthesis of racemic **128** for this work it was decided to use a modification of the synthesis described by Mori.[238] Rather than synthesise the paraconic acid (**129**) and reduce it to the butanolide (**130**), this compound was produced directly using a modification of the work described by Mori in a later publication.[239] In this paper he describes the synthesis of optically pure paraconic acid from the diol diacetate (**131**) *via* a monoacetylated diol (**132**) produced by the stereoselective hydrolysis of one of the acetate groups using pig pancreatic lipase (**Fig. 2.54**).



(**131**) (**132**) (*R*)-(**130**)

Fig. 2.54

In 1978 Griesbaum described the cleavage of alkenes to form ester fragments.[243] This was achieved by treating symmetrical alkenes with ozone in a solution of alcohol containing hydrogen chloride at –70 °C (**Fig. 2.55**).

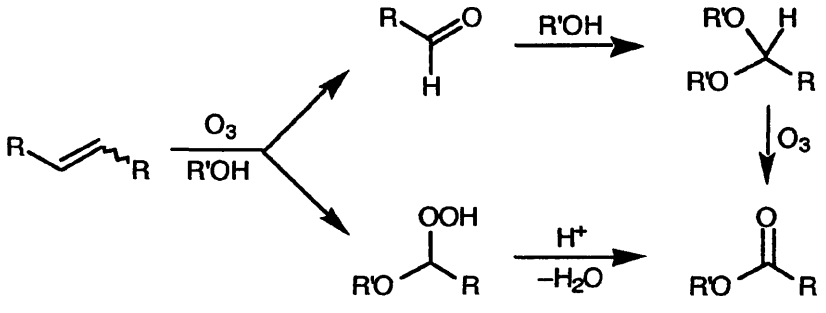


Fig. 2.55

Yields for this reaction were given as 65% to 85% for ten examples. If this transformation could be carried out on the diacetate (**131**) in methanol then the resulting fragments should consist of methyl formate and the triester (**133**). The former could

easily be removed from the reaction *in vacuo*, whilst the latter should solvolyse and cyclise under the reaction conditions to produce racemic **130** directly (**Fig. 2.56**).

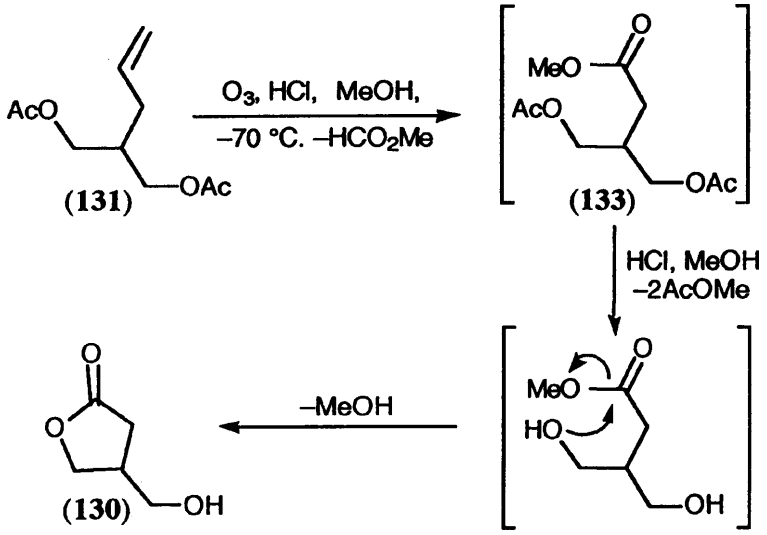


Fig. 2.56

In order to carry out this reaction the diester was synthesised in two steps from diethyl allylmalonate. In the first step diethyl allylmalonate (**134**) was treated with lithium aluminium hydride in dry ether to produce the diol (**135**) in 80% yield. This material was then diacetylated using acetic anhydride in acetonitrile. This resulted in an isolated yield of 78% for the diester (**131**) (**Fig. 2.57**).

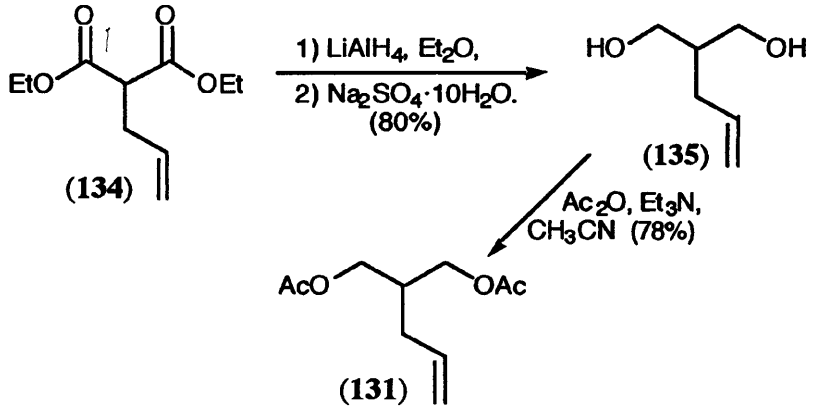


Fig. 2.57

The ozonolysis of **131** was carried out to give **130** directly in 50% yield. It was found that the final, transesterification step would only proceed to completion under refluxing conditions (**Fig. 2.58**).

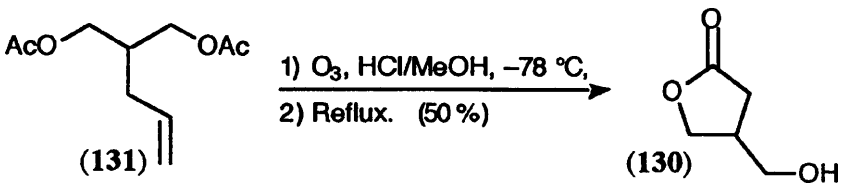


Fig. 2.58

Mori's work (**Fig. 2.53**) describes the preparation of A-factor from **130**, but this route uses a trimethylsilyl protecting group on the alcohol. It has already been established that Selectfluor™ may react with unprotected hydroxyl groups in an unpredictable manner, so the protecting group chosen at this stage of the synthesis should be such that it can withstand the conditions used for both the acylation and the fluorination reactions. Both of these steps require the use of strong bases, so the alcohol could not be protected as an ester. A silyl ether would withstand the basic conditions, but the stability of this group had not been established in the presence of Selectfluor™. This was of particular concern because the salt exchange reaction (tetrafluoroborate for fluoride) in the fluorination step does not proceed with 100% exchange. This means that even commercially available Selectfluor™ contains a small amount of fluoride ions. This could pose a particular problem for using the reagent in the presence of silyl ethers as fluoride is the most commonly used deprotecting agent for these groups.[244]

In order to ascertain the stability of the silyloxy group in the presence of Selectfluor™ hexan-1-ol (**136**) was derivatised with three of the more widely used silyl protecting groups (**Fig. 2.59**).

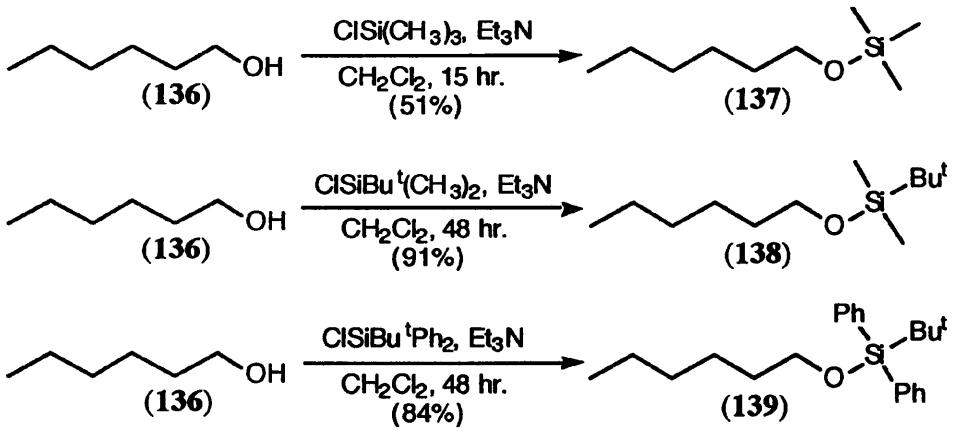


Fig. 2.59

These compounds were then dissolved in D_3-acetonitrile (0·5 ml) placed in an NMR tube with 1·2 equivalents of Selectfluor™. After 24 hours the amount of silyl ether was determined by integration of the of the ^1H NMR signal (200 MHz, CD_3CN) due to the 1-$C\underline{H_2}OR$ group. This signal appears as a triplet at δ3·54, 3·64, 3·67, 3·74 ppm for **136**, **137**, **138** and **139** respectively. The experiments were repeated using fresh samples, but were heated to 50 °C for 17 hours. Both sets of experiments were carried out using two different batches of Selectfluor™. The results are shown in **Fig. 2.60** and **Table 2.8**.

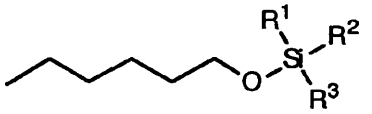


Fig. 2.60

Silyl ether	R^1	R^2	R^3	Silyl ether present after 24 hr at 20 °C		Silyl ether present after 17 hr at 50 °C	
				Synthesised[a]	Commercial[b]	Synthesised[a]	Commercial[b]
137	CH_3	CH_3	CH_3	53%	0%	0%	0%
138	CH_3	CH_3	$C(CH_3)_3$	77%	20%	0%	0%
139	Ph	Ph	$C(CH_3)_3$	100%	100%	63%	0%

[a]Selectfluor™ which had been synthesised at UMIST. (F^- content 1·35%).
[b]Selectfluor™ which had been donated by Air Products and Chemicals Inc. (F^- content 1·85%).

Table 2.8

Analysis of the commercial material showed it to contain 98·2% active fluorinating reagent, but it also contained 1·85% fluoride by mass. The material which was synthesised at UMIST was shown to contain 95·6% active fluorinating reagent, but contained slightly less fluoride (1·35% by mass).

The results **Table 2.8** indicate that the stability of the protecting group increases as the size of the groups attached to the silicon atom increase. There is also a difference in the ability of the two different batches of Selectfluor™ to deprotect the silyl ethers. This difference is unlikely to be due to the differing amount of active material as the commercial compound has only 3% extra active N–F. However, there is 37% more fluoride in the commercial material than in the batch which was synthesised at UMIST. Fluoride compounds are the reagents of choice for the deprotection of silyl ethers, so the difference between the fluoride content of the two batches is the most likely cause of the differing abilities to deprotect silyl ethers.

The results also show that, of the three silyl groups tested, only the *tert*-butyldiphenylsilyl group is capable of withstanding the presence of Selectfluor™ for any extended period, even at room temperature. It is for this reason that this group was chosen for the protection of the lactone (**130**) in the synthesis of A-factor (**128**). This protection was carried with a 79% yield using *tert*-butyldiphenylsilyl chloride in DMF with imidazole as a base (**Fig. 2.61**).

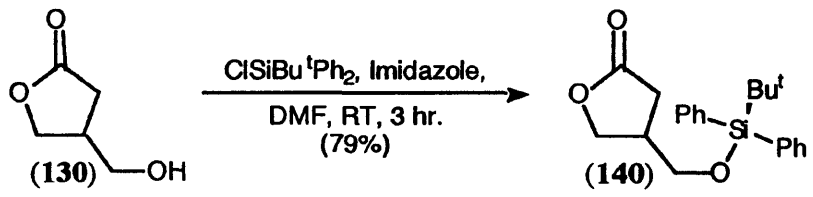


Fig. 2.61

The next step of the synthesis involves deprotonation of **140** followed by treatment with 6-methylheptanoyl chloride. Neither this material or the corresponding acid were available commercially, so the compound was synthesised from 4-methylpentanoic acid (**141**) using an established route (**Fig. 2.62**).[245]

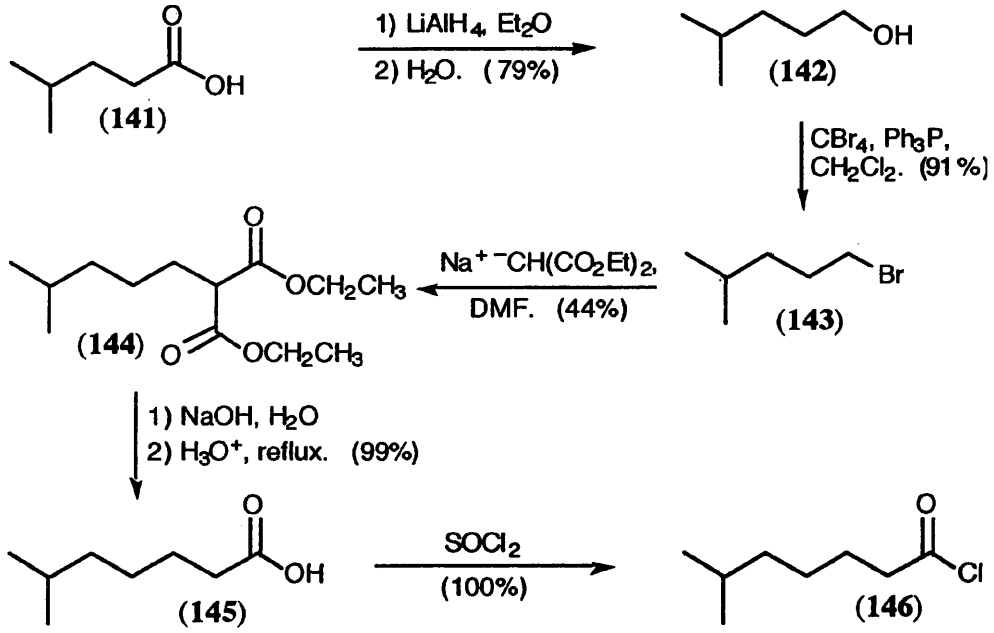


Fig. 2.62

The 4-methylpentanoic acid (**141**) was reduced to the corresponding alcohol (**142**) in 79% isolated yield using lithium aluminium hydride in diethyl ether. This alcohol was converted to 1-bromo-4-methylpentane (**143**) using carbon tetrabromide and triphenylphosphine in dichloromethane. This resulted in a 91% yield of **143** after distillation. The carbon chain was then extended by displacement of the bromine atom by the sodium salt of diethyl malonate in DMF. This reaction proved to be rather troublesome, hence the low (44%) yield. The main problem with this reaction was due to the formation of the dialkylated product (**147**) (**Fig. 2.63**).

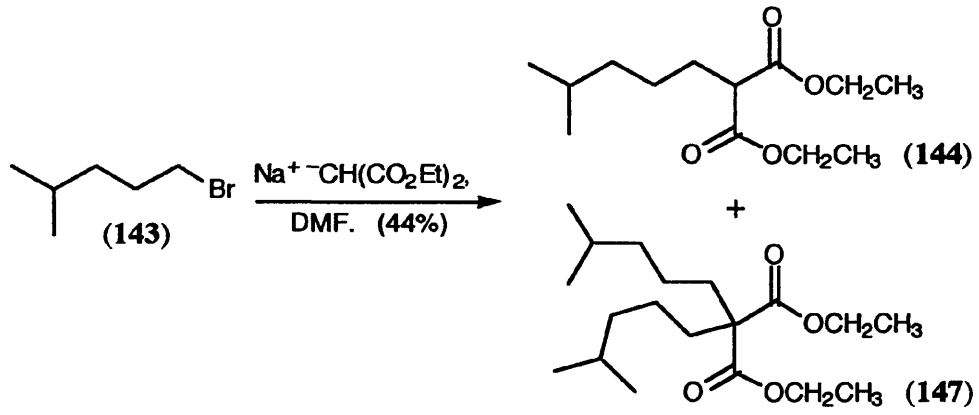


Fig. 2.63

The most effective way to separate the desired product (**144**) from the unwanted material (**147** and unreacted diethyl malonate) was by chromatography (to remove the more polar diethyl malonate followed by distillation (to remove the higher boiling **147**). This resulted in a yield of 44% for the isolated diethyl isohexylmalonate (**144**). This was efficiently hydrolysed with aqueous sodium hydroxide and decarboxylated with dilute hydrochloric acid to give **145** in 99% isolated yield. This acid was then converted quantitatively to 6-methylheptanoyl chloride (**146**) in refluxing thionyl chloride.

The two fragments of A-factor (**140** and **146**) were then brought together as shown in **Fig. 2.64.**

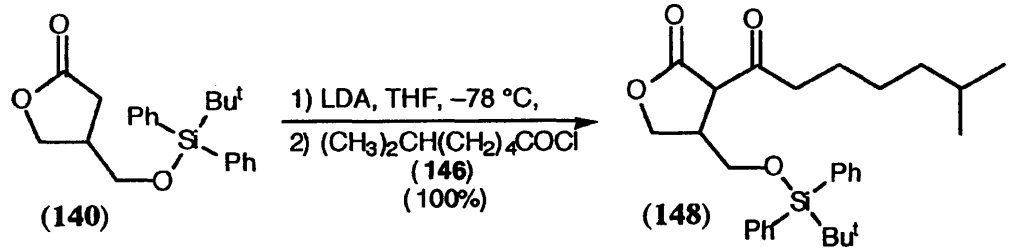


Fig. 2.64

This reaction proceeded in quantitative yield to produce **148** as a yellow oil. This compound was deprotonated with sodium hydride in THF and fluorinated with a slight (10%) excess of Selectfluor™ to give the protected 2-fluoro-A-factor (**149**) (**Fig. 2.65**).

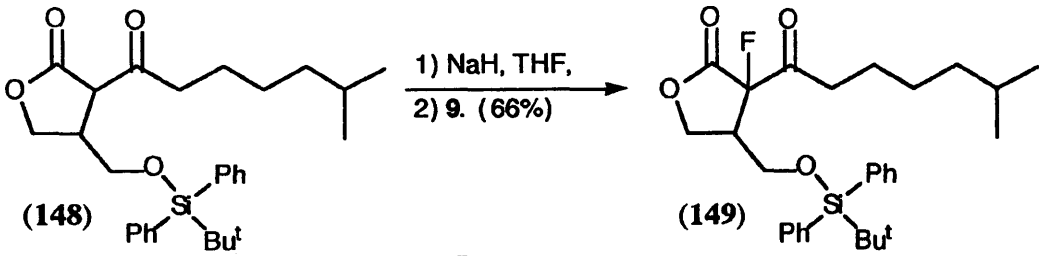


Fig. 2.65

The final step in the synthesis of 2-fluoro-A-factor (**150**) was the removal of the silyl protecting group. Several attempts were made to carry out this reaction using tetra-*n*-butylammonium fluoride. The reaction was carried out several times using tetrahydrofuran, dichloromethane and acetonitrile as solvent, at temperatures ranging from between 21 °C to 40 °C. These reactions were carried out in the presence and absence of water, but the result was the same each time. Neither starting material nor any identifiable compound was recovered from the reaction mixture. At higher temperatures the odour of the reaction products suggested that isooctanoic acid (**145**) had been produced, but it was not possible to cleanly separate any of the reaction products to validate this speculation.

The deprotection was then attempted using Amberlite™ IR-120(+) ion exchange resin and water in deuterated acetonitrile at 45 °C. The NMR analysis (200 MHz, CD_3CN) of the reaction mixture after 17 hours showed that the starting material had been consumed and in its place was a compound which had a spectrum similar enough to that expected for the target material (**150**) to warrant further investigation. The concentrated reaction

mixture was subjected to chromatography to give the desired material in 14% yield. However, when this reaction was repeated under the same conditions on a preparative scale, the starting material was recovered, unaffected by the ion exchange resin. A reaction could be achieved by raising the temperature to 60 °C, but this resulted in a poor yield (5% isolated) of product with no recovery of starting material. This was improved to 8% by using the ion exchange resin and pyridine hydrofluoride in dry acetonitrile at 60 °C. By lowering the reaction temperature and including water in the latter reaction the yield was further improved to 21%. The use of Amberlyst™ A-26(F) in place of the IR-120(+) further improved the efficiency of the reaction to 28%.[246] The results of these experiments are shown in **Table 2.9**.

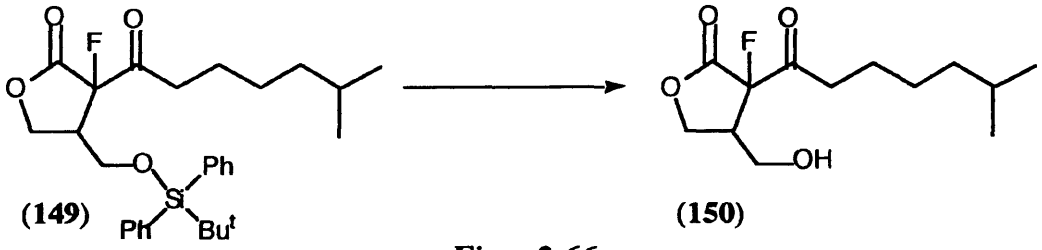


Fig. 2.66

Entry	Solvent	Temp. (°C)	Time (hr)	TBAF (eq.)	Water (eq.)	Resin (g/mmol)	Py·HF (g/mol)	**149** isolated	**150** isolated
1	THF	21	17	3·0	1·3	–	–	0%	0%
2	THF	25	24	16·0	2·0	–	–	0%	0%
3	CH_2Cl_2	21	19	3·0	–	–	–	0%	0%
4	$CDCl_3$	21	45	1·0	2·3	–	–	88%	0%
5	CH_3CN	40	17	0·2	11·2	–	–	0%	0%
6	CD_3CN	45	16	0·4	–	–	–	0%	0%
7	CD_3CN	45	17	–	2·0	IR-120(+) 5·9	–	0%	14%
8	CH_3CN	45	24	–	2·2	IR-120(+) 6·0	–	100%	0%
9	CH_3CN	60	52	–	2·2	IR-120(+) 6·7	–	0%	5%
10	CH_3CN	60	22	–	–	IR-120(+) 6·7	137	0%	8%
11	CH_3CN	55	22	–	2·2	IR-120(+) 6·7	137	0%	21%
12	CH_3CN	55	20	–	20·8	A-26(F) 6·8	193	0%	28%

Note: All reagent quantities are quoted relative to compound **149**

Table 2.9

These results demonstrate that deprotection of **149** must be carried out in an acidic medium with an excess of water present. Reactions carried out in TBAF (very slightly basic) generally resulted in the loss of starting material, with the production of many-component mixtures. The best combination of conditions found were those shown in **Entry 10** this reaction resulted in a 21% yield of **150** as a waxy, off-white solid. The yield could probably be further optimised with an increase in the pyridine hydrofluoride and water content of the reaction. However, a lack of time and sufficient quantities of **149** prevented further optimisation of this step. All of the **150** generated so far will be submitted for biological assay against A-factor itself.

2.8 Concluding comments

Selectfluor™ has been shown to be a versatile fluorinating reagent, which is easily prepared in high yield (70% overall) from inexpensive starting materials. It is also commercially available for those researchers that do not have the facilities for handling elemental fluorine.

The synthesis of this reagent is relatively non-hazardous when compared to some of the alternatives. For example DesMarteau's reagent[152] (**27**) (p 22) is prepared by condensing liquid fluorine onto a perfluoroimide in a stainless steel bomb. This procedure is hazardous and the risk of fire and/or explosion means that it is not suitable for large-scale preparations. Selectfluor™, on the other hand, can be routinely and safely prepared in batches of greater than 100 g.

The reactivity of this reagent is such that prolonged reaction times and elevated temperatures are not always necessary. However, the results of the thermal stability experiments have shown that the reagent does decompose slowly in contact with acetonitrile and glass, especially at elevated temperatures. This decomposition appears to begin at temperatures above 40 °C, with a slight increase in the effect as the boiling point of acetonitrile (82 °C) is reached. Allowance should be made for this in any reaction which requires the reagent to be heated in acetonitrile.

The ability of Selectfluor™ to fluorinate neutral 1,3-dicarbonyl compounds and aromatic ring systems puts the reactivity of the reagent close to the top of the list of the commercially available N–F electrophilic fluorinating reagents, although this inevitably means that it can also act as a fairly powerful oxidising reagent. Indeed, the experiments have demonstrated that benzylic alcohols and benzaldehydes are oxidised by the Selectfluor™ reagent in moderate yield. Although this method is only likely to compete with established oxidising agents under special circumstances, the intermediacy of acyl fluorides offers potential advantages should acyl derivatives be the ultimate target molecules.

This oxidative power can sometimes result in interesting products [such as those observed in the reaction with (–)-menthol, **Section 2.5**], but such reaction it is usually

undesirable. This means that readily oxidisable functionalities, such as hydroxyl groups, should be protected before the compound can be treated with Selectfluor™. This, in itself, can also present a problem as it has been shown that silyl ethers are readily cleaved by the presence of Selectfluor™ in the reaction mixture. Thus it is undesirable to protect groups in the substrate using the commonly used silyl groups such as TMS, TBDMS and TBDPS if prolonged contact with Selectfluor™ is expected.

The reaction of Selectfluor™ with acetophenone demonstrates that it is possible to substitute fluorine for activated hydrogen atoms such as where there is an α-carbonyl group even if the enol content is very low, although the low yield and lengthy reaction time for this reaction mean that it would only become a desirable synthesis if an alternative route could not be found.

The first synthesis of 2-fluoro-A-factor was achieved using Selectfluor™. The biological activity of this material will be compared to that of A-factor itself.

3. Experimental

"What we anticipate seldom occurs; what we least expected generally happens."
-Benjamin Disraeli, *Henrietta Temple.*

3.0 General Procedures

Solvents and reagents: "Petrol" refers to the fraction of light petroleum-ether boiling between 40-60 °C. Anhydrous solvents and reagents were obtained as follows:

CH_3CN -HPLC grade from Aldrich stored over molecular sieves (4 Å) under nitrogen.

DMF -refluxed over CaH_2 under nitrogen for 2 hours, distilled under a reduced pressure of nitrogen and stored over molecular sieves (4 Å) under nitrogen.

THF -distilled from sodium/benzophenone ketyl under nitrogen shortly prior to use.

Toluene -stirred over CaH_2 under nitrogen for 24 hours, distilled under a reduced pressure of nitrogen and stored over molecular sieves (4 Å) under nitrogen.

All other reagents were purified in accordance with the recommendations collected in D. D. Perrin and W. L. F. Armarego's "Purification of Laboratory Chemicals", third edition, Pergamon Press, London (1988), or used as obtained from commercial sources. All chemicals and apparatus were handled in accordance with the safety instructions identified in L. M. Harwood and C. J. Moody's "Experimental Organic Chemistry, Principles and Practice", Blackwell Scientific Publications, Oxford (1989).

Chromatography: Flash chromatography was performed on silica gel [Fluka Silica gel 60 220-440 mesh (35-70 μm)] according to the method of W. C. Still.[247] "Dry" flash chromatography was performed on silica gel (Fluka Silica gel H 5-40 μm) according to the method of Harwood.[248] TLC was performed on aluminium backed plates pre-coated with silica (0·2 mm, 60 F_{254}) which were developed using standard visualising agents: UV fluorescence (254 nm), ninhydrin/Δ, molybdic acid/Δ, potassium permanganate/Δ and anisaldehyde/Δ. R_f values are reported to the nearest 0·01. Mixed solvent system compositions are quoted as a percentage by weight (w/w).

Melting points: These are uncorrected and were determined using an Electrothermal 9200 apparatus.

Optical rotations: These were measured using an Optical Activity Ltd. AA-1C00 polarimeter equipped with a cell of 10 cm length. Concentrations are quoted in grammes per 100 ml.

Microanalyses: These were performed at UMIST by Dr. R. Perry and his colleagues.

Infra red spectra: These were recorded neat as thin films (between CsI plates) or as KBr disks on a Perkin-Elmer 783 spectrometer. Only selected absorbances (υ_{max}) are reported (in wavenumbers).

^{1}H NMR spectra: These were recorded at 200 MHz on a Bruker AC-200 instrument or at 300 MHz on a Bruker AC-300 instrument. Chemical shifts (δH) are quoted in parts per million (ppm), relative to tetramethylsilane and are referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0·5 Hz. Resonances and coupling constants for AB quartets were calculated using the following equations:

$$J_{AB} = (\upsilon_4 - \upsilon_3) = (\upsilon_2 - \upsilon_1); \qquad \delta A - \delta B = \sqrt{(\delta_4 - \delta_1)(\delta_3 - \delta_2)}.$$

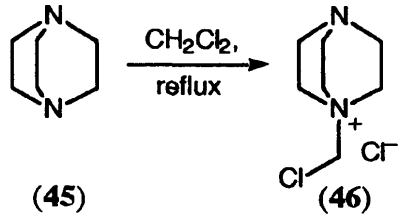
^{13}C NMR spectra: These were recorded at either 50 MHz on a Bruker AC-200 instrument or at 75·5 MHz on a Bruker AC-300 instrument. Chemical shifts (δC) are quoted in ppm, relative to tetramethylsilane and are referenced to the appropriate solvent peak. Coupling constants (*J*) are reported to the nearest 0·5 Hz.

^{19}F NMR spectra: These were recorded at 188 MHz on a Bruker AC-200 instrument. Chemical shifts (δH) are quoted in parts per million (ppm), relative to trifluoroacetic acid and are referenced to the appropriate residual solvent peak. Coupling constants (*J*) are reported to the nearest 0·5 Hz.

Mass spectra: These were recorded on VG70-70 EQ (FAB, EI$^+$, CI$^+$) and MS50 (FAB) spectrometers, with only major peaks being reported. Intensities are quoted as percentages (to the nearest 5%) of the highest peak.

3.1 Synthesis of the Selectfluor™ reagent

1.01: 1-Chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride ($C_7H_{14}ClN_2^+\ Cl^-$, MW = 197·11) (**46**):

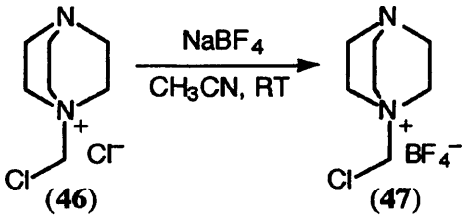


(**45**) (**46**)

1,4-Diazabicyclo[2.2.2]octane (DABCO®) (**45**) (112·2 g, 1·00 mol) was dissolved in dichloromethane (500 ml). The solution was refluxed for 2 hours, after which time a dense white precipitate had formed. The suspension was cooled strongly and the white solid was collected by suction filtration, washed with dichloromethane and stored in an

air-tight vessel. The filtrate was refluxed for a further 20 hours to give another suspension which was cooled strongly. The white solid was collected by suction filtration, washed with dichloromethane and combined with the first crop. The white crystalline solid (**46**)[249] thus derived was dried *in vacuo* to constant weight (187·5 g, 95%):
m.p. = dec≥150 °C; υ_{max} **(KBr disk)** 3425(s, br) 2985(s) 1640(w) 1495(m) 1465(s) 1370(s) 1095(s) 1055(s) 990(m) 840(m) 775(m) 685(m) 540(m) cm^{-1}; **δH (200 MHz, D_2O)** 3·36 [6H, t, *J* = 7·5 Hz, -($CH_2C\underline{H}_2)_3N$], 3·67 [6H, t, *J* = 7·5 Hz, -($CH_2C\underline{H}_2)_3N^+CH_2Cl$], 5·24 [2H, s, (-$CH_2)_3N^+C\underline{H}_2Cl$]; **δC (50 MHz, D_2O)** 46·6 [-($CH_2\underline{C}H_2)_3N$], 53·9 [-($CH_2\underline{C}H_2)_3N^+CH_2Cl$], 70·9 [(-$CH_2)_3N^+\underline{C}H_2Cl$]; **m/z (Ar FAB$^+$)** 361 (2M –$Cl^-$, 10%), 360 (2M –$Cl^-$, 5%), 359 (2M –$Cl^-$, 25%), 358 (2M –$Cl^-$, 5%), 357 (2M –$Cl^-$, 25%), 164 (M –$Cl^-$, 5%), 163 (M –$Cl^-$, 50%), 162 (M –$Cl^-$, 10%), 161 (M –$Cl^-$, 100%).

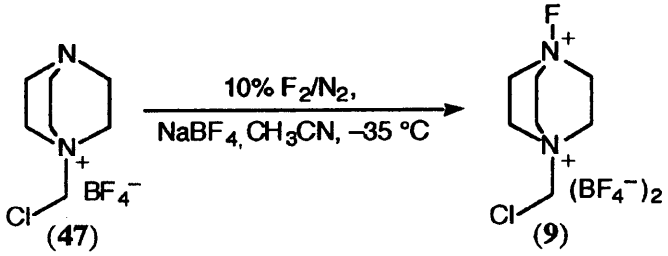
1.02: Stock acetonitrile solution of 1-Chloromethyl-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate ($C_7H_{14}ClN_2^+$ BF^-_4, MW = 248·47) (**47**):



A suspension of sodium tetrafluoroborate (51·2 g, 0·466 mol) in dry acetonitrile (500 ml) was poured into a stirred slurry of **46** (91·9 g, 0·466 mol) in dry acetonitrile (500 ml). The resulting suspension was heated to 40 °C for 30 minutes, then allowed to stir at room temperature for 3 days. The precipitated sodium chloride was collected by suction filtration and washed with dry acetonitrile. The filtrate (1030 ml total volume) was stored in an air-tight winchester for use as a stock solution for **Expt. 1.03**. A portion of the solution (50 ml) was concentrated *in vacuo* to give **47** as a white amorphous powder which was subjected to high vacuum until the weight was constant (5·4 g). It was calculated from this that the total yield of **47** in the solution was 111·2 g (96%). The solid thus obtained was used in the characterisation:
m.p. = 123-125 °C (Lit.[250] m.p. = 132 °C); **Found** C, 33·6; H, 5·9; N, 11·2; BF_4, 34·9%, $C_7H_{14}Cl_2N^+$ BF^-_4 requires C, 33·84; H, 5·68; N, 11·27; BF_4 34·94%; υ_{max} **(KBr disk)** 3070(m) 2985(m) 1465(m) 1345(m) 1060(s, br) 905(m) 840(m) 795(w) 775(m) 690(m) 540(m) 520(m) cm^{-1}; **δH (200 MHz, D_2O)** 3·35 [6H, t, *J* = 7·5 Hz, -($CH_2C\underline{H}_2)_3N$], 3·65 [6H, t, *J* = 7·5 Hz, -($CH_2C\underline{H}_2)_3N^+CH_2Cl$], 5·20 [2H, s, (-$CH_2)_3N^+C\underline{H}_2Cl$]; δC **(50 MHz, D_2O)** 46·6 [-($CH_2\underline{C}H_2)_3N$], 53·9 [-($CH_2\underline{C}H_2)_3N^+CH_2Cl$], 70·9 [(-$CH_2)_3N^+\underline{C}H_2Cl$]; **δF (188 MHz, D_2O)** –71·8 (s, $B\underline{F}^-_4$); **m/z (Ar FAB$^+$)** 411 (2M –BF^-_4, 10%), 410 (2M –BF^-_4, 5%), 409 (2M –BF^-_4,

15%), 408 (2M –BF^-_4, 5%), 164 (M –BF^-_4, 5%), 163 (M –BF^-_4, 45%), 162 (M –BF^-_4, 10%), 161 (M –BF^-_4, 100%).

1.03: 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate (Selectfluor™) [$C_7H_{14}ClFN_2^{2+}$ (BF^-_4)$_2$, MW = 354·28] (**9**):



A portion of the stock solution from **Expt. 1.02** [920 ml containing 99·4 g of **47** (0·4 mol)] was diluted with dry acetonitrile (to 1400 ml). Sodium tetrafluoroborate (43·9 g, 0·4 mol) was added and the stirred suspension was cooled to –40 °C under nitrogen in a dry ice/methylated spirit bath. A stream of fluorine gas (≈10%) in a nitrogen carrier was bubbled through the reaction mixture at such a rate as to deliver 18·5 g (0·49 mol) fluorine over a period of 5 hours. Completion of the reaction was indicated by the presence of fluorine in the exhaust gas from the reaction. When this occurred the reaction mixture was purged of fluorine by passing nitrogen through it for at least 1 hour whilst allowing it to warm to room temperature. Another portion of dry acetonitrile (400 ml) was added to the stirred reaction mixture to ensure complete solution of the product. The reaction was allowed to stand overnight to allow the sodium fluoride to settle out. The solution was filtered through Celite® which was then washed with dry acetonitrile. The combined filtrate was concentrated *in vacuo* to about one third of its volume. The resulting solid was collected by suction filtration, washed with dry acetonitrile, then dried *in vacuo* to constant weight. This gave **9** as an amorphous white powder. The process was then repeated on the filtrate to yield a second and third crop of the desired compound. These were also dried *in vacuo* to constant weight. ^{1}H NMR (200 MHz, deuterium oxide) of each crop showed the following composition:

Crop	Yield (g)	Yield if crop was pure (%)	% N–F (**9**)		% N–H (**64**)		% N (**47**)		Corrected Yield (%)
			molar	mass	molar	mass	molar	mass	
1	110·2	78	95	96	3	3	2	1	75
2+3	15·7	11	87	88	10	9	3	2	10
Total	125·9	89	Ave:	95	Ave:	4	Ave:	1	85

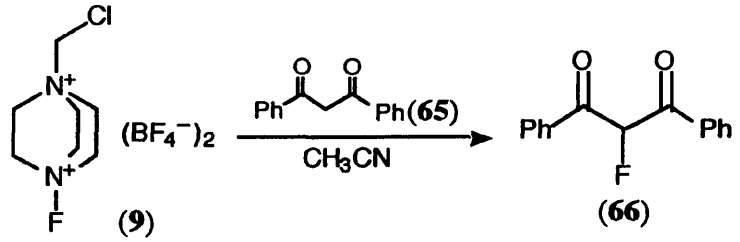
The first crop was used in the characterisation:

m.p. = dec.≥225 °C [Lit.[14] m.p. = 220-224 °C (dec.)]; υ_{max} **(KBr disk)** 3070(m) 3010(m) 2980(m) 2070(w, br) 1835(w) 1525(s, br) 1470(s) 1360(s) 1300(m) 1230(s) 1070(s, br) 840(s) 805(s) 685(w) 535(s) 520(s) 490(w) cm^{-1}; **δH (200 MHz, D_2O)**

4·68 [6H, m, J = 7·5 Hz, -($CH_2\underline{CH_2}$)$_3N^+CH_2Cl$], 5·13 [6H, q, J = 7·5 Hz, -($CH_2\underline{CH_2}$)$_3N^+F$], 5·66 [2H, s, (-CH_2)$_3N^+\underline{CH_2}Cl$]; **δC (50 MHz, D_2O)** 54·9 [m, J = 3·0 Hz, -($CH_2\underline{C}H_2$)$_3N^+CH_2Cl$], 58·4 [d, J = 15·0 Hz, -($CH_2\underline{C}H_2$)$_3N^+F$], 70·1 [(-CH_2)$_3N^+\underline{C}H_2Cl$]; **δF (188 MHz, D_2O)** –72·0 (s, $B\underline{F}^-_4$), +125·61 [s, -(CH_2CH_2)$_3N^+\underline{F}$]; **m/z (Ar FAB$^+$)** 392 (40%), 391 (100%), 329 (30%), 314 (45%), 164 ($M^{\bullet-}$ –F$^\bullet$ –2BF^-_4, 5%), 163 ($M^{\bullet-}$ –F$^\bullet$ –2BF^-_4, 40%), 162 ($M^{\bullet-}$ –F$^\bullet$ –2BF^-_4, 10%), 161 ($M^{\bullet-}$ –F$^\bullet$ –2BF^-_4, 100%).

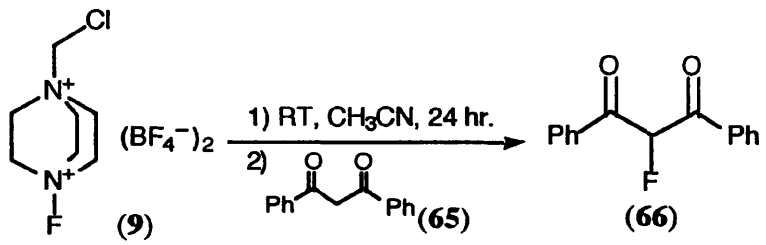
3.2 Thermal stability of Selectfluor™

2.01: Unheated (control) reaction:



To a solution of Selectfluor™ (**9**) (1·90 g 93% = 1·77 g, 5·0 mmol) in dry acetonitrile (50 ml) was added dibenzoylmethane (**65**) (1·12 g, 5·0 mmol). The reaction was allowed to stir at room temperature for 20 hours. After this time the suspension was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed twice with water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **66** (1·21 g, 99·9% mass balance) as a yellow oil which rapidly solidified. This solid was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of pure dibenzoylfluoromethane (**66**), thus giving an effective crude yield of 100%.
Data as for **Expt. 3.06** below.

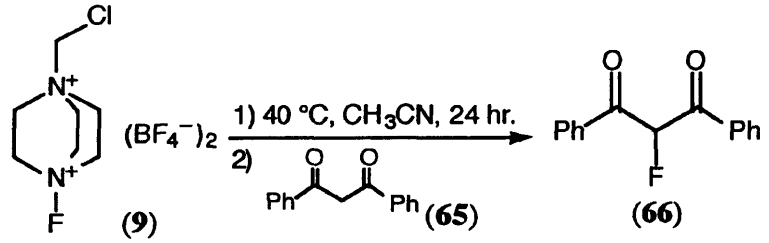
2.02: Room temperature reaction:



A solution of Selectfluor™ (**9**) (1·90 g 93% = 1·77 g, 5·0 mmol) in dry acetonitrile (50 ml) was stirred at 20 °C under nitrogen for 24 hours. After this time dibenzoylmethane (**65**) (1·12 g, 5·0 mmol) was added to the solution. The reaction was allowed to stir at

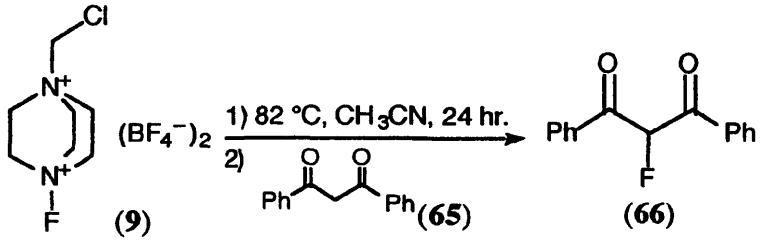
room temperature for 20 hours. After this time the suspension was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed twice with water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **66** (1·19 g, 98·2% mass balance) as a yellow oil which rapidly solidified. This solid was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of pure dibenzoylfluoromethane (**66**), thus giving an effective crude yield of 98%.
Data as for **Expt. 3.06** below.

2.03: 40 °C reaction:



A solution of Selectfluor™ (**9**) (1·90 g 93% = 1·77 g, 5·0 mmol) in dry acetonitrile (50 ml) was stirred at 40 °C under nitrogen for 24 hours. After this time dibenzoylmethane (**65**) (1·12 g, 5·0 mmol) was added to the solution. The reaction was allowed to stir at room temperature for 20 hours. After this time the suspension was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed twice with water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **66** (1·18 g, 97·4% mass balance) as a yellow oil which rapidly solidified. This tacky solid was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of 96·8(mass)% dibenzoylfluoromethane (**66**) contaminated with 3·2(mass)% dibenzoylmethane (**65**), thus giving an effective crude yield of 94·3%.
Data as for **Expt. 3.06** below.

2.04: 82 °C reaction:



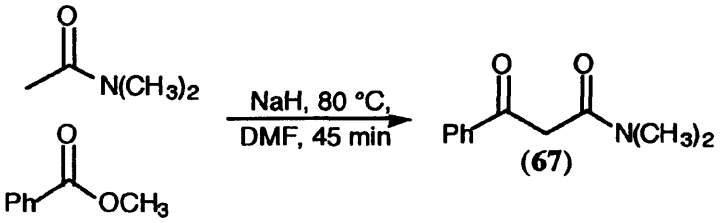
A solution of Selectfluor™ (**9**) (1·90 g 93% = 1·77 g, 5·0 mmol) in dry acetonitrile (50 ml) was stirred at 82 °C under nitrogen for 24 hours. After this time dibenzoylmethane (**65**) (1·12 g, 5·0 mmol) was added to the solution. The reaction was allowed to stir at

room temperature for 20 hours. After this time the suspension was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed twice with water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **66** (1·19 g, 98·2% mass balance) as a yellow oil which rapidly solidified. This tacky solid was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of 94·8(mass)% dibenzoylfluoromethane (**66**) contaminated with 5·2(mass)% dibenzoylmethane (**65**), thus giving an effective crude yield of 93·1%.
Data as for **Expt. 3.06** below.

3.3 Fluorinations with Selectfluor™

3.3.1 Fluorination of 1,3-dicarbonyl compounds

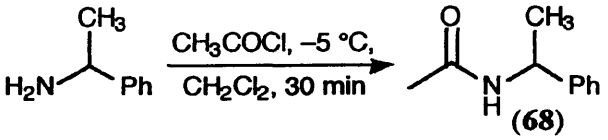
3.01: *N,N*-Dimethylbenzoylacetamide ($C_{11}H_{13}NO_2$, MW = 191·23) (**67**):



To a stirred solution of methyl benzoate (13·60 g, 100 mmol) and *N,N*-dimethylacetamide (8·70 g, 100 mmol) in dry DMF (100 ml) was added oil-free sodium hydride (2·64g, 110 mmol). The reaction was slowly heated to 80 °C, and was maintained at this temperature until no further hydrogen was evolved (about 45 minutes). The cloudy yellow solution thus obtained was allowed to cool to room temperature over 2 hours, then was poured into 0·5M aqueous hydrochloric acid (500 ml). This mixture was then extracted four times into dichloromethane (100 ml). The combined organics were washed three times with water (200 ml), then dried ($MgSO_4$). The yellow solution thus obtained was concentrated *in vacuo* to give crude **67** (22·40 g, 117% mass balance) as a yellow oil. The oil was subjected to dry flash chromatography eluting with 47% ethyl acetate in petrol to give **67** (11·40 g, 60% mass balance) as a yellow oil which solidified. This tacky solid was recrystallised from ethyl acetate in petrol to give **67** (8·10 g, 42%) as a white solid. ^1H NMR (200 MHz, $CDCl_3$) showed that the keto and enol forms of *N,N*-dimethylbenzoylacetamide (**67**) are in equilibrium (ratio ≈ 2:1) at room temperature:
R_f = 0·20 (47% EtOAc in petrol); m.p. = 74-75 °C (Lit.[251] m.p. = 79-81 °C); υ_{max} **(KBr disk)** 2930(w, br) 1620(s, br) 1575(m, br) 1495(s) 1435(m) 1315(s, br) 1250(w) 1160(s) 1170(m) 1080(m) 965(m, br) 770(s) 720(m) 690(m) 665(w) 610(w) 590(w) 410(w) cm^{-1}; δH_{keto} **(200 MHz, $CDCl_3$)** 3·05 [6H, s, $N(C\underline{H}_3)_2$], 4·11 [2H, s, $COC\underline{H}_2CON(CH_3)_2$], 7·42-7·58 (3H, m, *m*-,*p*-ArC<u>H</u>), 7·93-8·09 (2H, *o*-ArC<u>H</u>);

δH_{enol} (200 MHz, $CDCl_3$) 2·99 [6H, s, $N(C\underline{H}_3)_2$], 5·79 [1H, s, br, $Ph(HO)C=C\underline{H}CON(CH_3)_2$], 7·42-7·58 (3H, m, *m*-,*p*-Ar$C\underline{H}$), 7·67-7·86 (2H, m, br, *o*-Ar$C\underline{H}$); **δC_{keto} (75·5 MHz, $CDCl_3$)** 37·8 [$N(\underline{C}H_3)_2$], 45·7 [$CO\underline{C}H_2CON(CH_3)_2$], 128·4, 128·5 (*o*-,*m*-Ar$\underline{C}H$), 133·4 (*p*-Ar$\underline{C}H$), 136·1 (Ar *ipso*-$\underline{C}$), 172·1 [$CH_2\underline{C}ON(CH_3)_2$], 193·7 ($Ph\underline{C}OCH_2$); **$\delta C_{enol}$ (75·5 MHz, $CDCl_3$)** 35·3 [$N(\underline{C}H_3)_2$], 84·4 [$Ph(HO)C=\underline{C}HCON(CH_3)_2$], 125·7 (*p*-Ar$\underline{C}H$), 128·2 (*o*-Ar$\underline{C}H$), 130·4 (*m*-Ar$\underline{C}H$), 134·9 (Ar *ipso*-$\underline{C}$), 166·8 [$Ph(HO)\underline{C}=CHCON(CH_3)_2$], 171·0 [$\underline{C}ON(CH_3)_2$]; **m/z (EI$^+$)** 191 ($M^{\bullet+}$, 80%), 147 [$M^{\bullet+}$ $-(CH_3)_2N^{\bullet}$, 50%], 120 [$M^{\bullet+}$ $-(CH_3)_2NCO^{\bullet}$, 50%], 105 ($PhCO^+$, 80%), 77 ($C_6H_5^+$, 80%), 69 ($C_5H_9^+$, 65%), 51 ($C_4H_3^+$, 65%), 45 (80%), 44 [$(CH_3)_2N^+$, 100%].

3.02: (±)-*N*-(1-Phenylethyl)acetamide ($C_{10}H_{13}NO$, MW = 163·22) (**68**):

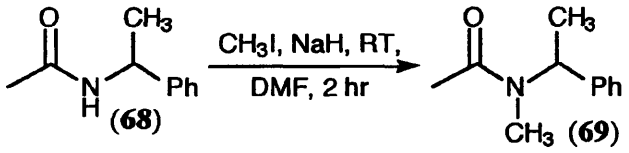


(68)

A stirred solution of (±)-α-methylbenzylamine (24·2 g, 200 mmol) in dichloromethane (200 ml) was cooled to –5 °C and a solution of acetyl chloride (7·9 g, 100 mmol) in dichloromethane (50 ml) was added dropwise keeping the temperature below 15 °C. On complete addition the reaction mixture was allowed to stir at room temperature for 30 minutes. The solution was then washed with water (150 ml), 2 M aqueous hydrochloric acid (150 ml) and once again with water (150 ml). The organic solution was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **68** as a colourless oil which quickly solidified on treatment with ethyl acetate in petrol. The resulting solid was collected by suction filtration to give **68** (14·3 g, 88%) as a white powder:

R_f = 0·28 (67% EtOAc in petrol); m.p. = 73-75 °C (Lit.[252] m.p. = 73-75 °C); **υ_{max} (KBr disk)** 3290(s, br) 3070(m, br) 2980(m) 1650(s, br) 1550(s, br) 1495(m) 1455(m) 1375(s) 1300(m) 1280(m) 1215(w) 1140(s) 1030(w) 960(w) 775(s) 770(s) 700(s) 690(m) 670(m) 585(m) 520(m) 500(m) 395(w) 255(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·48 [3H, d, J = 7·0 Hz, $NCH(C\underline{H}_3)Ph$], 1·97 (3H, s, $C\underline{H}_3CON$), 5·12 [1H, quin, J = 7·5 Hz, $NC\underline{H}(CH_3)Ph$], 5·89 (1H, s, br, $CON\underline{H}$), 7·23-7·38 (5H, m, Ar$C\underline{H}$); **δC (75·5 MHz, $CDCl_3$)** 21·8 [$NCH(\underline{C}H_3)Ph$], 32·1 ($\underline{C}H_3CON$), 48·7 [$N\underline{C}H(CH_3)Ph$], 126·1, 127·1 (*o*-,*p*-Ar$\underline{C}H$), 128·5 (*m*-Ar$\underline{C}H$), 143·4 (Ar *ipso*-$\underline{C}$), 169·3 ($CH_3\underline{C}ONH$); **m/z (EI$^+$)** 163 ($M^{\bullet+}$, 35%), 148 ($M^{\bullet+}$ $-CH_3^{\bullet}$, 10%), 120 ($M^{\bullet+}$ $-CH_3CO^{\bullet}$, 35%), 106 (100%), 105 (30%), 104 (50%), 77 ($C_6H_5^+$, 55%), 51 ($C_4H_3^+$, 30%), 43 (CH_3CO^+, 90%).

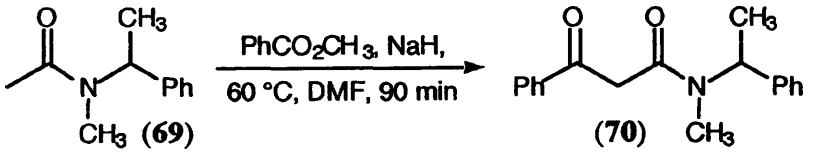
3.03: (±)-*N*-Methyl-*N*-(1-phenylethyl)acetamide ($C_{11}H_{15}NO$, MW = 177·22) (**69**):



A stirred solution of (±)-*N*-(1-phenylethyl)acetamide (**68**) (5·0 g, 30·6 mmol) and methyl iodide (10·9 g, 76·6 mmol) in dry DMF (50 ml) was cooled to 0 °C and oil-free sodium hydride (0·78 g, 33·7 mmol) was carefully added. The reaction was stirred at 0 °C for 10 minutes, then at room temperature for 2 hours. The reaction was quenched by adding methanol (1 ml), then the solution was poured into 0·5 M aqueous hydrochloric acid (200 ml). This mixture was then extracted four times into dichloromethane (50 ml). The combined organics were washed four times with water (150 ml), then dried ($MgSO_4$). The yellow solution thus obtained was concentrated *in vacuo* to give crude **69**[253] (5·4 g, 100% mass balance) as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) showed the oil to consist of ≈94% *N*-methyl-*N*-(1-phenylethyl)acetamide (**69**) contaminated with ≈6% *N*-(1-phenylethyl)acetamide (**68**). Thus the effective yield was 94%. ^1H NMR (200 MHz, $CDCl_3$) also showed that **69** existed as an equilibrium of two rotamers (ratio ≈ 2:1) about the amide bond:

R_f = 0·30 (67% EtOAc in petrol); **υ_{max} (Neat)** 2980(m) 2940(m) 1645(s, br) 1500(m) 1455(s) 1405(s) 1325(m) 1145(m) 1050(m) 1030(m) 1015(m) 790(m) 770(m) 720(m) 700(s) 630(w) 600(w) 580(w) 535(w) cm^{-1}; **δH_{Maj} (200 MHz, $CDCl_3$)** 1·48 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 2·13 (3H, s, $C\underline{H}_3CON$), 2·65 (3H, s, $NC\underline{H}_3$), 6·07 [1H, q, *J* = 7·0 Hz, $NC\underline{H}(CH_3)Ph$], 7·22-8·01 (5H, m, ArC$\underline{H}$); **δH_{Min} (200 MHz, $CDCl_3$)** 1·61 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 2·24 (3H, s, $C\underline{H}_3CON$), 2·67 (3H, s, $NC\underline{H}_3$), 5·10 [1H, q, *J* = 7·0 Hz, $NC\underline{H}(CH_3)Ph$], 7·22-8·01 (5H, m, ArC$\underline{H}$); **δC_{Maj} (75·5 MHz, $CDCl_3$)** 15·5 [NCH($\underline{C}H_3$)Ph], 22·2 ($\underline{C}H_3CON$), 30·1 ($N\underline{C}H_3$), 50·0 [$N\underline{C}H(CH_3)Ph$], 126·4, 127·2 (*o*-,*p*-Ar$\underline{C}$H), 128·4 (*m*-Ar$\underline{C}$H), 140·7 (Ar *ipso*-$\underline{C}$), 170·5 ($CH_3\underline{C}ON$); **δC_{Min} (75·5 MHz, $CDCl_3$)** 17·6 [NCH($\underline{C}H_3$)Ph], 21·7 ($\underline{C}H_3CON$), 27·6 ($N\underline{C}H_3$), 55·7 [$N\underline{C}H(CH_3)Ph$], 126·2 , 127·5 (*o*-,*p*-Ar$\underline{C}$H), 128·7 (*m*-Ar$\underline{C}$H), 140·3 (Ar *ipso*-$\underline{C}$), 169·3 ($CH_3\underline{C}ON$); **m/z (EI$^+$)** 177 ($M^{\bullet+}$, 35%), 176 ($M^{\bullet+}$ –H$^\bullet$, 50%), 175 ($M^{\bullet+}$ –H_2, 20%), 132 ($M^{\bullet+}$ –H_2 –$CH_3CO^\bullet$, 70%), 119 ($M^{\bullet+}$ –$CH_3^\bullet$ –$CH_3CO^\bullet$, 55%), 107 (55%), 100 (M^+ –Ph$^\bullet$, 50%), 86 (MH^+ –$CH_3^\bullet$ –Ph$^\bullet$, 100%), 74 (90%), 65 (70%), 52 (70%), 51 ($C_4H_3^+$, 75%), 50 ($C_4H_2^{\bullet+}$, 75%), 44 (80%), 39 (90%), 30 (90%), 28 ($N_2^{\bullet+}$, $CO^{\bullet+}$, 80%).

3.04: (±)-*N*-Methyl-*N*-(1-phenylethyl)-2-benzoylacetamide ($C_{18}H_{19}NO_2$, MW = 281·36) (**70**):

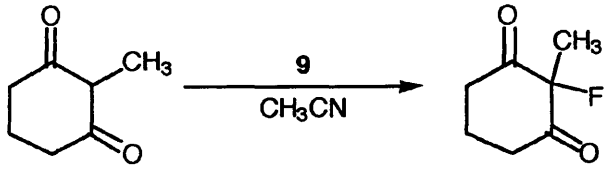


To a stirred solution of methyl benzoate (3·8 g, 28·2 mmol) and (±)-*N*-methyl-*N*-(1-phenylethyl)acetamide (**69**) (5·0 g, 28·2 mmol) in dry DMF (100 ml) was added oil-free sodium hydride (0·92 g, 38·3 mmol). The reaction was slowly heated to 60 °C, and was maintained at this temperature until no further hydrogen was evolved (about 90 minutes). The cloudy yellow solution thus obtained was cooled to room temperature, then was poured into 0·5 M aqueous hydrochloric acid (200 ml). This mixture was then extracted four times into dichloromethane (50 ml). The combined organics were washed four times with water (150 ml), then dried ($MgSO_4$). The yellow solution thus obtained was concentrated *in vacuo* to give crude **70** (8·2 g, 103% mass balance) as a pale brown oil. The oil was subjected to dry flash chromatography eluting with 25-33% ethyl acetate in petrol to give **70** (4·1 g, 52% mass balance) as a thick orange oil. ^1H NMR (200 MHz, $CDCl_3$) showed the oil to be contaminated with a trace of starting material (**69**), so the oil was again subjected to dry flash chromatography eluting with 25% ethyl acetate in petrol to give (**70**) (3·4 g, 43%) as a thick orange oil. ^1H NMR (200 MHz, $CDCl_3$) showed that the keto and enol forms of (**70**) are in equilibrium (ratio ≈ 2·4:1) at room temperature. The keto form exists as two rotamers (ratio ≈ 2·3:1):

R_f = 0·57 (67% EtOAc in petrol); υ_{max} **(Neat)** 3065(w) 3035(w) 2980(w) 2940(w) 1715(m) 1690(s) 1630(s, br) 1605(s) 1580(s) 1490(s) 1455(s) 1330(m, br) 1215(m) 1115(w) 1085(w) 1030(w) 765(m, br) 715(m) 700(m, br) 600(w, br) cm^{-1}; **$\delta H_{keto,Maj}$ (200 MHz, $CDCl_3$)** 1·54 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 2·67 (3H, s, $NC\underline{H}_3$), 4·23 (2H, s, $PhCOC\underline{H}_2CO$), 6·12 [1H, q, *J* = 7·0 Hz, $NC\underline{H}(CH_3)Ph$], 7·28-7·63 (8H, m, Ar$C\underline{H}$), 8·00-8·13 (2H, m, $\underline{Ph}COCH_2$ *o*-Ar$C\underline{H}$); **$\delta H_{keto,Min}$ (200 MHz, $CDCl_3$)** 1·63 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 2·74 (3H, s, $NC\underline{H}_3$), 4·32 (2H, s, $PhCOC\underline{H}_2CO$), 5·16 [1H, q, *J* = 7·0 Hz, $NC\underline{H}(CH_3)Ph$], 7·28-7·63 (8H, m, Ar$C\underline{H}$), 8·00-8·13 (2H, m, $\underline{Ph}COCH_2$ *o*-Ar$C\underline{H}$); **δH_{enol} (200 MHz, $CDCl_3$)** 1·56 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 2·78 (3H, s, $NC\underline{H}_3$), 5·82 [1H, s, br, $Ph(HO)C{=}C\underline{H}CON(CH_3)_2$], 6·11 [1H, q, *J* = 7·0 Hz, $NC\underline{H}(CH_3)Ph$], 7·28-7·63 (8H, m, Ar$C\underline{H}$), 7·80-7·83 (2H, m, $\underline{Ph}(HO)C{=}CH$ *o*-Ar$C\underline{H}$); **$\delta C_{keto,Maj}$ (75·5 MHz, $CDCl_3$)** 15·6 [NCH($\underline{C}H_3$)Ph], 30·3 ($NC\underline{H}_3$), 46·2 ($PhCOC\underline{H}_2CON$), 50·9 [$NC\underline{H}(CH_3)Ph$], 126·0-133·7 (Ar$C\underline{H}$), 136·3 ($\underline{Ph}COCH_2$ Ar *ipso*-$\underline{C}$), 140·1 [$NCH(CH_3)\underline{Ph}$ Ar *ipso*-$\underline{C}$], 171·8 [$CH_2\underline{C}ONCH(CH_3)Ph$], 194·1 ($Ph\underline{C}OCH_2$); **$\delta C_{keto,Min}$ (75·5 MHz, $CDCl_3$)** 17·5 [NCH($\underline{C}H_3$)Ph], 28·4 ($NC\underline{H}_3$), 46·0 ($PhCOC\underline{H}_2CON$), 55·9 [$NC\underline{H}(CH_3)Ph$], 126·0-133·7 (Ar$C\underline{H}$), 136·3 ($\underline{Ph}COCH_2$ Ar *ipso*-$\underline{C}$), 139·7 [$NCH(CH_3)\underline{Ph}$ Ar *ipso*-$\underline{C}$], 172·2 [$CH_2\underline{C}ONCH(CH_3)Ph$], 194·2

(Ph<u>C</u>OCH$_2$); **δC$_{enol}$ (75·5 MHz, CDCl$_3$)** 15·8 [NCH(<u>C</u>H$_3$)Ph], 29·6 (N<u>C</u>H$_3$), 49·9 [N<u>C</u>H(CH$_3$)Ph], 85·2 [Ph(HO)C=<u>C</u>HCON], 126·0-133·7 (Ar<u>C</u>H), 135·1 [<u>Ph</u>(HO)C=CHCON Ar *ipso*-<u>C</u>], 140·4 [NCH(CH$_3$)<u>Ph</u> Ar *ipso*-<u>C</u>], 167·5 [Ph(HO)<u>C</u>=CHCON], 168·0 [<u>C</u>ONCH(CH$_3$)Ph]; **m/z (EI$^+$)** 281 (M$^{\bullet+}$, 80%), 178 (30%), 121 (85%), 120 (100%), 77 (C$_6$H$_5^+$, 100%), 51 (C$_4$H$_3^+$, 35%).

3.05: 2-Fluoro-2-methylcyclohexane-1,3-dione (C$_7$H$_9$FO$_2$, MW = 144·15) (**71**):

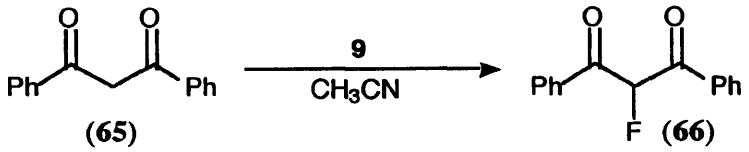


(71)

To a stirred solution of 2-methylcyclohexane-1,3,dione (1·3 g, 10·3 mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (4·2 g 93% = 3·9 g, 11·0 mmol). The reaction was allowed to stir at room temperature for 19 hours. After this time TLC analysis showed only one major product, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was then <u>triturated</u> with three portions of boiling dichloromethane (50 ml). The combined <u>extracts</u> were filtered then concentrated *in vacuo* to give crude **71** (1·9g, 128% mass balance) as a yellow oil. This was triturated into boiling petrol (40 ml) six times. The cooled petrol extracts were concentrated *in vacuo* to form a slush which was cooled strongly, then filtered. The resulting solid was washed with cold petrol, and then dried *in vacuo* to give **71** (1·3 g, 87% containing 3% water, thus effective yield was 84%) as an off-white crystalline solid (needles):

R_f = 0·44 (67% EtOAc in petrol); m.p. = 75-76 °C; **Found** C, 56·6; H, 6·4; F, 12·4%, C$_7$H$_9$FO$_2$ (+ 3% H$_2$O) requires C, 56·6; H, 6·1; F 12·8%; **υ$_{max}$ (KBr disk)** 3415(m, br) 2970(w) 2915(w) 1720(s, br) 1450(m) 1425(m) 1380(m) 1345(m) 1315(m) 1235(m) 1130(m) 1100(m) 1020(s) 935(w) 860(m) 630(m) 565(m) 455(w) 410(m) 320(w) cm^{-1}; **δH (200 MHz, CDCl$_3$)** 1·69 (3H, d, *J* = 22·0 Hz, CFC<u>H</u>$_3$), 1·72-2·10 (3H, m, 4,5,6-C<u>H$_{ax}$</u>H$_{eq}$), 2·65-2·94 (3H, m, 4,5,6-CH$_{ax}$<u>H$_{eq}$</u>); **δC (75·5 MHz, CDCl$_3$)** 16·4 (d, *J* = 24·5 Hz, 5-<u>C</u>H$_2$), 18·4 (d, *J* = 114·5 Hz, 2-CF<u>C</u>H$_3$), 21·1 (d, *J* = 25·0 Hz, 4,6-<u>C</u>H$_2$), 100·9 (d, *J* = 199·0 Hz, 2-<u>C</u>FCH$_3$), 201·9 (d, *J* = 17·0 Hz, 1,3-<u>C</u>=O); **δF (188 MHz, CDCl$_3$)** –82·42 (q, *J* = 22·0 Hz, C<u>F</u>CH$_3$); **m/z (EI$^+$)** 145 [MH$^+$ (self CI), 30%], 116 (45%), 101 (20%), 98 (30%), 89 (30%), 88 (35%), 74 (85%), 73 (90%), 56 (50%), 55 (100%), 46 (60%), 45 (60%), 42 (65%), 41 (60%), 39 (65%), 27 (75%).

3.06: Dibenzoylfluoromethane ($C_{15}H_{11}FO_2$, MW = 242·25) (**66**):

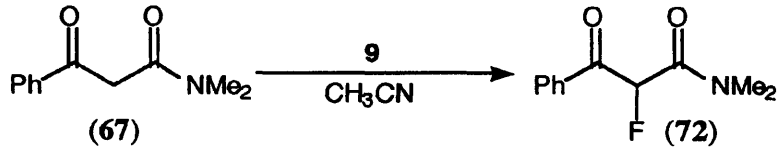


(**65**) (**66**)

To a stirred solution of dibenzoylmethane (2·2g, 9·8mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (3·8g 93% = 3·5g, 10·0mmol). The reaction was allowed to stir at room temperature for 5 hours. After this time TLC analysis showed only one major product, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (75 ml) and water (75 ml). The layers were separated and the organics were washed with a further two portions of water (75 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **66** (2·5 g, 105% mass balance) as a yellow oil which rapidly solidified. This tacky solid was recrystallised from ethyl acetate in petrol to give **66** (2·0 g, 84%) as a white crystalline solid:

R_f = 0·31 (25% EtOAc in petrol); m.p. = 68-70 °C (Lit.[64] m.p. = 65-67 °C); **Found** C, 74·2; H, 4·7; F, 8·1%, $C_{15}H_{11}FO_2$ requires C, 74·37; H, 4·58; F, 7·84%; υ_{max} **(KBr disk)** 3070(w) 2940(w) 1705(m) 1675(s) 1595(s) 1575(m) 1450(s) 1285(m) 1230(s) 1180(m) 1095(s) 965(m) 935(m) 870(m) 780(m) 705(m) 680(s) 655(m) 555(m) 455(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 6·54 (1H, d, *J* = 49·0 Hz, C<u>H</u>F), 7·44-7·52 (4H, m, *m*-ArC<u>H</u>), 7·58-7·66 (2H, m, *p*-ArC<u>H</u>), 8·07-8·12 (4H, m, *o*-ArC<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 96·3 (d, *J* = 199·0 Hz, <u>C</u>HF), 128·6, 129·6 (*o*-,*m*-Ar<u>C</u>H), 133·4 (Ar *ipso*-<u>C</u>), 134·3 (*p*-Ar<u>C</u>H), 191·0 (d, *J* = 20·0 Hz, Ph<u>C</u>OCHF); **δF (188 MHz, $CDCl_3$)** –109·12 (d, *J* = 49·0 Hz, CH<u>F</u>); **m/z (EI+)** 242 ($M^{\bullet+}$, 50%), 165 ($M^{\bullet+}$ –Ph$^{\bullet}$, 10%), 109 (45%), 106 (40%), 105 ($PhCO^+$, 100%), 78 ($C_6H_6^{\bullet+}$, 30%), 76 ($C_6H_4^{\bullet+}$, 25%), 75 (25%), 51 (90%), 50 ($CF_2^{\bullet+}$, 55%), 39 (30%), 27 (20%).

3.07: (±)-*N*,*N*-Dimethyl-2-benzoyl-2-fluoroacetamide ($C_{11}H_{12}FNO_2$, MW = 209·22) (**72**):



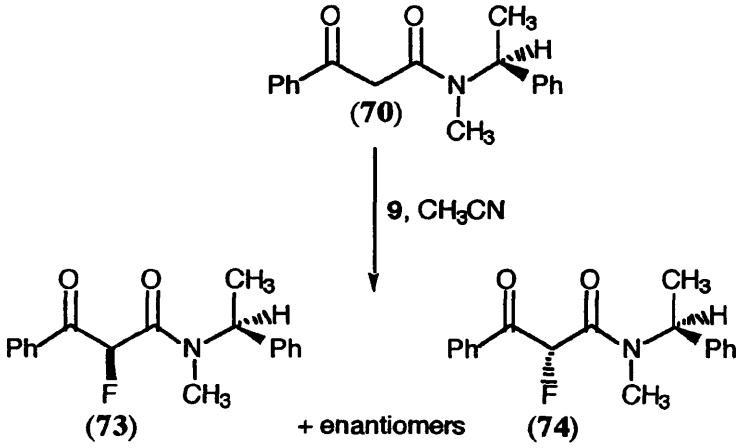
(**67**) (**72**)

To a stirred solution of *N*,*N*-dimethylbenzoylacetamide (**67**) (1·9 g, 9·9 mmol) in dry acetonitrile (75 ml) was added Selectfluor™ (**9**) (3·8 g 93% = 3·5 g, 10·0 mmol). The reaction was allowed to stir at room temperature for 3 hours. After this time TLC analysis showed only one major product, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (75 ml) and water (75 ml). The layers were separated and the organics were washed with a further two portions

of water (75 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **72** (2·0 g, 96% mass balance) as a yellow oil which rapidly solidified exothermically. This tacky solid was recrystallised from ethyl acetate in petrol to give **72** (1·8 g, 87%) as a white crystalline solid:

R_f = 0·44 (67% EtOAc in petrol); m.p. = 102-104 °C; **Found** C, 63·1; H, 5·8; N, 6·6; F, 9·5%, $C_{11}H_{12}FNO_2$ requires C, 63·15; H, 5·78; N, 6·69; F 9·08%; υ_{max} **(KBr disk)** 3390(w) 2975 (w) 2940(w) 1705(s) 1645(s, br) 1495(m, br) 1455(m) 1405(m) 1295(w) 1235(m) 1155(m) 1085(m) 1005(m) 950(m) 890(m) 830(m) 770(m) 715(m) 700(s) 665(s) 290(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 2·98 [3H, d, *J* = 1·0 Hz, N($C\underline{H}_3$)$_2$], 3·13 [3H, d, *J* = 2·0 Hz, N($C\underline{H}_3$)$_2$], 6·17 (1H, d, *J* = 49·0 Hz, C<u>H</u>F), 7·44-7·53 (2H, m, *m*-ArC<u>H</u>), 7·58-7·66 (1H, m, *p*-ArC<u>H</u>), 8·12-8·17 (2H, m, *o*-ArC<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 36·5 [*cis*-N($\underline{C}H_3$)$_2$], 36·7 [d, *J* = 6·5 Hz, *trans*-N($\underline{C}H_3$)$_2$], 92·1 (d, *J* = 197·5 Hz, <u>C</u>HF), 128·6 (*m*-Ar<u>C</u>H), 129·5 (d, *J* = 3·0 Hz, *o*-Ar<u>C</u>H), 133·4 (Ar *ipso*-<u>C</u>), 134·2 (*p*-Ar<u>C</u>H), 163·8 [d, *J* = 20·0 Hz, <u>C</u>ON(CH_3)$_2$], 191·4 (d, *J* = 20·0 Hz, Ph<u>C</u>OCHF); **δF (188 MHz, $CDCl_3$)** −109·27 (d, *J* = 49·0 Hz, CH<u>F</u>); **m/z (EI$^+$)** 209 ($M^{\bullet+}$, 55%), 190 ($M^{\bullet+}$ –F$^\bullet$, 55%), 138 (45%), 109 (40%), 78 ($C_6H_6^{\bullet+}$, 80%), 76 ($C_6H_4^{\bullet+}$, 45%), 51 ($C_4H_3^+$, 100%), 50 ($C_4H_2^{\bullet+}$, 80%), 49 (80%), 44 [$(CH_3)_2N^+$, 95%], 43 (60%), 42 (95%), 18 ($H_2O^{\bullet+}$, 85%).

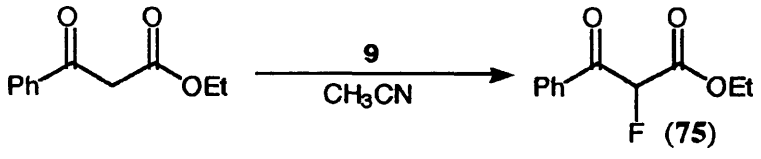
3.08: (±)-*N*-Methyl-*N*-(1-phenylethyl)-2-benzoyl-2-fluoroacetamides ($C_{18}H_{18}FNO_2$, MW = 299·35) (73 and 74):



To a stirred solution of (±)-*N*-Methyl-*N*-(1-phenylethyl)-2-benzoylacetamide (**70**) (1·4 g, 5·0 mmol) in dry acetonitrile (75 ml) was added Selectfluor™ (**9**) (1·9 g 93% = 1·8 g, 5·0 mmol). The reaction was allowed to stir at room temperature for 67 hours, after which time the suspension was concentrated *in vacuo* to give a pale yellow semi-solid. This was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (100 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **73** and **74** (1·3 g, 87% mass balance) as a yellow oil. This oil was subjected to dry flash chromatography eluting with 25% ethyl acetate in petrol to give **73** and **74** (1·2 g,

80%) as a pale yellow oil which partially solidified on standing. ^{1}H NMR (200 MHz, $CDCl_3$) showed that **73** and **74** exists as two rotamers (ratio ≈ 1·6:1) at room temperature. The diastereoisomers appeared to be produced in the ratio 53:47 by ^{19}F NMR (188 MHz, $CDCl_3$), but their ^{1}H spectra were inextricable:
R_f = 0·60 (67% EtOAc in petrol); **Found** C, 72·0; H, 6·4; N, 4·7; F, 6·0%, $C_{18}H_{18}FNO_2$ requires C, 72·2; H, 6·1; N, 4·7; F, 6·4%; **υ_{max} (KBr disk)** 3030(w) 2980 (w) 2940(w) 1705(s) 1645(s) 1600(m) 1585(m) 1495(m) 1450(s) 1410(s) 1350(m) 1275(m) 1230(s) 1125(m) 1090(m) 1045(w) 1030(w) 1000(w) 980(w) 920(w) 885(m) 780(m) 740(m) 725(m) 690(s) 665(m) 610(m) 560(w) 535(w) 505(w) cm^{-1}; **δH Major rotamer (200 MHz, $CDCl_3$)** 1·50, 1·50 [3H, d, *J* = 7·0 Hz, NCH(C<u>H</u>$_3$)Ph], 2·74, 2·75 (3H, d, *J* = 1·5 Hz, NC<u>H</u>$_3$), 5·96, 5·96 [1H, quin, *J* = 6·5 Hz, NC<u>H</u>(CH$_3$)Ph], 6·17, 6·18 (1H, d, *J* = 49·0 Hz, C<u>H</u>F), 7·12-7·41 [5H, m, <u>Ph</u> CH(CH$_3$)N ArC<u>H</u>], 7·47-7·55 (2H, m, <u>Ph</u>COCHF *m*-ArC<u>H</u>), 7·61-7·69 (1H, m, <u>Ph</u>COCHF *p*-ArC<u>H</u>), 8·06-8·18 (2H, m, <u>Ph</u>COCHF *o*-ArC<u>H</u>); **δH Minor rotamer (200 MHz, $CDCl_3$)** 1·48, 1·64 [3H, d, *J* = 7·0 Hz, NCH(C<u>H</u>$_3$)Ph], 2·63, 2·63 (3H, d, *J* = 0·5 Hz, NC<u>H</u>$_3$), 5·52, 5·52 [1H, sext, *J* = 6·5 Hz, NC<u>H</u>(CH$_3$)Ph], 6·35, 6·37 (1H, d, *J* = 49·0 Hz, C<u>H</u>F), 7·12-7·41 [5H, m, <u>Ph</u>CH(CH$_3$)N ArC<u>H</u>], 7·47-7·55 (2H, m, <u>Ph</u>COCHF *m*-ArC<u>H</u>), 7·61-7·69 (1H, m, <u>Ph</u>COCHF *p*-ArC<u>H</u>), 8·06-8·18 (2H, m, <u>Ph</u>COCHF *o*-ArC<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 15·0, 15·2, 16·9, 17·2 [NCH(<u>C</u>H$_3$)Ph], 28·6, 28·8, 29·0, 29·0 (N<u>C</u>H$_3$), 51·5, 51·7, 54·0, 54·3 [N<u>C</u>H(CH$_3$)Ph], 92·0, 92·4, 93·0, 93·1 (t, *J* = 197·5, 198·5, 198·0, 199·0 Hz, <u>C</u>HF), 126·6-128·7 (Ar<u>C</u>H), 129·4, 129·7, 134·2, 134·4 [<u>Ph</u>CH(CH$_3$)N *p*-Ar<u>C</u>H], 133·4, 133·6 (<u>Ph</u>COCHF Ar *ipso*-<u>C</u>), 138·9, 139·1, 139·2 [<u>Ph</u>CH(CH$_3$)N Ar *ipso*-<u>C</u>], 163·9, 164·2, 164·2 (d, *J* = 20·0, 21·0, 20·0 Hz, <u>C</u>ON), 191·6, 191·7 (d, *J* = 20·5 Hz, PhCOCHF); **δF Major rotamer (188 MHz, $CDCl_3$)** −109·21 (d, *J* = 49·0 Hz, CH<u>F</u>); **δF Minor rotamer (188 MHz, $CDCl_3$)** −108·40 (d, *J* = 49·0 Hz, major diastereomer CH<u>F</u>), −107·67 (d, *J* = 49·0 Hz, minor diastereomer CH<u>F</u>); **m/z (Ar FAB$^+$)** 300 (MH$^+$, 55%), 196 (MH$^+$ −PhC≡O$^•$, 70%), 105 (PhC≡O$^{•+}$, 100%).

3.09: (±)-Ethyl 2-fluorobenzoylacetate ($C_{11}H_{11}FO_3$, MW = 210·20) (**75**):



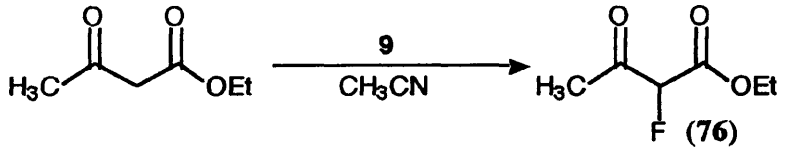
(**75**)

To a stirred solution of ethyl benzoylacetate (3·8 g, 19·8 mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (7·5 g 93% = 7·0 g, 19·8 mmol). The reaction was allowed to stir at room temperature for 54 hours. After this time a sodium iodide test showed that no active fluorine remained, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further

two portions of water (100 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **75**[155(ii)] (4·0 g, 96%) as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$) showed that the oil consisted of 92% **75** contaminated with 4% starting material and 4% ethyl 2,2-difluorobenzoylacetate (**78**). The oil was subjected to flash chromatography eluting with 25% ethyl acetate in petrol. This process yielded **75** (0·9 g, 22%) as a colourless oil:

R_f = 0·18 (20% EtOAc in petrol), R_f = 0·45 (33% EtOAc in petrol); **Found** C, 62·6; H, 5·2; F, 8·7%, $C_{11}H_{11}FO_3$ requires C, 62·85; H, 5·27; F 9·04%; υ_{max} **(Neat)** 2990(w) 2935(w) 1765(s) 1700(s) 1600(m) 1455(m) 1375(w) 1245(s, br) 1105(m, br) 1025(w, br) 695(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·24 (3H, t, *J* = 7·0 Hz, $OCH_2C\underline{H}_3$), 4·29 (2H, q, *J* = 7·0 Hz, $OC\underline{H}_2CH_3$), 5·88 (1H, d, *J* = 49·0 Hz, C<u>H</u>F), 7·45-7·50 (2H, m, *m*-ArC<u>H</u>), 7·52-7·68 (1H, m, *p*-ArC<u>H</u>), 8·00-8·07 (2H, m, *o*-ArC<u>H</u>); **δC (50 MHz, $CDCl_3$)** 13·8 ($OCH_2\underline{C}H_3$), 62·6 ($O\underline{C}H_2CH_3$), 90·0 (d, *J* = 197·5 Hz, <u>C</u>HF), 128·8, 129·5, (*o*-,*m*-Ar<u>C</u>H), 133·3 (Ar *ipso*-<u>C</u>), 134·5 (*p*-Ar<u>C</u>H), 164·9 (d, *J* = 25·0 Hz, $\underline{C}O_2CH_2CH_3$), 189·5 (d, *J* = 19·5 Hz, Ph<u>C</u>OCHF); **δF (188 MHz, $CDCl_3$)** −112·66 (d, *J* = 48·5 Hz, CH<u>F</u>); **m/z (NH_3 CI$^+$)** 229 (MNH_4^+, 15%), 228 (MNH_4^+, 100%), 211 (MH^+, 10%), 210 ($M^{\bullet+}$, 10%), 208 (MNH_4^+ −HF, 5%), 193 (MH^+ −H_2O, 15%), 191 (MH^+ −HF, 10%), 105 ($PhCO^+$, 30%), 35 (5%).

3.10: (±)-Ethyl 2-fluoroacetoacetate ($C_6H_9FO_3$, MW = 148·14) **(76)**:



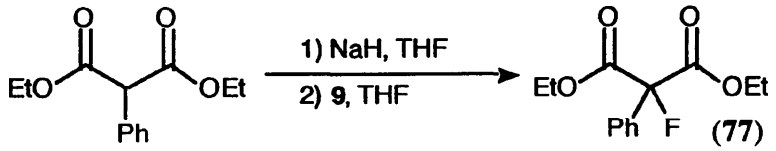
(76)

To a stirred solution of ethyl acetoacetate (1·3 g, 10·0 mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (3·8 g 93% = 3·5 g, 10·0 mmol). The reaction was allowed to stir at room temperature for 120 hours. After this time a negative sodium iodide test showed that no Selectfluor™ remained, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (150 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (75 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **76**[155(ii)] (1·0 g, 68%) as a colourless oil. ^1H NMR (200 MHz, $CDCl_3$) showed that the oil consisted of ≈85% **76** contaminated with ≈15% (molar) ethyl acetoacetate, thus giving an effective yield of 57% **76**. This compound was not purified further due to its volatile nature:

δH (200 MHz, $CDCl_3$) 1·32 (3H, t, *J* = 7·0 Hz, $OCH_2C\underline{H}_3$), 2·35 (3H, d, *J* = 4·0 Hz, $C\underline{H}_3COCH_2$), 4·31 (2H, q, *J* = 7·0 Hz, $OC\underline{H}_2CH_3$), 5·19 (1H, q, *J* = 49·5 Hz, C<u>H</u>F); **δC (75·5 MHz, $CDCl_3$)** 14·0 ($OCH_2\underline{C}H_3$), 26·1 ($\underline{C}H_3COCHF$), 62·8 ($O\underline{C}H_2CH_3$), 91·6 (d, *J* = 198·0 Hz, $CO\underline{C}FCO_2$), 164·1 (d, *J* = 1·0 Hz, $COCF\underline{C}O_2$),

199·1 (d, J = 1·0 Hz, $\underline{C}OCFCO_2$); **δF (188 MHz, $CDCl_3$)** –115·68 (dq, J = 49·5, 4·0 Hz, CH$\underline{F}$); **m/z (Ar FAB$^+$)** 154 (35%), 149 (MH^+, 100%), 147 (35%), 137 (40%), 136 (55%), 121 (50%), 97 (40%), 95 (45%), 91 (55%).

3.11: Diethyl 2-fluoro-2-phenylmalonate ($C_{13}H_{15}FO_4$, MW = 254·26) (**77**):

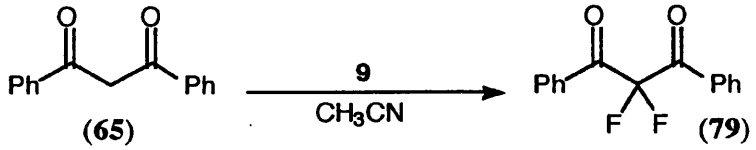


(**77**)

A solution of diethyl 2-phenylmalonate (2·4 g, 10·2 mmol) in dry THF (150 ml) was added to a stirred suspension of oil-free sodium hydride (0·3 g, 12·5 mmol) in dry THF (20 ml). The cloudy solution thus formed was stirred at room temperature until hydrogen evolution had ceased (about 15 min). After this time Selectfluor™ (**9**) (4·2 g 93% = 3·9 g, 11·0 mmol) was added and the reaction was allowed to stir at room temperature for 20 hours. The reaction was then concentrated *in vacuo* to give the crude product. This was partitioned between dichloromethane (200 ml) and water (200 ml). The layers were separated and the organics were washed with a further two portions of water (200 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give **77**[155(ii)] (2·5 g, 96%) as a yellow oil. The oil was subjected to dry flash chromatography eluting with 25% ethyl acetate in petrol. This process yielded **77** (2·4 g, 93%) as a colourless oil:

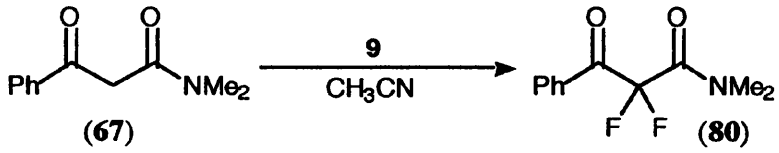
R_f = 0·49 (33% EtOAc in petrol), R_f = 0·60 (67% EtOAc in petrol); **Found** C, 61·5; H, 6·3; F 7·7%, $C_{13}H_{15}FO_4$ requires C, 61·41; H, 5·95; F, 7·47%; **υ_{max} (Neat)** 2990(w) 1775(s, br) 1455(s, br) 1370(m) 1270(s, br) 1220(s) 1045(s) 860(m) 735(m) 695(m) 630(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·31 (6H, t, J = 7·0 Hz, $OCH_2\underline{C}H_3$), 4·33 (4H, q, J = 7·0 Hz, $OC\underline{H}_2CH_3$), 7·39-7·44 (6H, m, *m*-,*p*-Ar$\underline{C}$H), 8·05-8·10 (4H, m, *o*-Ar$\underline{C}$H); **δC (75·5 MHz, $CDCl_3$)** 13·9 ($OCH_2\underline{C}H_3$), 63·0 ($O\underline{C}H_2CH_3$), 94·1 (d, J = 200·0 Hz, $\underline{C}$FPh), 125·7 (d, J = 8·5 Hz, *o*-Ar$\underline{C}$H), 128·3, 129·4, (*m*-,*p*-Ar$\underline{C}$H), 133·2 (Ar *ipso*-$\underline{C}$), 165·6 (d, J = 25·5 Hz, $\underline{C}O_2CH_2CH_3$); **δF (188 MHz, $CDCl_3$)** –83·09 (s, C$\underline{F}$Ph); **m/z (EI$^+$)** 256 [MH^+ self CI (isotopic), 10%], 255 (MH^+ self CI, 70%), 254 ($M^{\bullet+}$, 25%), 236 (10%), 235 (55%), 210 (35%), 206 (25%), 183 (30%), 154 (95%), 153 (65%), 137 (45%), 136 (75%), 109 (10%), 108 (40%), 107 (90%), 106 (75%), 105 ($PhCO^+$, 100%), 77 (Ph^+, 60%), 63 (25%), 29 (90%), 28 (60%).

3.12: Dibenzoyldifluoromethane ($C_{15}H_{10}F_2O_2$, MW = 260·25) (**79**):



To a stirred solution of dibenzoylmethane (2·2 g, 9·8 mmol) in dry acetonitrile (150 ml) was added Selectfluor™ (**9**) (9·9 g 93% = 9·1 g, 26·0 mmol). The reaction was allowed to stir at room temperature for 192 hours. After this time TLC analysis showed only one major product, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (100 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **79** (2·5 g, 98%) as a pale yellow oil. The oil was recrystallised from ethyl acetate in petrol to give **79** (2·0 g, 78%) as an off-white crystalline solid:
R_f = 0·38 (25% EtOAc in petrol); m.p. = 58-60 °C (Lit.[64] m.p. = 56-57 °C); **Found** C, 69·5; H, 3·9; F, 14·5%, $C_{15}H_{10}F_2O_2$ requires C, 69·23; H, 3·87; F, 16·60%; **υ_{max} (KBr disk)** 3385(w) 3070(m) 1700(s) 1595(s) 1580(m) 1450(s) 1255(s) 1160(s) 1140(s) 1000(m) 945(s) 890(s) 775(m) 720(s) 680(s) 665(s) 570(m) 525(m) 260(s) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 7·46-7·55 (4H, m, *m*-ArC<u>H</u>), 7·61-7·70 (2H, m, *p*-ArC<u>H</u>), 8·07-8·11 [4H, m (*ca.* dd, *J* = 8·5, 1·0 Hz), *o*-ArC<u>H</u>]; **δC (75·5 MHz, $CDCl_3$)** 112·8 (t, *J* = 266·0 Hz, <u>C</u>F_2), 129·0 (*m*-Ar<u>C</u>H), 130·3 (t, *J* = 2·5 Hz, *o*-Ar<u>C</u>H), 131·7 (Ar *ipso*-<u>C</u>), 135·1 (*p*-Ar<u>C</u>H), 187·4 (t, *J* = 27·0 Hz, Ph<u>C</u>O<u>C</u>F_2); **δF (188 MHz, $CDCl_3$)** –24·90 (s, <u>C</u>F_2); **m/z (EI+)** 260 ($M^{\bullet+}$, 5%), 108 (5%), 107 (10%), 106 (55%), 78 ($C_6H_6^{\bullet+}$, 40%), 76 ($C_6H_4^{\bullet+}$, 45%), 75 (45%), 52 (20%), 51 (95%), 50 ($CF_2^{\bullet+}$, 100%), 40 (25%), 39 (15%), 27 (30%), 18 (15%).

3.13: *N,N*-Dimethyl-2-benzoyl-2,2-difluoroacetamide ($C_{11}H_{11}F_2NO_2$, MW = 227·21) (**80**) **Method I**:

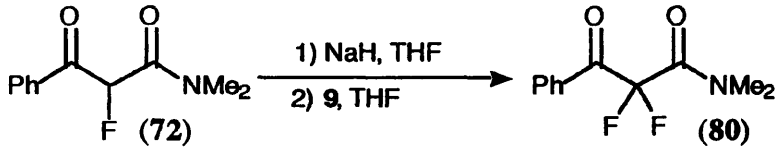


To a stirred solution of *N,N*-dimethylbenzoylacetamide (**67**) (1·0 g, 5·2 mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (4·2 g 93% = 3·9 g, 11·0 mmol). The reaction was allowed to stir at 40 °C for 647 hours adding further Selectfluor™ (**9**) (1·9 g 93% = 1·8 g, 5·0 mmol) after 288 hours had elapsed. After this time TLC analysis showed only one major product, so the suspension was concentrated *in vacuo* to give a pale yellow semi-solid. This was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two

portions of water (100 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **80** (1·1 g, 93% mass balance) as a pale yellow oil. This oil was subjected to dry flash chromatography eluting with 33% ethyl acetate in petrol to give **80** (1·08 g, 91%) as a pale yellow oil:

R_f = 0·58 (67% EtOAc in petrol); **Found** C, 58·3; H, 5·0; N, 6·4; F, 16·5%, $C_{11}H_{11}F_2NO_2$ requires C, 58·15; H, 4·88; N, 6·16; F, 16·72%; υ_{max} **(Neat)** 3070(w, br) 2950 (w, br) 1715(s, br) 1620(s, br) 1600(m) 1455(m) 1410(m) 1285(m, br) 1260(m) 1210(w) 1160(s) 1105(s, br) 1065(m) 945(m) 865(m) 720(m) 690(m) 670(m) 585(w, br) 410(w, br) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 3·03 [3H, t, *J* = 1·0 Hz, $N(C\underline{H}_3)_2$], 3·14 [3H, t, *J* = 1·5 Hz, $N(C\underline{H}_3)_2$], 7·45-7·53 [2H, m (*ca.* tt, *J* = 7·5, 1·5 Hz), *m*-ArC<u>H</u>], 7·59-7·68 [1H, m (*ca.* tt, *J* = 7·5, 2·0 Hz), *p*-ArC<u>H</u>], 8·06-8·10 [2H, m (*ca.* dd, *J* = 8·5, 1·0 Hz), *o*-ArC<u>H</u>]; **δC (75·5 MHz, $CDCl_3$)** 36·5 [t, *J* = 5·0 Hz, $N(\underline{C}H_3)_2$], 111·4 (t, *J* = 264·5 Hz, $\underline{C}F_2$), 128·8 (*m*-Ar<u>C</u>H), 129·9 (*o*-Ar<u>C</u>H), 131·6 (Ar *ipso*-<u>C</u>), 134·5 (*p*-Ar<u>C</u>H), 161·7 [t, *J* = 27·0 Hz, $\underline{C}ON(CH_3)_2$], 186·4 (t, *J* = 27·5 Hz, Ph<u>C</u>OCF_2); **δF (188 MHz, $CDCl_3$)** –25·06 (s, $C\underline{F}_2$); **m/z (EI⁺)** 228 ($M^{\bullet+}$, 20%), 227 ($M^{\bullet+}$, 80%), 156 (20%), 106 (80%), 78 ($C_6H_6^{\bullet+}$, 75%), 76 ($C_6H_4^{\bullet+}$, 45%), 51 ($C_4H_3^+$, 45%), 50 ($C_4H_2^{\bullet+}$, 95%), 44 [$(CH_3)_2N^+$, 45%], 43 (50%), 42 (100%), 28 ($N_2^{\bullet+}$, $CO^{\bullet+}$, 65%).

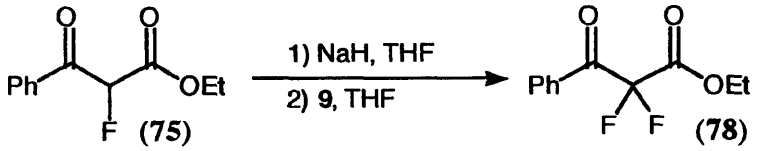
3.14: *N,N*-Dimethyl-2-benzoyl-2,2-difluoroacetamide ($C_{11}H_{11}F_2NO_2$, MW = 227·22) **(80) Method II**:



A solution of (±)-*N,N*-dimethyl-2-benzoyl-2-fluoroacetamide (**72**) (1·1 g, 5·3 mmol) in dry THF (100 ml) was added to a stirred suspension of oil-free sodium hydride (0·18 g, 7·5 mmol) in dry THF (20 ml). The cloudy solution thus formed was stirred at room temperature until hydrogen evolution had ceased (about 15 min). After this time Selectfluor™ (**9**) (2·4 g 93% = 2·2 g, 6·3 mmol) was added and the reaction was allowed to stir at room temperature for 27 hours. The reaction was then concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (100 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give **80** (1·0 g, 83%) as a yellow oil. The oil was subjected to dry flash chromatography eluting with 25-33% ethyl acetate in petrol. This process yielded **80** (0·88g, 73%) as a yellow oil:

Physical data as for **Expt. 3.13**.

3.15: Ethyl 2,2-difluorobenzoylacetate ($C_{11}H_{10}FO_3$, MW = 228·20) (**78**):

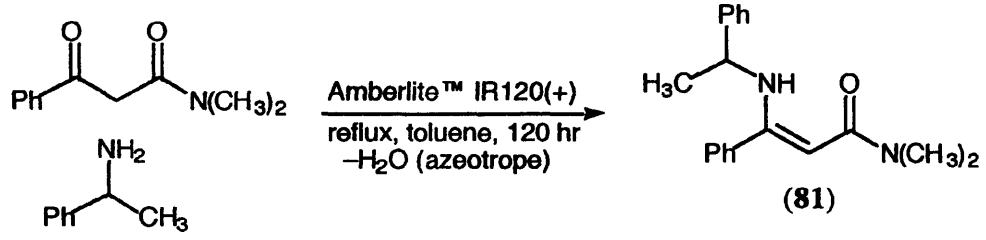


A solution of crude (±)-ethyl 2-fluorobenzoylacetate (**75**) (3·0 g, 14·3 mmol) in dry THF (200 ml) was added to a stirred suspension of oil-free sodium hydride (0·43 g, 18·0 mmol) in dry THF (20 ml). The cloudy solution thus formed was stirred at room temperature until hydrogen evolution had ceased (about 15 min). After this time Selectfluor™ (**9**) (6·1 g 93% = 5·7 g, 16·0 mmol) was added and the reaction was allowed to stir at room temperature for 24 hours. The reaction was then concentrated *in vacuo* to give a white semi-solid. This was partitioned between dichloromethane (200 ml) and water (200 ml). The layers were separated and the organics were washed with a further two portions of water (200 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give **78**[155(ii)] (3·1g, 95%) as a yellow oil which did not require further purification:

R_f = 0·38 (20% EtOAc in petrol), R_f = 0·55 (33% EtOAc in petrol); **Found** C, 57·6; H, 4·4; F, 16·7%, $C_{11}H_{10}FO_3$ requires C, 57·9; H, 4·4; F 16·7%; υ_{max} **(Neat)** 2990(w) 1775(s) 1715(s) 1700(s) 1600(m) 1450(s) 1375(m) 1315(s) 1260(s) 1160(s, br) 1100(s) 1005(w) 925(s) 835(m) 715(m) 690(m) 585(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·31 (3H, t, *J* = 7·0 Hz, $OCH_2\underline{C}H_3$), 4·37 (2H, q, *J* = 7·0 Hz, $OC\underline{H}_2CH_3$), 7·48-7·57 (2H, m, *m*-ArC<u>H</u>), 7·64-7·72 (1H, m, *p*-ArC<u>H</u>), 8·05-8·10 [2H, m (*ca.* dd, *J* = 8·5, 1·0 Hz), *o*-ArC<u>H</u>]; **δC (75·5 MHz, $CDCl_3$)** 13·8 ($OCH_2\underline{C}H_3$), 63·8 ($O\underline{C}H_2CH_3$), 109·9 (t, *J* = 264·5 Hz, $\underline{C}F_2$), 129·0 (*m*-Ar<u>C</u>H), 130·0 (t, *J* = 2·5 Hz, *o*-Ar<u>C</u>H), 131·2 (Ar *ipso*-<u>C</u>), 135·2 (*p*-Ar<u>C</u>H), 161·9 (t, *J* = 30·5 Hz, $CF_2\underline{C}O_2CH_2CH_3$), 185·6 (t, *J* = 27·5 Hz, $Ph\underline{C}OCF_2$); **δF (188 MHz, $CDCl_3$)** –28·92 (s, C<u>H</u>F); **m/z (NH_3 CI$^+$)** 248 (MNH_4^+, 10%), 247 (MNH_4^+, 55%), 246 (MNH_4^+, 100%), 229 ($M^{\bullet+}$, 5%), 228 ($M^{\bullet+}$, 10%), 106 (20%), 105 ($PhC{\equiv}O^+$, 85%), 94 (20%), 77 (Ph^+, 10%).

<u>3.3.2 Stereoselective fluorination</u>

3.16: (±)-*N*,*N*-Dimethyl-3-phenyl-3-(1-phenylethylamino)prop-2-enamide ($C_{19}H_{22}N_2O$, MW = 294·40) (**81**):

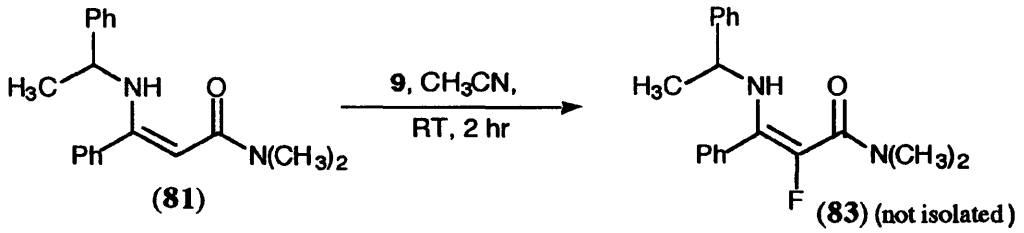


To a solution of *N*,*N*-dimethylbenzoylacetamide (1·91 g, 10·0 mmol) in toluene (70 ml) was added α-methylbenzylamine (1·21 g, 10·0 mmol) and ion exchange resin

Amberlite™ A-120(+) (1·0 g, cat.). The reaction mixture was then refluxed using a Dean and Stark apparatus, running off the water as it collected in the trap. Regular TLC analysis (67% ethyl acetate in petrol) versus starting material showed that the reaction had stopped after 72 hours, so a further portion of α-methylbenzylamine (1·21 g, 10·0 mmol) in toluene (10 ml) was added. Reflux was resumed and TLC analysis (67% ethyl acetate in petrol) versus starting material showed that the reaction had gone to completion after a further 48 hours. The reaction mixture was cooled, then filtered through Celite®. The filtrate was concentrated *in vacuo* to give **81** (3·9 g, 132% mass return) as a yellow oil which was purified by flash chromatography. The column was eluted with 20% ethyl acetate in petrol. Fractions 9 to 18 were combined and concentrated *in vacuo* to give **81** (1·83 g, 62%) as a yellow oil which solidified on standing. ^{1}H NMR (200 MHz, $CDCl_3$) showed the material to be >95% pure, but a sample was recrystalised from petrol for characterisation:

R_f = 0·46 (67% EtOAc in petrol); m.p. = 77-78 °C; **Found** C, 77·3; H, 7·5; N, 9·4%, $C_{19}H_{22}N_2O$ requires C, 77·52; H, 7·53; N, 9·52%; **υ_{max} (KBr disk)** 3150(w, br) 3060(m) 2985(m) 2960(m) 2920(m) 1615(s, br) 1575(s) 1495(s) 1445(s) 1365(s) 1275(m) 1165(m) 1125(s) 920(m) 815(m) 790(m) 765(m) 750(s) 700(s) 670(m) 655(m) 545(m) 530(m) 400(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·44 [3H, d, *J* = 7·0 Hz, NHCH(C<u>H</u>$_3$)Ph], 2·98 [6H, s, CON(C<u>H</u>$_3$)$_2$], 4·36 [1H, dq, *J* = 9·5, 7·0 Hz, NHC<u>H</u>(CH$_3$)Ph], 4·71 [1H, s, Ph(NR)C=C<u>H</u>CON], 7·08-7·36 (10H, m, Ar-C<u>H</u>), 9·93 (1H, d, *J* = 9·5 Hz, N<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 25·0 [NHCH(<u>C</u>H$_3$)Ph], 35·4, 37·5 [CON(<u>C</u>H$_3$)$_2$, hindered rotation], 53·8 [NH<u>C</u>H(CH$_3$)Ph], 86·1 [Ph(NR)C=<u>C</u>HCON], 125·9-128·8 (Ar-<u>C</u>H), 137·7 [<u>Ph</u>(NR)C=CHCON Ar *ipso*-<u>C</u>], 145·6 [NHCH(CH$_3$)<u>Ph</u> Ar *ipso*-<u>C</u>], 162·2 [Ph(NR)<u>C</u>=CHCON], 170·9 [<u>C</u>ON(CH$_3$)$_2$]; **m/z (Ar FAB$^+$)** 295 (MH$^+$, 60%), 294 (M$^{\bullet+}$, 55%), 250 (MH$^+$ –Me$_2$NH, 60%), 191 (MH$^+$ –PhCH=CH$_2$, 20%), 146 (MH$^+$ –Me$_2$NH –PhCH=CH$_2$, 95%), 105 (PhC$^{\bullet+}$HCH$_3$, 100%), 72 [(CH$_3$)$_2$NC≡O$^+$, 30%).

3.17: (±)-*N*,*N*-Dimethyl-2-fluoro-3-phenyl-3-(1-phenylethylamino)prop-2-enamide ($C_{19}H_{21}FN_2O$, MW = 312·40) **(83)**:



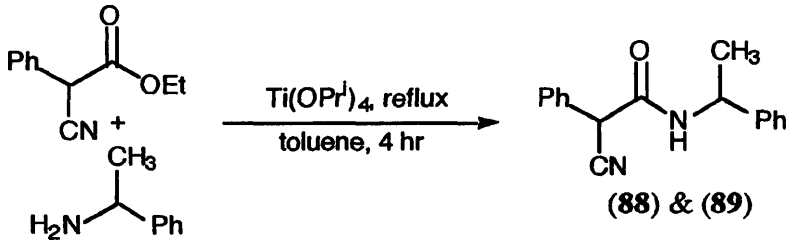
A solution of **81** (1·47 g, 5·0 mmol) and Selectfluor™ (**9**) (1·87 g 94·5% = 1·77 g, 5·0 mmol) in dry acetonitrile (50 ml) was stirred at room temperature under nitrogen. After 2 hours a sodium iodide test for Selectfluor™ was negative, so the reaction was allowed to cool and was then concentrated *in vacuo* to give a white semi-solid which was triturated

twice with dichloromethane (20 ml). The combined organic extracts were filtered through Celite and then concentrated *in vacuo* to give crude **83** (1·81 g, 115% mass return) as a viscous, pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) at this stage showed the oil to contain about 40(molar)% of **83** contaminated with **81**. Chromatography of the oil produced mainly the hydrolysis product of **83** (*N*,*N*-dimethyl-2-bezoyl-2-fluoroacetamide, **72**), thus data for (**83**) is limited to that obtained from the crude material:

R_f = 0·23 (33% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 1·38 [3H, d, *J* = 6·5 Hz, NHCH($C\underline{H}_3$)Ph], 3·00 [6H, s, CON($C\underline{H}_3$)$_2$], 4·55 [1H, q, *J* = 6·5 Hz, NHC$\underline{H}$(CH_3)Ph], 7·11-7·49 (10H, m, Ar-C$\underline{H}$), 9·93; **δF (188 MHz, $CDCl_3$)** −108·26 [s, Ph(NR)C=C$\underline{F}$CON(CH_3)$_2$]; **m/z (Ar FAB$^+$)** 331 [MH$^+$ (**83**), + H_2O, 60%], 313 [MH$^+$ (**83**), 20%], 295 [MH$^+$ (**81**), 95%], 294 [M$^{\bullet+}$ (**81**) & MH$^+$ (**83**) −F$^\bullet$, 100%], 250 [MH$^+$ (**81**) −Me_2NH, 90%], 227 (45%), 191 [MH$^+$ (**81**) −PhCH=CH_2, 15%], 146 [MH$^+$ (**81**) −Me_2NH −PhCH=CH_2, 60%], 105 (PhC$^{\bullet+}$$HCH_3$, 95%), 72 [$(CH_3)_2NC{\equiv}O^+$, 40%).

3.3.3 A new route to an existing chiral derivatising reagent

3.18: (±)-*N*-(1-Phenylethyl)cyanophenylacetamides ($C_{17}H_{16}N_2O$, MW = 264·33) (**88** and **89**):



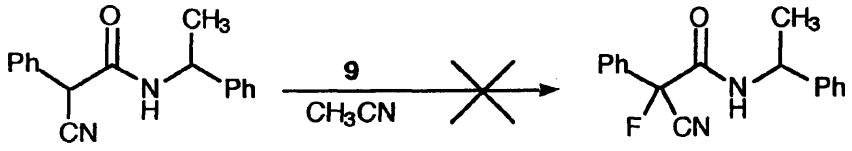
(88) & (89)

To a stirred solution of ethyl (±)-cyanofluoroacetate (1·9 g, 10·0 mmol) and (±)-α-methylbenzylamine (12·1 g, 100 mmol) in toluene (40 ml) under nitrogen was added titanium tetraisopropoxide (5 drops). The solution was then refluxed for 4 hours, cooled to room temperature and concentrated *in vacuo*. The resulting thick oil was dissolved in dichloromethane (150 ml), washed twice with 2 M aqueous hydrochloric acid (100 ml), then washed with water (100 ml). The organic solution was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **88** and **89** (3·2 g, 121% mass balance) as an off-white solid. This solid was triturated with petrol, then dried *in vacuo* to give **88** and **89** (2·7 g, 100%) as an off-white tacky solid:

(**88** and **89**): R_f = 0·30 and 0·50 (47% EtOAc in petrol); m.p. = 109-116 °C; **υ_{max} (KBr disk)** 3305(s, br) 3070(m) 2975(w) 2935(w) 1650(s) 1555(s) 1500(m) 1455(m) 1350(m) 1325(m) 1260(w) 1215(w) 760(m) 730(s) 700(s) 540(w) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·46, 1·49 [3H, d, *J* = 7·0 Hz, NCH($C\underline{H}_3$)Ph], 4·64, 4·66 (1H, s, α-C$\underline{H}$) 5·05, 5·07 [1H, quin, *J* = 7·0 Hz, NC$\underline{H}$(CH_3)Ph], 6·21, 6·21 (1H, s, br, *J* ≈ 8Hz, CONH), 7·11-7·51 (10H, m, ArC$\underline{H}$); δC (**75·5 MHz, $CDCl_3$**) 21·3, 21·4

[NCH(CH$_3$)Ph], 44·7, 44·7 (α-CH), 49·8, 49·9 [NCH(CH$_3$)Ph], 116·8, 116·9 (α-CN), 125·7, 125·8, 127·5, 127·5, 127·6 127·7, 128·6, 129·0, 129·3, 129·3 (ArCH), 130·6, 130·6, 141·8, 141·9 (Ar *ipso*-C), 162·9, 162·9 (CONH); **m/z (EI$^+$)** 264 (M$^{\bullet+}$, 10%), 221 (M$^{\bullet+}$ –CH$_4$ –HCN, 15%), 117 (PhCH$_2$CN$^{\bullet+}$, 60%), 116 (PhCHCN$^+$, 55%), 79 (C$_6$H$_7^+$, 50%), 77 (C$_6$H$_5^+$, 75%) 51 (C$_4$H$_3^+$, 45%), 49 (100%); **Found (NH$_3$ CI$^+$)** 265·1344 (MH$^+$), C$_{17}$H$_{17}$N$_2$O requires 265·1341 (MH$^+$).

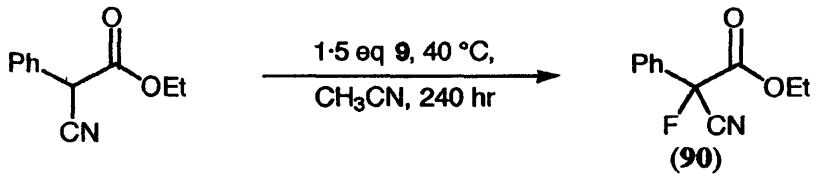
3.19: Attempted fluorination of (±)-*N*-(1-Phenylethyl)cyanophenylacetamides (88 and 89):



(88) & (89) **(86) & (87)**

A solution of **88 & 89** (1·32 g, 5·0 mmol) and Selectfluor™ (**9**) (2·10 g 93% = 1·95 g, 5·5 mmol) in dry acetonitrile (50 ml) was stirred at 20 °C under nitrogen. After 17 hours TLC analysis (47% ethyl acetate in petrol) showed that a compound with the same R_f as the starting material was still present and that no new spots had formed. A sodium iodide test for Selectfluor™ was positive, suggesting that no reaction had occurred so the reaction mixture was heated to 40 °C for 71 hours. After this time the TLC analysis (47% ethyl acetate in petrol) was unchanged, but the sodium iodide test for Selectfluor™ was weaker. The reaction mixture was allowed to cool and was then concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (75 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil (1·00 g, 76% mass balance) which was shown by ^{1}H NMR (200 MHz, $CDCl_3$) to be returned **88 & 89**.
Data as for **Expt. 3.18** above.

3.20: (±)-Ethyl cyanofluorophenylacetate (C$_{11}$H$_{10}$FNO$_2$, MW = 207·20) (**90**):



(90)

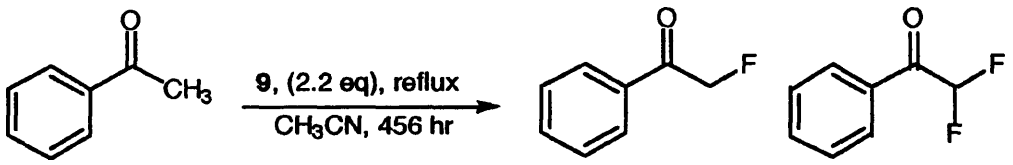
To a stirred solution of ethyl (±)-cyanophenylacetate (1·9 g, 10·0 mmol) in dry acetonitrile (100 ml) was added Selectfluor™ (**9**) (5·7 g 93% = 5·3 g, 15·0 mmol). The reaction mixture was allowed to stir at 40 °C for 240 hours. After this time TLC analysis (33% ethyl acetate in petrol) showed that no ethyl cyanophenylacetate remained, so the suspension was concentrated *in vacuo* to give a white semi-solid. This was partitioned

between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed with a further two portions of water (75 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude **90**[210] (2·1 g, 101% mass balance) as a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$) showed that the oil consisted of ≈96% **90** contaminated with ≈4% ethyl cyanophenylacetate. The oil was subjected to dry flash chromatography eluting with 0-14% ethyl acetate in petrol. This process yielded **90** (1·9 g, 92%) as a colourless oil:

R_f = 0·48 (33% EtOAc in petrol); **Found** C, 63·5; H, 4·6; N, 7·0; F 9·2%, $C_{11}H_{10}FNO_2$ requires C, 63·8; H, 4·9; N, 6·7; F, 9·2%; υ_{max} **(Neat)** 2990(w, br) 1775(s) 1755(s) 1455(m) 1255(s, br) 1215(m) 1130(m) 1100(m) 1075(s) 1055(s) 1005(m) 855(w) 775(m) 730(m) 695(s) 660(w) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 1·30 (3H, t, *J* = 7·0 Hz, $OCH_2\underline{CH_3}$), 4·26-4·43 (2H, m, $OC\underline{H_2}CH_3$), 7·43-7·53 (3H, m, *m*-,*p*-Ar$\underline{C}$H), 7·59-7·66 (2H, m, *o*-Ar$\underline{C}$H); **δC (75·5 MHz, $CDCl_3$)** 13·7 ($OCH_2\underline{C}H_3$), 64·3 ($O\underline{C}H_2CH_3$), 87·1 (d, *J* = 197·0 Hz, α-$\underline{C}$F), 114·0 (d, *J* = 33·0 Hz, α-$\underline{C}$N), 125·5 (d, *J* = 5·5 Hz, *m*-Ar$\underline{C}$H), 129·2, (*p*-Ar$\underline{C}$H), 131·0 (d, *J* = 22·2Hz, *o*-Ar$\underline{C}$H), 131·5 (d, *J* = 23·0 Hz, Ar *ipso*-$\underline{C}$), 162·9 (d, *J* = 29·5 Hz, $\underline{C}O_2CH_2CH_3$); **δF (188 MHz, $CDCl_3$)** –68·46 (s, α-C$\underline{F}$); **m/z (EI$^+$)** 208 [MH^+ (self CI), 40%], 189 (MH^+ –F•, 20%), 182 (30%), 165 (40%), 160 (50%), 133 (50%), 115 (65%), 114 (55%), 109 (65%), 106 (60%), 105 (75%), 89 (85%), 82 (70%), 81 (70%), 63 (85%), 62 (75%), 57 (80%), 50 ($C_4H_2^{\bullet+}$, 75%), 39 (95%), 29 ($C_2H_5^+$, 100%), 18 ($H_2O^{\bullet+}$, 5%).

3.3.4 Fluorination of acetophenone

3.20: α-Fluoroacetophenone (C_8H_7FO, MW = 138·14) (**91**):



(**91**) (**92**) (trace)

A stirred solution of acetophenone (0·60 g, 5·0 mmol) and Selectfluor™ (**9**) (4·02 g 97% = 3·90 g, 11·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen. After 456 hours TLC (33% ethyl acetate in petrol) showed no acetophenone, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude α-fluoroacetophenone (**91**)[154] (0·54 g, 78%) as a brown oil. This oil was shown by ^1H NMR to consist of 78% **91** contaminated with 22% acetophenone and a trace of α,α-difluoroacetophenone (**92**).[64,193] Thus the effective crude yield of **91** was 61%. Data for **91** and **92** are limited as the compounds proved impossible to separate from the contaminating acetophenone:

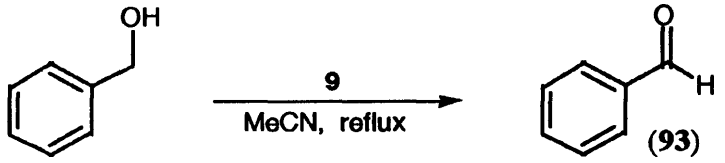
(**91**): R_f = 0·37 (33% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 5·54 (2H, d, *J* = 47·0 Hz, $COC\underline{H}_2F$), 7·43-7·98 (5H, m, Ar-C<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 83·4 (d, *J* = 182·5 Hz, $CO\underline{C}H_2F$), 127·7 (d, *J* = 3·0 Hz, *o*-Ar<u>C</u>H), 128·8 (*m*-Ar<u>C</u>H), 134·1 (*p*-Ar<u>C</u>H), 137·0 (Ar *ipso*-<u>C</u>), 193·4 (d, *J* = 15·5 Hz, Ph<u>C</u>OCH$_2$F); **δF (188 MHz, $CDCl_3$)** –153·37 (t, *J* = 47·0 Hz, $CH_2\underline{F}$).

(**92**): R_f = 0·41 (33% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 6·41 (1H, t, *J* = 53·5 Hz, $COC\underline{H}F_2$), 7·43-7·98 (5H, m, Ar-C<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 111·0 (t, *J* = 249·0 Hz, $\underline{C}HF_2$), 128·2 (*m*-Ar<u>C</u>H), 128·4 (t, *J* = 5·0 Hz, *o*-Ar<u>C</u>H), 133·0 (*p*-Ar<u>C</u>H), 130·0 (Ar *ipso*-<u>C</u>), 198·2 (t, *J* = 22·0 Hz, Ph<u>C</u>OCHF$_2$); **δF (188 MHz, $CDCl_3$)** –44·48 (d, *J* = 53·5 Hz, $CH\underline{F}_2$); **m/z (Ar FAB$^+$)** 154 (95%), 139 (MH^+, 20%), 138 ($M^{\bullet+}$, 35%), 137 (50%), 136 (75%), 120 ($MH^+ - F^\bullet$, 15%), 107 (30%), 105 ($PhC{\equiv}O^+$, 100%), 89 (35%), 77 (50%), 65 (20%), 63 (25%), 51 (30%),.

3.4 Selectfluor™ as an oxidising agent

3.4.1 Oxidation of benzyl alcohols

4.01: Benzaldehyde (C_7H_6O, MW = 106·12) (**93**):

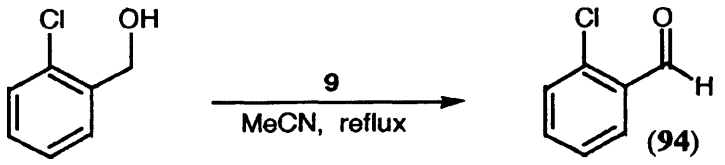


(**93**)

A stirred solution of benzyl alcohol (0·54 g, 5·0 mmol) and Selectfluor™ (**9**) (1·97 g 94·5% = 1·86 g, 5·25 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 18 hours TLC (33% ethyl acetate in petrol) showed no benzyl alcohol and a sodium iodide test for Selectfluor™ was negative. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo* keeping the water-bath temperature below 35 °C. The resulting white semi-solid was then partitioned between dichloromethane (50 ml) and water (30 ml). The layers were separated and the organics were washed with a further two portions of water (30 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude benzaldehyde (**93**) (0·46 g, 87%) as a yellow oil which appeared to be about 60% pure by ^1H NMR (200 MHz, $CDCl_3$). The main contaminants were benzyl alcohol and benzoic acid. This oil was purified by flash chromatography eluting with petrol to collect four 20 ml fractions and then eluting with 20% ethyl acetate in petrol to collect another four 20 ml fractions. Fractions 6 and 7 were concentrated *in vacuo* to give **93** (0·23 g, 43%) as a colourless oil. Tlc R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **93** obtained from Aldrich:

R_f = 0·45 (33% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 7·47-7·68 (3H, m, *m*-,*p*-Ar<u>C</u>H), 7·89 (2H, m *ca.* dd, *J* = 8·0, 1·5 Hz, *o*-Ar<u>C</u>H), 10·03 (1H, s, PhC<u>H</u>O).

4.02: 2-Chlorobenzaldehyde (C_7H_5ClO, MW = 140·57) (**94**):

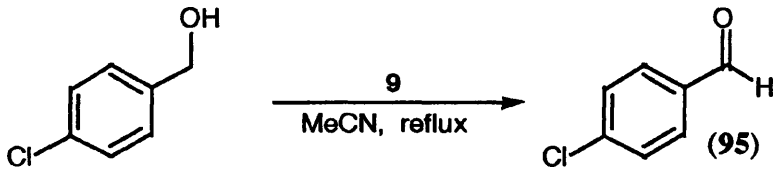


(**94**)

A stirred solution of 2-chlorobenzyl alcohol (0·71 g, 5·0 mmol) and Selectfluor™ (**9**) (3·65 g 97% = 3·54 g, 10·0 mmol) in dry acetonitrile (60 ml) was refluxed under nitrogen. After 45 hours TLC (33% ethyl acetate in petrol) showed no 2-chlorobenzyl alcohol. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with a further portion of water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude 2-chlorobenzaldehyde (**94**) (0·63 g, 90%) as a brown oil which appeared to be about 55% pure by ^1H NMR (200 MHz, $CDCl_3$). The main contaminants were 2-chlorobenzyl alcohol and 2-chlorobenzoic acid. This oil was purified by flash chromatography eluting with petrol to collect two 20 ml fractions and then eluting with 20% ethyl acetate in petrol to collect another eight 20 ml fractions. Fractions 4 to 5 were concentrated *in vacuo* to give **94** (0·30g, 42%) as a pale yellow oil. Tlc R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **94** obtained from Aldrich:

R_f = 0·50 (33% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 7·35-7·58 (3H, m, 3-,4-,5-ArC<u>H</u>), 7·93 (1H, m *ca.* dd, *J* = 8·0, 1·5 Hz, 6-ArC<u>H</u>), 10·49 (1H, s, ArC<u>H</u>O).

4.03: 4-Chlorobenzaldehyde (C_7H_5ClO, MW = 140·57) (**95**):



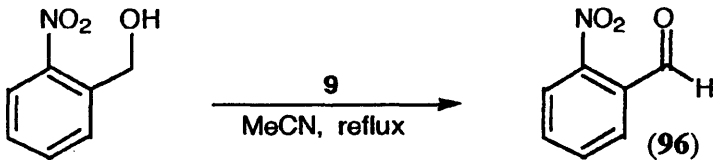
(**95**)

A stirred solution of 4-chlorobenzyl alcohol (0·71 g, 5·0 mmol) and Selectfluor™ (**9**) (2·74 g 97% = 2·66 g, 7·5 mmol) in dry acetonitrile (60 ml) was refluxed under nitrogen. After 15 hours TLC (20% ethyl acetate in petrol) showed no 4-chlorobenzyl alcohol, but 4-chlorobenzoyl fluoride was evident. The reaction was allowed to cool to room temperature and water (5 ml) was added. The reaction mixture was stirred for 12 hours under nitrogen, then was concentrated *in vacuo* to give a white solid which was partitioned between dichloromethane (75 ml) and water (50 ml). The layers were separated and the organics were washed twice with 50% saturated sodium bicarbonate solution in water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude 4-chlorobenzaldehyde (**95**) as a tacky yellow solid which appeared to be about 75% pure by ^1H NMR (200 MHz, $CDCl_3$). The main

contaminants were 4-chlorobenzyl alcohol and 4-chlorobenzoic acid. This solid was purified by flash chromatography eluting with petrol to collect two 20 ml fractions and then eluting with 20% ethyl acetate in petrol to collect another eight 20 ml fractions. Fraction 5 was concentrated *in vacuo* to give **95** (0·26 g, 37%) as a white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **95** obtained from Aldrich:

R_f = 0·43 (33% EtOAc in petrol); m.p. = 43-46 °C (Lit.[220] m.p. = 47-50 °C); **δH (200 MHz, $CDCl_3$)** 7·51, 7·82 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, 2-,3-ArC<u>H</u>), 9·98 (1H, s, ArC<u>H</u>O).

4.04: 2-Nitrobenzaldehyde ($C_7H_5NO_3$, MW = 151·12) (**96**):

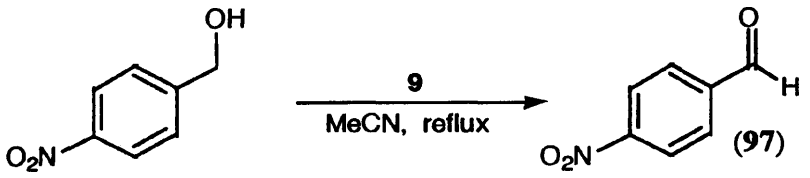


(**96**)

A stirred solution of 2-nitrobenzyl alcohol (0·76 g, 5·0 mmol) and Selectfluor™ (**9**) (2·06 g 94·5% = 1·95 g, 5·5 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 435 hours TLC (33% ethyl acetate in petrol) showed little or no 2-nitrobenzyl alcohol and a sodium iodide test for Selectfluor™ was negative. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with a further 2 portions of water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude 2-nitrobenzaldehyde (**96**) (0·58 g, 77%) as an orange oil which appeared to be about 75% pure by ^1H NMR (200 MHz, $CDCl_3$). The main contaminant was 2-nitrobenzyl alcohol. This oil was purified by flash chromatography eluting with 25% ethyl acetate in petrol to collect six 20 ml fractions. Fractions 2 and 3 were concentrated *in vacuo* to give **96** (0·43 g, 56%) as a pale yellow solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **96** obtained from Aldrich:

R_f = 0·28 (33% EtOAc in petrol); m.p. = 42-44 °C (Lit.[220] m.p. = 43-46 °C); **δH (200 MHz, $CDCl_3$)** 7·71-7·85 (2H, m, 4-,5-ArC<u>H</u>), 7·90-7·99 (1H, m, 6-ArC<u>H</u>), 8·07-8·16 (1H, m, 3-ArC<u>H</u>), 10·41 (1H, s, ArC<u>H</u>O).

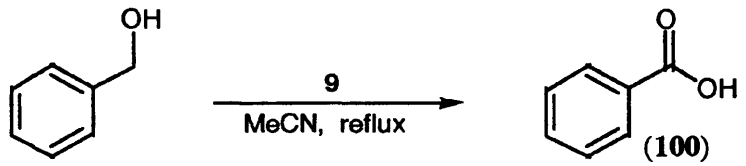
4.05: 4-Nitrobenzaldehyde ($C_7H_5NO_3$, MW = 151·12) (**97**):



A stirred solution of 2-nitrobenzyl alcohol (0·76 g, 5·0 mmol) and Selectfluor™ (**9**) (2·07 g 94% = 1·95 g, 5·5 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 65 hours TLC (33% ethyl acetate in petrol) showed little or no 4-nitrobenzyl alcohol and a sodium iodide test for Selectfluor™ was negative. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo* to give a white solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with 20% saturated sodium bicarbonate solution in water (60 ml). The dichloromethane layer was then washed with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude 4-nitrobenzaldehyde (**97**) (0·64 g, 85%) as a yellow solid which appeared to be about 75% pure by ^1H NMR (200 MHz, $CDCl_3$). The main contaminant was 4-nitrobenzyl alcohol. This solid was purified by flash chromatography eluting with 25% ethyl acetate in petrol to collect five 20 ml fractions and then with 33% ethyl acetate in petrol to collect three 20 ml fractions. Fractions 1 to 5 were concentrated *in vacuo*, then recrystallised from a mixture of IPA and petrol to give **97** (0·47 g, 62%) as an off-white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **97** obtained from Aldrich:

R_f = 0·30 (33% EtOAc in petrol); m.p. = 102-104 °C (Lit.[220] m.p. = 105-108 °C); **δH (200 MHz, $CDCl_3$)** 8·08, 8·40 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, 2-,3-ArC<u>H</u>), 10·16 (1H, s, ArC<u>H</u>O).

4.06: Benzoic acid ($C_7H_6O_2$, MW = 122·12) (**100**):

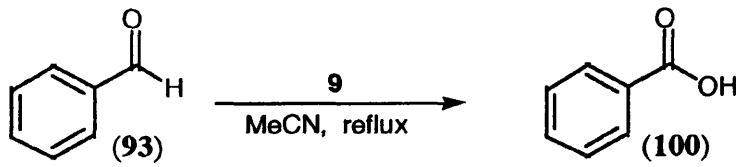


A stirred solution of benzyl alcohol (0·54 g, 5·0 mmol) and Selectfluor™ (**9**) (4·15 g 94% = 3·90 g, 11·0 mmol) in dry acetonitrile (60 ml) was refluxed under nitrogen. After 48 hours TLC (33% ethyl acetate in petrol) showed no benzyl alcohol and a sodium iodide test for Selectfluor™ was weak. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo*. The resulting white solid was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with a further two portions of water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give benzoic acid (**100**) (0·53 g, 87%)

as an off-white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **100** obtained from Aldrich:
R_f = 0·51 (67% EtOAc in petrol); m.p. = 119-120 °C (Lit.[220] m.p. = 122-123 °C); **δH (200 MHz, $CDCl_3$)** 7·44-7·52 (2H, m, *m*-ArC<u>H</u>), 7·58-7·67 (1H, m, *p*-ArC<u>H</u>), 8·10-8·16 (2H, m, *o*-ArC<u>H</u>).

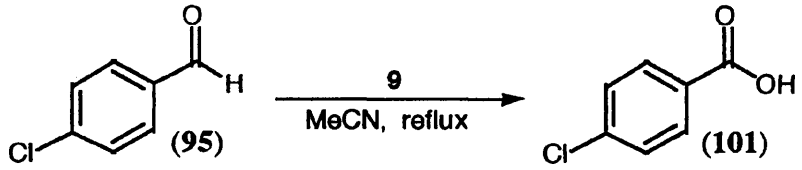
<u>3.4.2 Oxidation of benzaldehydes</u>

4.07: Benzoic acid ($C_7H_6O_2$, MW = 122·12) **(100)**:



A stirred solution of benzaldehyde (**93**) (0·53 g, 5·0 mmol) and Selectfluor™ (**9**) (2·19 g 97% = 2·13 g, 6·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen. After 31 hours TLC (33% ethyl acetate in petrol) showed no benzaldehyde and a sodium iodide test for Selectfluor™ was weak. The reaction was allowed to cool to room temperature and water (20 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 12 hours, then was concentrated *in vacuo* to give a white solid which was stirred for 30 minutes in water (20 ml). The suspension was cooled to 5 °C, then the solid was filtered off, washed with cold water, then dried to give benzoic acid (**100**) (0·28 g, 46%) as a white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **100** obtained from Aldrich:
R_f = 0·51 (67% EtOAc in petrol); m.p. = 120-121 °C (Lit.[220] m.p. = 122-123 °C); **δH (200 MHz, $CDCl_3$)** 7·44-7·52 (2H, m, *m*-ArC<u>H</u>), 7·58-7·67 (1H, m, *p*-ArC<u>H</u>), 8·10-8·16 (2H, m, *o*-ArC<u>H</u>).

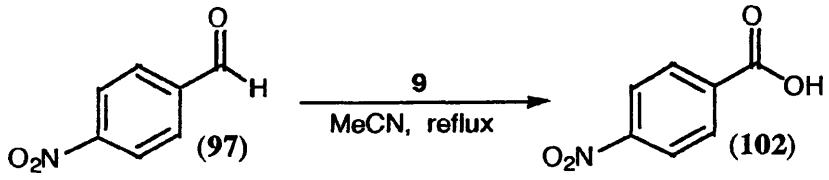
4.08: 4-Chlorobenzoic acid ($C_7H_5ClO_2$, MW = 156·57) **(101)**:



A stirred solution of 4-chlorobenzaldehyde (**95**) (0·70 g, 5·0 mmol) and Selectfluor™ (**9**) (2·56g 97% = 2·48g, 7·0mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen. After 66 hours TLC (33% ethyl acetate in petrol) showed no 4-chlorobenzaldehyde and a sodium iodide test for Selectfluor™ was weak. The reaction was allowed to cool to room temperature and water (20 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 12 hours, then was concentrated *in vacuo* to give a white solid which was stirred for 1 hour in water (20 ml). The suspension was cooled to 5 °C, then the solid was filtered off, washed with cold water, then dried to give 4-chlorobenzoic acid

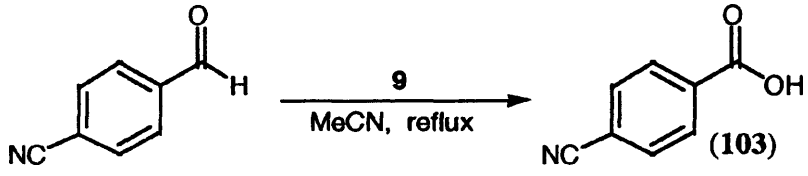
(**101**) (0·73g, 93%) as a white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **101** obtained from Aldrich:
R_f = 0·40 (67% EtOAc in petrol); m.p. = 235-237 °C (sublimes) (Lit.[220] m.p. = 239-241 °C); **δH (200 MHz, $CDCl_3$)** 7·46, 8·05 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, 2-,3-ArC<u>H</u>).

4.09: 4-Nitrobenzoic acid ($C_7H_5NO_4$, MW = 167·12) (**102**):



A stirred solution of 4-nitrobenzaldehyde (**97**) (0·76 g, 5·0 mmol) and Selectfluor™ (**9**) (2·19 g 97% = 2·13 g, 6·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen. After 384 hours TLC (33% ethyl acetate in petrol) showed that about half of the 4-nitrobenzaldehyde remained and a sodium iodide test showed that there was still active Selectfluor™ in the reaction mixture. The reaction was allowed to cool to room temperature and water (20 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 24 hours, then was concentrated *in vacuo* to give a white solid which was stirred for 30 minutes in water (20 ml). The suspension was cooled to 5 °C, then the solid was filtered off, washed with cold water, then dried. This pale yellow solid was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of 50% 4-nitrobenzoic acid (**102**) contaminated with 50% 4-nitrobenzaldehyde (**97**). Tlc R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **102** obtained from Aldrich:
R_f = 0·18 (67% EtOAc in petrol); **δH (200 MHz, $CDCl_3$)** 7·99, 8·04 (4H, *ca.* ABq, J_{AB} = 9·0 Hz, 2-,3-ArC<u>H</u>).

4.10: 4-Cyanobenzoic acid ($C_8H_5NO_2$, MW = 147·13) (**103**):

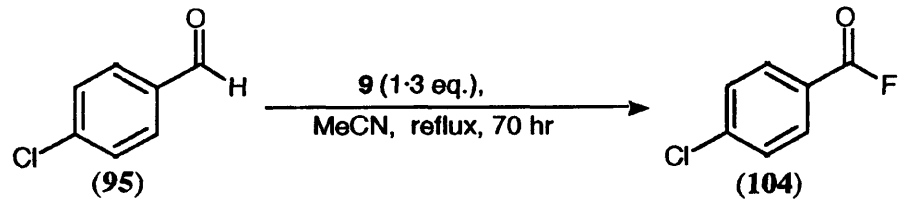


A stirred solution of 4-cyanobenzaldehyde (0·66 g, 5·0 mmol) and Selectfluor™ (**9**) (2·19 g 97% = 2·13 g, 6·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen. After 80 hours TLC (33% ethyl acetate in petrol) showed no 4-cyanobenzaldehyde and a sodium iodide test for Selectfluor™ was weak. The reaction was allowed to cool to room temperature and water (20 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 12 hours, then was concentrated *in vacuo* to give a white solid which was stirred for 30 minutes in water (20 ml). The suspension was cooled to 5 °C, then the solid was filtered off, washed with cold water, then dried to give 4-cyanobenzoic

acid (**103**) (0·64 g, 87%) as a white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **103** obtained from Aldrich:
R_f = 0·21 (67% EtOAc in petrol); m.p. = 218-220 °C (dec.) [Lit.[220] m.p. = 220-222 °C (dec.)]; **δH (200 MHz, $CDCl_3$)** 7·78, 8·19 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, 2-,3-ArC<u>H</u>).

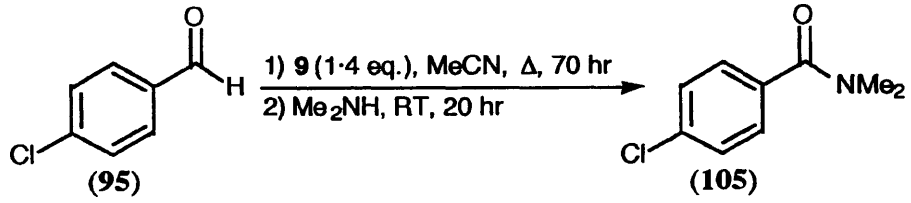
<u>3.4.3 Reactions involving 4-chlorobenzoyl fluoride from 4-chlorobenzaldehyde</u>

4.11: 4-Chlorobenzoyl fluoride (C_7H_4ClFO, MW = 158·56) (**104**):



A stirred solution of 4-chlorobenzaldehyde (**95**) (0·70 g, 5·0 mmol) and Selectfluor™ (**9**) (2·38 g 97% = 2·31 g, 6·5 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen in a Teflon® FEP vessel. After 70 hours TLC (20% ethyl acetate in petrol) showed no 4-chlorobenzaldehyde, but 4-chlorobenzoyl fluoride was evident. The reaction was allowed to cool to room temperature, then was concentrated *in vacuo* to give a white semi-solid which was triturated three times into dichloromethane (20 ml). The dichloromethane solution was concentrated *in vacuo* and the resulting tacky solid was again triturated into dichloromethane (20 ml). The dichloromethane solution was filtered, concentrated *in vacuo* to give crude 4-chlorobenzoyl fluoride (**104**) (0·52 g, 66%) as a tacky off-white solid. This solid was then dissolved in petrol (3 ml), leaving behind a yellow residue. The supernatant fluid was decanted and concentrated *in vacuo* to give **104** (0·46 g, 58%) as a white solid:
R_f = 0·60 (25% EtOAc in petrol); m.p. = 55-57 °C (Lit.[254] m.p. = 59-60 °C); **υ_{max} (KBr disk)** 1820(s) 1595(m) 1490(m) 1400(m) 1255(s) 1175(m) 1095(s) 1030(s) 1010(s) 845(m) 780(w) 745(m) 675(w) 525(m) 485(w) 470(m) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 7·52, 7·99 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, J_{AF} = 1·0 Hz, 2-,3-ArC<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 123·3 (d, J = 62·5 Hz, 1-Ar *ipso*-<u>C</u>), 129·5 (s, 3-Ar<u>C</u>H), 132·6 (d, J = 4·0 Hz, 2-Ar<u>C</u>H), 142·1 (s, 4-Ar *ipso*-<u>C</u>), 156·5 (d, J = 344·0 Hz, Ar<u>C</u>OF); **δF (188 MHz, $CDCl_3$)** +96·15 (s, ArCO<u>F</u>); **m/z (NH_3 CI$^+$)** 160 [$M^{\bullet+}$ (isotopic), 35%], 158 ($M^{\bullet+}$, 35%), 141 [$M^{\bullet+}$ –F$^\bullet$ (isotopic), 15%], 139 ($M^{\bullet+}$ –F$^\bullet$, 50%), 132 [$M^{\bullet+}$ –CO (isotopic), 10%], 130 ($M^{\bullet+}$ –CO, 45%), 120 (100%); **Found (EI$^+$)** 157·9935 ($M^{\bullet+}$), C_7H_4ClFO requires 157·9935 ($M^{\bullet+}$).

4.12: *N,N*-Dimethyl-4-chlorobenzamide ($C_9H_{10}ClNO$, MW = 183·64) (**105**):

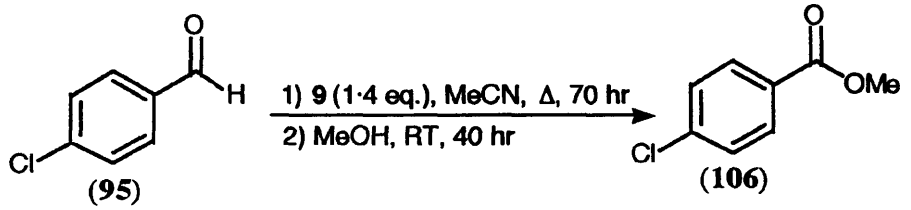


(**95**) (**105**)

A stirred solution of 4-chlorobenzaldehyde (**95**) (0·70 g, 5·0 mmol) and Selectfluor™ (**9**) (2·56 g 97% = 2·48 g, 7·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen in a Teflon® FEP vessel. After 70 hours TLC (20% ethyl acetate in petrol) showed no 4-chlorobenzaldehyde, but 4-chlorobenzoyl fluoride was evident. The reaction was allowed to cool to room temperature and a solution of 33% dimethylamine in alcohol was added (6·8 g, 50 mmol). The reaction mixture was stirred under nitrogen at room temperature for 20 hours, then was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed with saturated sodium bicarbonate solution (30 ml) and then water (50 ml). The dichloromethane layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give *N,N*-dimethyl-4-chlorobenzoate (**105**) (0·77 g, 84%) as a yellow solid. This oil was shown by ^1H NMR (200 MHz, $CDCl_3$) to be >98% pure. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **105** obtained from Aldrich:

R_f = 0·34 (67% EtOAc in petrol); m.p. = 58-59 °C (Lit.[255] m.p. = 58-59 °C); **δH (200 MHz, $CDCl_3$)** 2·97 [3H, s, ArCON($C\underline{H}_3$)$_2$], 3·09 [3H, s, ArCON($C\underline{H}_3$)$_2$], 7·37 (4H, s, 2-,3-Ar$C\underline{H}$).

4.13: Methyl 4-chlorobenzoate ($C_8H_7ClO_2$, MW = 170·60) (**106**):



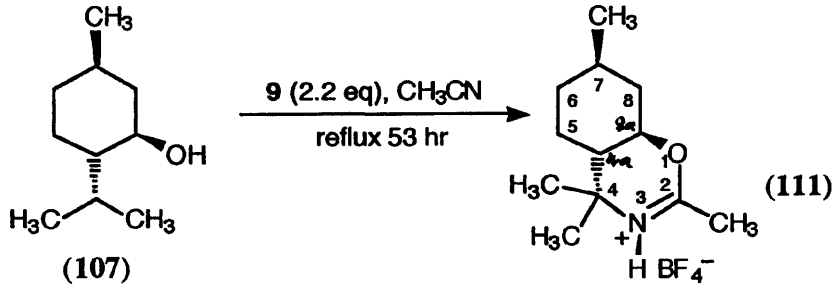
(**95**) (**106**)

A stirred solution of 4-chlorobenzaldehyde (**95**) (0·70 g, 5·0 mmol) and Selectfluor™ (**9**) (2·56 g 97% = 2·48 g, 7·0 mmol) in dry acetonitrile (50 ml) was refluxed under nitrogen in a Teflon® FEP vessel. After 70 hours TLC (20% ethyl acetate in petrol) showed no 4-chlorobenzaldehyde, but 4-chlorobenzoyl fluoride was evident. The reaction was allowed to cool to room temperature and methanol (20 ml) was added. The reaction mixture was stirred under nitrogen at room temperature for 40 hours, then was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and water (50 ml). The layers were separated and the organics were washed with saturated sodium bicarbonate solution (50 ml) and then water (50 ml). The dichloromethane layer

was then dried ($MgSO_4$) and concentrated *in vacuo* to give crude methyl 4-chlorobenzoate (**106**) (0·62 g, 73%) as a yellow oil. This oil was purified by recrystallisation from petrol to give **106** (0·55 g, 64%) as a white solid. Melting point, TLC R_f and ^1H NMR spectrum (200 MHz, $CDCl_3$) matched that of a sample of **106** obtained from Aldrich:
R_f = 0·46 (25% EtOAc in petrol); m.p. = 41-43 °C (Lit.[220] m.p. = 42-44 °C); **δH (200 MHz, $CDCl_3$)** 3·91 (3H, s, $ArCO_2C\underline{H}_3$), 7·53, 7·85 (4H, *ca.* ABq, J_{AB} = 8·5 Hz, 2-,3-ArC<u>H</u>).

3.5 Reactions between (–)-menthol and Selectfluor™

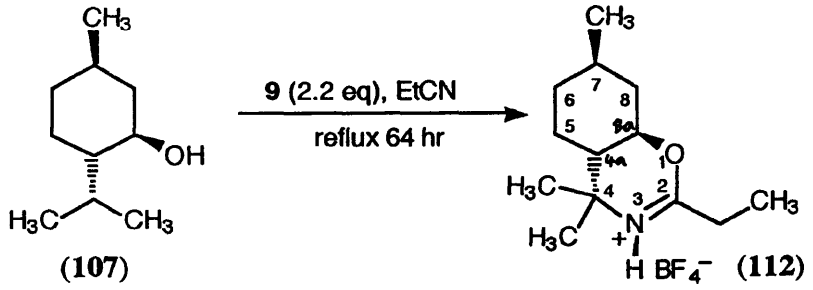
5.01: Reaction in acetonitrile to form (4a*S*,7*R*,8a*R*)-4a,5,7,8,8a-pentahydro-2,4,4,7-tetramethyl-4*H*-[1,3]-benzoxazinium tetrafluoroborate ($C_{12}H_{21}NO{\cdot}HBF_4$, MW = 283·12) (**111**):



A stirred solution of (–)-menthol (**107**) (0·78 g, 5·0 mmol) and Selectfluor™ (**9**) (4·15 g 94% = 3·90 g, 11·0 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 53 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed twice with water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **111** (1·50 g, 106%) as a tacky, orange solid. This semi-solid was treated with boiling ethyl acetate (6 ml), then cooled. The solid was collected by suction filtration, washed with cold ethyl acetate and dried to give **111** as a white solid (0·71 g, 50%):
R_f = 0·06 (67% EtOAc in petrol); m.p. = 176-177 °C; $[\alpha]_{589}^{26}$ +104·1 ° (c. 1·01, $CHCl_3$); **Found** C, 51·1; H, 7·7; N, 5·0%, $C_{12}H_{21}NO{\cdot}HBF_4$ requires C, 50·9; H, 7·8; N, 5·0%; **υ_{max} (KBr disk)** 3260(m) 3180(w) 3085(w) 2940(s) 2870(m) 2785(m) 2730(m) 1660(s) 1550(m) 1465(m) 1440(m) 1400(m) 1380(m) 1365(m) 1320(m) 1295(m) 1230(m) 1205(m) 1175(m) 1080(s, br) 920(m) 900(m) 840(m) 615(w) 535(w) 520(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·03 (3H, d, J = 6·5 Hz, 7-C<u>H</u>$_3$), 1·08-2·17 (7H, m, 7-C<u>H</u> & 5-,6-,8-C<u>H</u>$_2$), 1·34 (3H, s, 4-C<u>H</u>$_{3ax}$), 1·49 (3H, s, 4-C<u>H</u>$_{3eq}$), 2·23-2·35 (1H, m, *ca.* dt, 4a-C<u>H</u>), 2·42 (3H, s, 2-C<u>H</u>$_3$), 4·30 (1H, td, J = 11·0, 4·5 Hz, 8a-C<u>H</u>); δC

(75·5 MHz, $CDCl_3$) 19·9 (2-$\underline{C}H_3$), 21·5 (4-$\underline{C}H_{3ax}$), 23·3 (7-$\underline{C}H$), 23·6 (5-$\underline{C}H_2$), 25·5 (4-$\underline{C}H_{3eq}$), 30·7 (7-$\underline{C}H_3$), 33·0 (6-$\underline{C}H_2$), 38·6 (8-$\underline{C}H_2$), 44·0 (4a-$\underline{C}H$), 55·8 [4-$\underline{C}(CH_3)_2$], 79·5 (8a-$\underline{C}H$), 172·7 [2-(C=N)O]; **δF (188 MHz, $CDCl_3$)** –71·83 (s, $B\underline{F}_4^-$); **m/z (Ar FAB$^+$)** 480 (10%), 196 [M –(BF_4^-), 100%], 137 (10%).

5.02: Reaction in acetonitrile to form (4a*S*,7*R*,8a*R*)-2-ethyl-4a,5,7,8,8a-pentahydro-4,4,7-trimethyl-4*H*-[1,3]-benzoxazinium tetrafluoroborate ($C_{13}H_{23}NO{\cdot}HBF_4$, MW = 297·15) **(112)**:

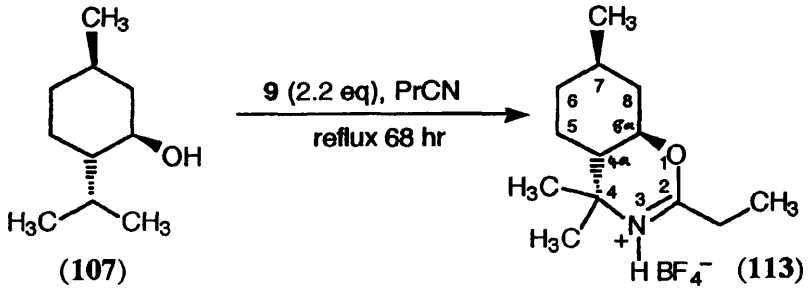


(107) **(112)**

A stirred solution of (–)-menthol **(107)** (0·78 g, 5·0 mmol) and Selectfluor™ **(9)** (4·02 g 97% = 3·90 g, 11·0 mmol) in dry propionitrile (40 ml) was refluxed under nitrogen. After 64 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed twice with water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product (1·52 g, 102%) as a tacky, orange solid. This semi-solid was treated with boiling ethyl acetate (3 ml), then cooled The solid was collected by suction filtration, washed with cold ethyl acetate and dried to give **112** as a white solid (0·46 g, 31%):

R_f = 0·07 (67% EtOAc in petrol); m.p. = 157-159 °C; $[\alpha]_{589}^{26}$ +98·3 ° (c. 1·02, $CHCl_3$); **Found** C, 52·6; H, 8·4; N, 4·8, BF_4^-, 29·4%, $C_{13}H_{23}NO{\cdot}HBF_4$ requires C, 52·6; H, 8·1; N, 4·7; BF_4^-, 29·2%; **υ_{max} (KBr disk)** 3305(m) 3250(m) 3170(m) 3080(w) 2970(m) 2940(m) 2895(w) 1655(s) 1550(m) 1465(m) 1410(w) 1385(m) 1370(w) 1340(m) 1305(m) 1250(w) 1235(w) 1205(m) 1180(s) 1095(s, br) 995(s, br) 940(m) 925(m) 905(m) 890(w) 845(m) 795(w) 765(m) 730(w) 660(w) 525(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·02 (3H, d, *J* = 6·5 Hz, 7-$\underline{C}H_3$), 1·04-1·31 (2H, m, 6-$\underline{C}H_2$), 1·24 (3H, t, *J* = 7·5 Hz, 2-$CH_2\underline{C}H_3$), 1·35 (3H, s, 4-$\underline{C}H_{3ax}$), 1·49 (3H, s, 4-$\underline{C}H_{3eq}$), 1·51-1·71 (2H, m, *ca.* dt, 5-$\underline{C}H_2$), 1·75-1·96 (3H, m, 7-$\underline{C}H$ & 8-$\underline{C}H_2$), 2·25-2·39 (1H, m, *ca.* dt, 4a-$\underline{C}H$), 2·69 (2H, q, *J* = 7·5 Hz, 2-$\underline{C}H_2CH_3$), 4·31 (1H, td, *J* = 11·0, 4·5 Hz, 8a-$\underline{C}H$); **δC (75·5 MHz, $CDCl_3$)** 9·0 (2-$CH_2\underline{C}H_3$), 21·5 (4-$\underline{C}H_{3ax}$), 23·2 (7-$\underline{C}H$), 23·6 (5-$\underline{C}H_2$), 25·5 (4-$\underline{C}H_{3eq}$), 27·1 (2-$\underline{C}H_2CH_3$), 30·6 (7-$\underline{C}H_3$), 33·0 (6-$\underline{C}H_2$), 38·6 (8-$\underline{C}H_2$), 44·3 (4a-$\underline{C}H$), 55·7 [4-$\underline{C}(CH_3)_2$], 79·5 (8a-$\underline{C}H$), 175·8 [2-(C=N)O]; **δF (188 MHz, $CDCl_3$)** –71·87 (s, $B\underline{F}_4^-$); **m/z (Ar FAB$^+$)** 210 [M –(BF_4^-), 100%].

5.03: Reaction in acetonitrile to form (4a*S*,7*R*,8a*R*)-4a,5,7,8,8a-pentahydro-4,4,7-trimethyl-2-propyl-4*H*-[1,3]-benzoxazinium tetrafluoroborate ($C_{14}H_{25}NO{\cdot}HBF_4$, MW = 311·17) (**113**):

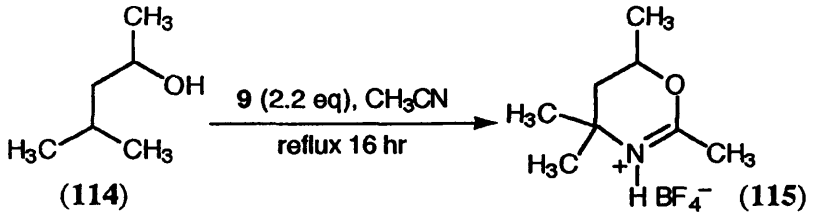


(**107**) (**113**)

A stirred solution of (–)-menthol (**107**) (1·56 g, 10·0 mmol) and Selectfluor™ (**9**) (8·03 g 97% = 7·79 g, 22·0 mmol) in dry butyronitrile (60 ml) was refluxed under nitrogen. After 64 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (100 ml) and water (100 ml). The layers were separated and the organics were washed twice with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **113** (2·23 g, 72%) as a tacky, orange solid. This semi-solid was purified by boiling in a mixture of ethyl acetate (1 ml) and diethyl ether (4 ml). After this was collected by suction filtration, washed with cold ethyl acetate and dried **113** was obtained as a white solid (0·66 g, 21%):

R_f = 0·07 (67% EtOAc in petrol); m.p. = 119-121 °C; $[\alpha]_{589}^{26}$ +89·5 ° (c. 1·03, $CHCl_3$); **Found** C, 54·3; H, 8·1; N, 4·6; BF_4^-, 28·3%, $C_{14}H_{25}NO{\cdot}HBF_4$ requires C, 54·0; H, 8·4; N, 4·5; BF_4^-, 27·9%; υ_{max} **(KBr disk)** 3305(w) 3250(m) 3080(w) 2950(s) 2880(m) 1660(s) 1550(s) 1460(s) 1405(w) 1385(m) 1370(w) 1335(m) 1285(w) 1250(w) 1230(m) 1205(m) 1180(s) 1090(s, br) 990(s, br) 955(m) 935(w) 910(w) 845(w) 810(w) 765(w) 750(w) 665(w) 525(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·99 (3H, t, *J* = 7·5 Hz, 2-$CH_2CH_2C\underline{H}_3$), 1·04 (3H, d, *J* = 6·5 Hz, 7-$C\underline{H}_3$), 1·08-1·31 (2H, m, 6-$C\underline{H}_2$), 1·36 (3H, s, 4-$C\underline{H}_{3ax}$), 1·50 (3H, s, 4-$C\underline{H}_{3eq}$), 1·56-1·64 (3H, m, 7-C<u>H</u> & 5-$C\underline{H}_2$), 1·72 (2H, tq, *J* = 7·5, 7·0 Hz, 2-$CH_2C\underline{H}_2CH_3$), 1·82-1·93 (2H, m, 8-$C\underline{H}_2$), 2·30-2·35 (1H, m, *ca.* dt, 4a-C<u>H</u>), 2·65 (2H, qd, *J* = 7·5, 1·5 Hz, 2-$C\underline{H}_2CH_2CH_3$), 4·29 (1H, td, *J* = 11·0, 4·5 Hz, 8a-C<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 13·1 (2-$CH_2CH_2\underline{C}H_3$), 19·0 (2-$CH_2\underline{C}H_2CH_3$), 21·7 (4-$\underline{C}H_{3ax}$), 23·5 (7-<u>C</u>H), 23·9 (5-$\underline{C}H_2$), 25·8 (4-$\underline{C}H_{3eq}$), 30·9 (7-$\underline{C}H_3$), 33·2 (6-$\underline{C}H_2$), 35·2 (2-$\underline{C}H_2CH_2CH_3$), 38·9 (8-$\underline{C}H_2$), 44·7 (4a-<u>C</u>H), 56·0 [4-<u>C</u>$(CH_3)_2$], 79·7 (8a-<u>C</u>H), 183·0 [2-(C=N)O]; **δF (188 MHz, $CDCl_3$)** –71·78 (s, $B\underline{F}_4^-$); **m/z (Ar FAB$^+$)** 535 [2M –(BF_4^-), 10%], 224 [M –(BF_4^-), 100%].

5.04: 5,6-Dihydro-2,4,4,6-tetramethyl-4*H*-[1,3]-oxazinium tetrafluoroborate ($C_8H_{15}NO{\cdot}HBF_4$, MW = 229·03) (**115**):

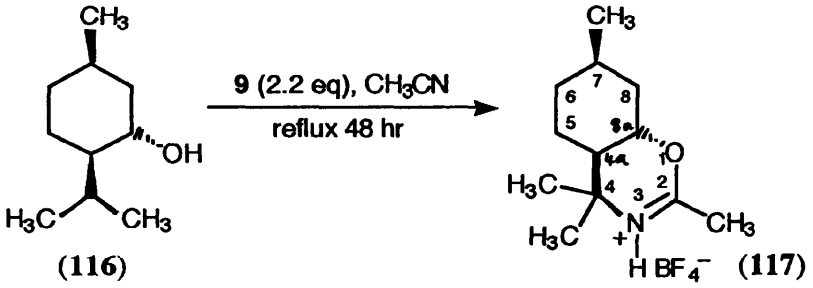


(**114**) (**115**)

A stirred solution of (±)-4-methylpentan-2-ol (**114**) (0·51 g, 5·0 mmol) and Selectfluor™ (**9**) (4·08 g 95·6% = 3·90 g, 11·0 mmol) in dry acetoonitrile (40 ml) was refluxed under nitrogen. After 16 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no **114**, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed twice with water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **114** (0·87 g, 76%) as a tacky, orange solid. This semi-solid was purified by boiling in ethyl acetate (1 ml) and diethyl ether (3 ml). After this was collected by suction filtration, washed with cold ethyl acetate and dried **114** was obtained as a white solid (0·56 g, 49%):

R_f = 0·05 (67% EtOAc in petrol); m.p. = 142-144 °C; **Found** C, 41·7; H, 7·3; N, 6·3; BF_4^-, 37·6%, $C_8H_{15}NO{\cdot}HBF_4$ requires C, 42·0; H, 7·0; N, 6·1; BF_4^-, 37·6%; υ_{max} **(KBr disk)** 3315(m) 3270(m) 3190(m) 3090(w) 3000(m) 2950(w) 1665(s) 1550(s) 1440(s) 1385(m) 1400(m) 1380(s) 1315(s) 1285(m) 1235(m) 1200(w) 1185(w) 1080(s, br) 995(s, br) 930(m) 895(m) 870(w) 830(m) 795(m) 765(m) 620(m) 600(w) 520(m) 495(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·48 (3H, s, 4-C$\underline{H}_{3ax}$), 1·51 (3H, s, 4-C$\underline{H}_{3eq}$), 1·55 (3H, d, J = 6·0Hz, 6-C$\underline{H}_3$), 2·23, 2·35 (2H, ABX, J_{AB} = 15·0 Hz, J_{AX} = 2·5 Hz, J_{BX} = 12·0 Hz, 5-C$\underline{H}_{2ax}$ & 5-C$\underline{H}_{2eq}$), 2·42 (3H, s, 2-C$\underline{H}_3$), 4·75 (1H, dqd, J = 12·0, 6·0, 2·5 Hz, 6-C$\underline{H}$); **δC (75·5 MHz, $CDCl_3$)** 20·0 (2-$\underline{C}H_3$), 20·3 (4-$\underline{C}H_{3ax}$), 27·9 (4-$\underline{C}H_{3eq}$), 27·9 (6-$\underline{C}H_3$), 39·5 (5-$\underline{C}H_2$), 53·2 [4-$\underline{C}(CH_3)_2$], 76·0 (6-$\underline{C}H$), 173·4 [2-(C=N)O]; **δF (188 MHz, $CDCl_3$)** –71·82 (s, $B\underline{F}_4^-$); **m/z (Ar FAB$^+$)** 371 [2M –(BF_4^-), 20%], 142 [M –(BF_4^-), 100%].

5.05: (4a*R*, 7*R*,8a*S*)-4a,5,7,8,8a-Pentahydro-2,4,4,7-tetramethyl-4*H*-[1,3]-benzoxazinium tetrafluoroborate ($C_{12}H_{21}NO{\cdot}HBF_4$, MW = 283·12) (**117**):

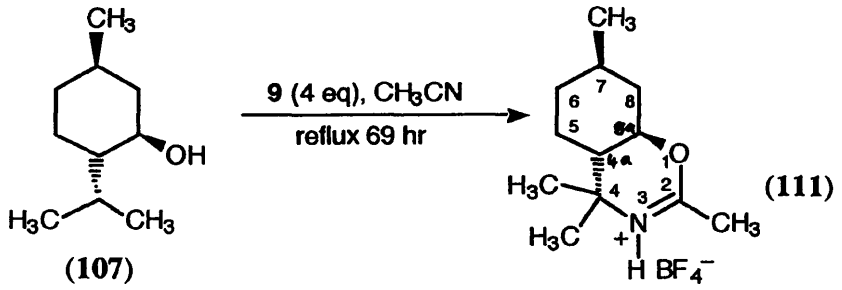


(**116**) (**117**)

A stirred solution of (1*S*,2*R*,5*R*)-(+)-isomenthol (**116**) (0·78 g, 5·0 mmol) and Selectfluor™ (**9**) (4·08 g 95·6% = 3·90 g, 11·0 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 48 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (+)-isomenthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed twice with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **117** (1·46 g, 103%) as a tacky, orange solid. This semi-solid was treated with boiling ethyl acetate (6 ml), then cooled. The solid was collected by suction filtration, washed with cold ethyl acetate and dried to give **117** as a white solid (0·29 g, 20%):

R_f = 0·06 (67% EtOAc in petrol); m.p. = 183-187 °C; $[\alpha]_{589}^{26}$ –78·8 ° (c. 1·02, $CHCl_3$); **υ_{max} (KBr disk)** 3310(w) 3245(m) 3170(m) 3090(w) 2960(m) 2880(w) 1660(s) 1555(s) 1475(m) 1440(m) 1405(w) 1388(m) 1370(w) 1345(m) 1325(s) 1305(w) 1290(w) 1235(m) 1205(m) 1175(m) 1085(s, br) 995(s, br) 905(m) 820(m) 790(w) 760(m) 680(w) 615(w) 520(m) 470(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·04 (3H, d, *J* = 7·5 Hz, 7-C<u>H</u>$_3$), 1·37 (3H, s, 4-C<u>H</u>$_{3ax}$),1·38-1·77 (7H, m, 7-C<u>H</u> & 5-,6-,8-C<u>H</u>$_2$), 1·49 (3H, s, 4-C<u>H</u>$_{3eq}$), 2·13-2·18 (1H, m, 4a-C<u>H</u>), 2·41 (3H, s, 2-C<u>H</u>$_3$), 4·50 (1H, td, *J* = 11·5, 4·5 Hz, 8a-C<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 18·0 (2-<u>C</u>H$_3$), 19·2 (5-<u>C</u>H$_2$), 20·3 (4-<u>C</u>H$_{3ax}$), 23·7 (7-<u>C</u>H), 25·7 (4-<u>C</u>H$_{3eq}$), 27·7 (7-<u>C</u>H$_3$), 30·1 (6-<u>C</u>H$_2$), 36·3 (8-<u>C</u>H$_2$), 45·4 (4a-<u>C</u>H), 56·0 [4-<u>C</u>(CH$_3$)$_2$], 77·4 (8a-<u>C</u>H), 173·2 [2-(C=N)O]; **δF (188 MHz, $CDCl_3$)** –71·77 (s, B<u>F</u>$_4^-$); **m/z (Ar FAB$^+$)** 479 [2M –(BF_4^-), 20%], 214 [M –(BF_4^-) +H_2O, 20%], 196 [M –(BF_4^-), 100%]; **Found (NH_3 CI$^+$)** 196·1698 (M –BF_4^-), $C_{12}H_{21}NO$ requires 196·1701 (M –BF_4^-).

5.06: Repeat of 5.01 using a greater excess of Selectfluor™ ($C_{12}H_{21}NO{\cdot}HBF_4$, MW = 283·12) (**111**):

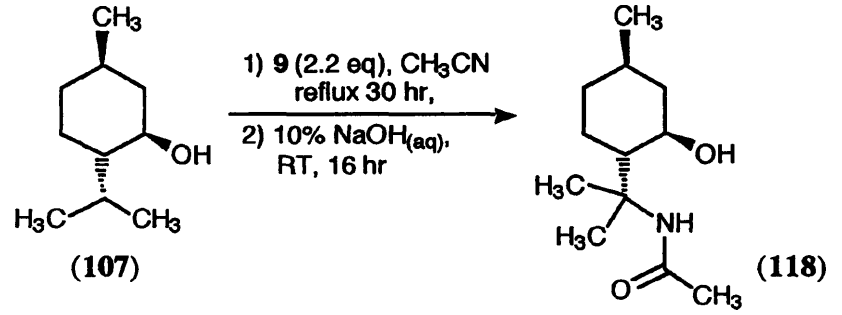


(**107**) (**111**)

A stirred solution of (–)-menthol (**107**) (0·78 g, 5·0 mmol) and Selectfluor™ (**9**) (7·41 g 95·6% = 7·09 g, 20·0 mmol) in dry acetonitrile (60 ml) was refluxed under nitrogen. After 69 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol and a sodium iodide test fot Selectfluor™ was negative, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (60 ml) and water (60 ml). The layers were separated and the organics were washed twice with water (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **111** (1·70 g, 120%) as a tacky, orange solid. This semi-solid was treated with boiling ethyl acetate (6 ml), then cooled. The solid was collected by suction filtration, washed with cold ethyl acetate and dried to give **111** as a white solid (0·67 g, 48%).

Data as for **Expt. 5.01** above.

5.07: *N*-{1-[(1*S*, 2*R*, 4*R*)-2-Hydroxy-4-methylcyclohexyl]-1-methylethyl}acetamide ($C_{12}H_{23}NO_2$ MW = 213·32) (**118**):



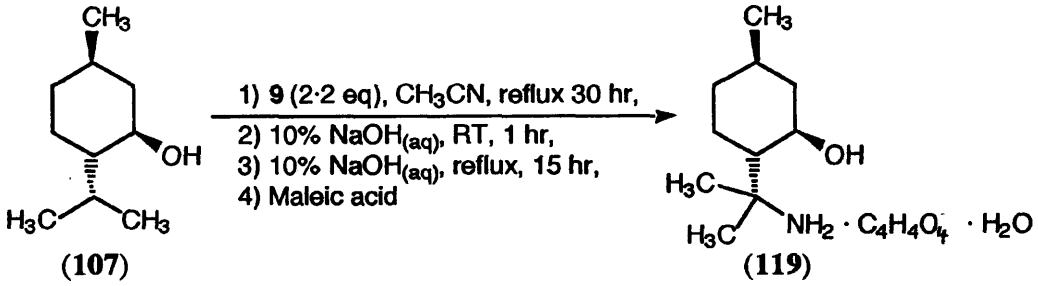
(**107**) (**118**)

A stirred solution of (–)-menthol (**107**) (0·78 g, 5·0 mmol) and Selectfluor™ (**9**) (4·08 g 95·6% = 3·90 g, 11·0 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 30 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and 10% aqueous sodium hydroxide solution (50 ml). This was stirred rapidly under nitrogen for 16 hours, then the layers were separated and the aqueous layer was extracted with dichloromethane (20 ml). The combined organic

layers were washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude **118** (0·89 g, 83%) as a pale yellow oil which was shown to be pure **118** by ^1H (200 MHz, $CDCl_3$) and ^{13}C (75·5 MHz, $CDCl_3$) NMR:

R_f = 0·31 (67% EtOAc in petrol); $[\alpha]_{589}^{26}$ +97·8 ° (c. 0·99, $CHCl_3$); υ_{max} **(Neat)** 3330(w, br) 2975(s) 2935(s) 2880(s) 1675(s) 1535(w) 1460(m) 1385(s) 1315(w) 1295(m) 1275(s) 1260(s) 1240(s) 1215(s) 1170(w) 1135(w) 1115(m) 1090(m) 1060(s) 1035(s) 1015(m) 935(m) 885(w)840(w) 630(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·96 (3H, d, J= 6·5 Hz, 4-$C\underline{H}_3$), 1·02 [3H, s, 1-CHC($C\underline{H}_3$)$_2$], 1·04-1·25 (3H, m, 4-C<u>H</u> & 5-$C\underline{H}_2$), 1·15 [3H, s, 1-CHC($C\underline{H}_3$)$_2$], 1·72-2·17 [5H, m, 1-C<u>H</u>C(CH_3)$_2$ & 3-,6-$C\underline{H}_2$], 1·88 (3H, s, $C\underline{H}_3CON$), 4·30 (1H, td, J = 10·5, 4·5 Hz, 2-C<u>H</u>OH); **δC (75·5 MHz, $CDCl_3$)** 21·8 ($\underline{C}H_3CON$), 22·1 [1-CHC($C\underline{H}_3$)$_2$], 24·7 (4-<u>C</u>H), 25·2 (6-$\underline{C}H_2$), 29·3 [1-CHC($C\underline{H}_3$)$_2$], 31·0 (4-$\underline{C}H_3$), 34·7 (5-$\underline{C}H_2$), 40·8 (3-$\underline{C}H_2$), 46·3 [1-<u>C</u>HC(CH_3)$_2$], 51·6 [1-CH<u>C</u>(CH_3)$_2$], 72·9 (2-<u>C</u>HOH), 172·7 ($CH_3\underline{C}ON$); **m/z (Ar FAB$^+$)** 214 (MH^+ 10%), 196 (MH^+–H_2O, 100%), 137 (10%); **Found (NH_3 CI$^+$)** 214·1799 (M –BF_4^-), $C_{12}H_{23}NO_2$ requires 214·1807 (M –BF_4^-).

5.08: (1*R*, 2*S*, 5*R*)-2-(1-Amino-1-methylethyl)-1-hydroxy-5-methylcyclohexane *Z*-but-2-ene-1,4-dioic acid salt hydrate ($C_{10}H_{21}NO{\cdot}C_4H_4O_4{\cdot}H_2O$ MW = 305·38) **(119)**:



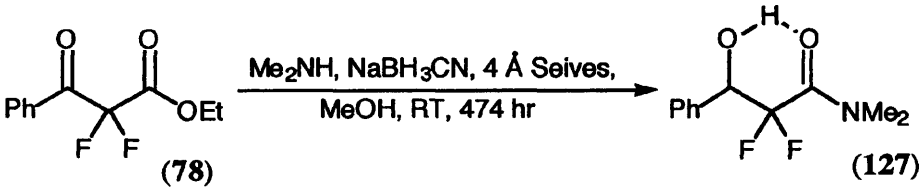
(107) **(119)**

A stirred solution of (–)-menthol (**107**) (0·78 g, 5·0 mmol) and Selectfluor™ (**9**) (4·08 g 95·6% = 3·90 g, 11·0 mmol) in dry acetonitrile (40 ml) was refluxed under nitrogen. After 30 hours TLC (67% ethyl acetate in petrol with ammonium molybdate stain) showed no (–)-menthol, so the reaction was allowed to cool to room temperature. The reaction mixture was concentrated *in vacuo* to give a white semi-solid which was partitioned between dichloromethane (50 ml) and 10% aqueous sodium hydroxide solution (50 ml). This was stirred rapidly under nitrogen for 1 hour, then the layers were separated and the aqueous layer was extracted with dichloromethane (20 ml). The combined organic layers were concentrated *in vacuo* to give a yellow oil which was stirred under nitrogen for 15 hours reflux in refluxing 10% aqueous sodium hydroxide solution (50 ml). The resulting emulsion was cooled ad extracted three times with dichloromethane (50 ml). The combined extracts were dried and treated with activated charcoal. The clear solution thus obtained was concentrated *in vacuo* to give a yellow oil (0·61 g, 71%) which was dissolved in ethyl acetate (1 ml) and added to a solution of maleic acid (0·41 g, 3·56

mmol) and water (0·10 g, 5·56 mmol) in warm ethyl acetate (4 ml). The resulting suspension was cooled, the solid was collected by suction filtration and washed with cold ethyl acetate and dried to give pure **119** (0·78 g, 51%) as a white powder:
R_f = 0·21 (67% EtOAc in petrol); m.p. = 101-105 °C; $[\alpha]_{589}^{26}$ −14·7 ° (c. 1·00, 1·0 M HCl); **Found** C, 55·0; H, 9·2; N, 4·5%, $C_{10}H_{21}NO{\cdot}C_4H_4O_4{\cdot}H_2O$ requires C, 55·1; H, 8·9; N, 4·6%; **υ_{max} (KBr disk)** 3425(s, br) 2955(s) 2960(w) 1585(s) 1505(s) 1360(s) 1190(w) 1025(m) 870(m) 700(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·87 (3H, d, *J* = 6·5 Hz, 5-C<u>H</u>$_3$), 0·80-1·03 (3H, m, 5-C<u>H</u> & 4-C<u>H</u>$_2$), 1·18 [3H, s, 2-CHC(C<u>H</u>$_3$)$_2$], 1·21 [3H, s, 2-CHC(C<u>H</u>$_3$)$_2$], 1·25-1·65 (4H, m, 6-,3-C<u>H</u>$_2$), 1·83-1·87 [1H, m, 2-C<u>H</u>C(CH$_3$)$_2$], 3·34 (2H, br s, <u>H</u>$_2$O), 3·53 (1H, td, *J* = 10·0, 2·5 Hz, 1-C<u>H</u>OH), 5·77 (1H, br s, 1-CHO<u>H</u>), 6·02 (2H, s, $HO_2CC\underline{H}{=}C\underline{H}CO_2^-$), 7·64 (3H, br s, -N<u>H</u>$_3^+$); **δC (75·5 MHz, $CDCl_3$)** 20·1 [2-CHC(C<u>H</u>$_3$)$_2$], 21·9 (5-<u>C</u>H), 24·8 (3-<u>C</u>H$_2$), 25·7 [2-CHC(C<u>H</u>$_3$)$_2$], 30·6 (5-<u>C</u>H$_3$), 34·1 (4-<u>C</u>H$_2$), 44·7 (6-<u>C</u>H$_2$), 49·3 [2-<u>C</u>HC(CH$_3$)$_2$], 56·3 [2-CH<u>C</u>(CH$_3$)$_2$], 71·2 (1-<u>C</u>HOH), 136·1 [$HO_2C\underline{C}H{=}\underline{C}HCO_2^-$], 167·5 [$HO_2\underline{C}CH{=}CH\underline{C}O_2^-$]; **m/z (Ar FAB$^+$)** 172 (M −$C_4H_3O_4^-$ −H_2O, 100%).

3.6 Attempted reductive amination of a difluorobenzoylacetate

6.01: Attempted reductive amination of ethyl 2-benzoyl-2,2-difluoroacetate resulting in *N*,*N*-Dimethyl-2,2-difluoro-3-hydroxy-3-phenylpropionamide ($C_{11}H_{13}F_2NO_2$, MW = 229·23) **(127)**:

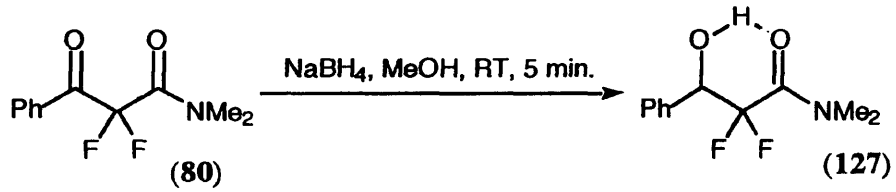


(78) **(127)**

To a solution of dimethylamine [4·10 g (33% w/w in alcohol), 30·0 mmol] in methanol (10 ml) was added ethyl benzoyl-2,2-difluoroacetate (1·14 g, 5·0 mmol), causing a slight exotherm. Sodium cyanoborohydride (0·31 g, 5·0 mmol) was then added, followed by Amberlite™ IR120(+) ion exchange resin (1 g after vac-drying, cat.) and 4Å molecular sieves (2 g, cat.). The resulting reaction mixture was stirred at room temperature until no further change was apparent in the TLC (67% ethyl acetate in petrol). This took 474 hours, after which time the only UV visible material was on the baseline of the TLC plate in the stated solvent system. The suspension was filtered through Celite® and the filtrate was concentrated *in vacuo* to give an oil which was partitioned between dichloromethane (20 ml) and 1 M sodium hydroxide solution (20 ml). The layers were separated and the aqueous layer was extracted twice with dichloromethane (20 ml). The combined organics were washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give (**127**) (0·43 g, 38%) as a yellow oil.

Data as for **Expt. 6.02** below.

6.02: *N,N*-Dimethyl-2,2-difluoro-3-hydroxy-3-phenylpropionamide ($C_{11}H_{13}F_2NO_2$, MW = 229·23) (**127**):



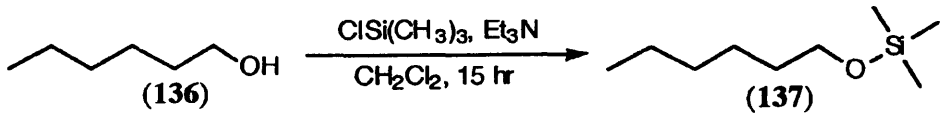
To a solution of *N,N*-dimethyl-2-benzoyl-2,2-difluoroacetamide (**80**) (0·68 g, 3·0 mmol) in methanol (10 ml) was added sodium borohydride (0·60 g, 1·5 mmol). There was a slight exotherm and a small amount of gas was evolved. The resulting solution was stirred for 5 minutes, then was concentrated *in vacuo* to give an oil which was partitioned between dichloromethane (20 ml) and water (50 ml). The layers were stirred together for 5 minutes, separated and the aqueous layer was extracted twice with dichloromethane (20 ml). The combined organics were washed with water (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give **127** (0·55 g, 80%) as a yellow oil:

R_f = 0·43 (67% EtOAc in petrol); **Found** C, 57·5; H, 5·4; N, 6·0; F, 16·8%, $C_{11}H_{13}F_2NO_2$ requires C, 57·64; H, 5·72; N, 6·11; F, 16·58%; υ_{max} **(Thin film, CsI)** 3400(m, br) 2940(m, br) 1655(s) 1495(m) 1455(m) 1405(m) 1260(m) 1385(m) 1090(s) 1060(s) 730(m) 700(s) 615(w) 565(w) cm^{-1}; **δH (200 MHz, $CDCl_3$)** 3·04 [3H, t, *J* = 1·0 Hz, $CON(C\underline{H}_3)_2$], 3·14 [3H, t, *J* = 1·0 Hz, $CON(C\underline{H}_3)_2$], 4·27 (1H, d, *J* = 3·5 Hz, CHO<u>H</u>), 5·25 [1H, ddd, *J* = 21·5, 3·5, 3·5 Hz, PhC<u>H</u>(OH)CF_2], 7·33-7·41 (3H, m, Ar-C<u>H</u>), 7·44-8·00 (2H, m, Ar-C<u>H</u>); **δC (75·5 MHz, $CDCl_3$)** 36·9 [dd *ca.* t, *J* = 7·0 Hz, $CON(\underline{C}H_3)_2$], 73·6 [dd, *J* = 29·5, 23·0 Hz, Ph<u>C</u>H(OH)CF_2], 114·9 [dd, *J* = 267·0, 258·5 Hz, PhCH(OH)<u>C</u>F_2], 128·0, 128·2, 128·4 (Ar <u>C</u>-H), 134·7 (Ar *ipso*-C), 163·9 [dd *ca.* t, *J* = 29·0. 29·0 Hz, <u>C</u>$ON(CH_3)_2$]; **δF (188 MHz, $CDCl_3$)** –40·56(B), –26·43(A), [AB_q *J* = 292·0 Hz, A is d, *J* = 1·0 Hz, B is dd, *J* = 21·5, 1·0 Hz, PhCH(OH)C<u>F</u>$_2$]; **m/z (Ar FAB$^+$)** 230 (MH^+, 50%), 212 [MH^+–H_2O, 10%], 72 [$(CH_3)_2NC{\equiv}O^+$, 100%).

3.7 Synthesis of 2-Fluoro-A-factor

3.7.1 Stability of silyl ethers

7.01: 1-Trimethylsilyloxyhexane ($C_9H_{22}OSi$, MW = 174·36) (**137**):

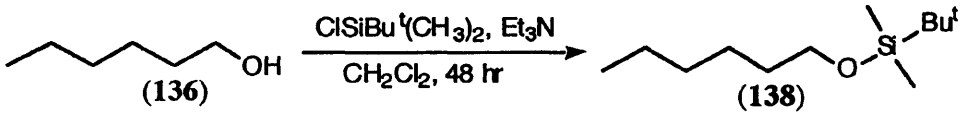


(**136**) (**137**)

To a solution of n-hexanol (**136**) (0·82 g, 8·0 mmol) in dichloromethane (10 ml) was added chlorotrimethylsilane (0·91 g, 8·4 mmol) and then triethylamine (1·62 g, 16·0 mmol). The addition of the chlorotrimethylsilane resulted in a vigorous exotherm. The resulting suspension was allowed to stir at room temperature for 15 hours. The reaction mixture was then concentrated *in vacuo* to give a semi-solid which was directly subjected to flash chromatography eluting with 0-20% ethyl acetate in petrol to give 1-trimethylsilyloxyhexane (**137**)[256] (0·71 g, 51%) as a colourless oil:

R_f = 0·69 (20% EtOAc in petrol); **Found** C, 61·9; H, 13·0; Si, 16·1%, $C_9H_{22}OSi$ requires C, 62·0; H, 12·7; Si 16·1%; υ_{max} **(Neat)** 2970(s) 2940(s) 2870(s) 1465(w) 1385(w) 1255(s) 1100(s) 995(m) 880(s) 845(s) 755(m) 690(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·11 [9H, s, 1-$CH_2OSi(C\underline{H}_3)_3$], 0·88 (3H, t, J = 6·5 Hz, 6-$C\underline{H}_3$), 1·28-1·31 (6H, m, 3,4,5-$C\underline{H}_2$), 1·52 (2H, tt, *ca.* quin, J = 7·0, 7·0 Hz, 2-$C\underline{H}_2$), 3·56 [2H, t, J = 6·5 Hz, 1-$C\underline{H}_2OSi(CH_3)_3$]; **δC (75·5 MHz, $CDCl_3$)** –0·4 [1-$CH_2OSi(\underline{C}H_3)_3$], 14·1 (6-$\underline{C}H_3$), 22·8 (5-$\underline{C}H_2$), 25·6 (3-$\underline{C}H_2$), 31·8 (4-$\underline{C}H_2$), 32·8 (2-$\underline{C}H_2$), 62·8 [1-$\underline{C}H_2OSi(CH_3)_3$]; **m/z (Ar FAB$^+$)** 189 ($M+CH_3^+$, 20%), 159 ($M^{\bullet+}-CH_3^{\bullet}$, 45%), 151 (30%), 133 [$CH_3Si(=O)CH_2Si(=O^+H)CH_3$, 45%], 105 (30%), 95 (45%), 91 [$(CH_3)_3SiOH+H^+$, 40%], 85 ($C_6H_{13}^+$, 100%).

7.02: 1-(*tert*-Butyldimethylsilyloxy)hexane ($C_{12}H_{28}OSi$, MW = 216·44) (**138**):

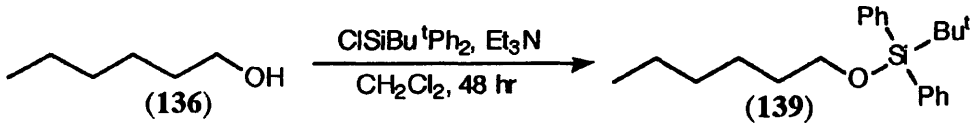


(**136**) (**138**)

To a solution of n-hexanol (**136**) (0·82 g, 8·0 mmol) in dichloromethane (10 ml) was added *tert*-butylchlorodimethylsilane (1·27 g, 8·4 mmol) and then triethylamine (1·62 g, 16·0 mmol). The resulting solution was allowed to stir at room temperature for 48 hours. The reaction mixture was washed with water (7 ml) and then twice with saturated sodium bicarbonate solution (7 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil which was subjected to flash chromatography eluting with 0-20% ethyl acetate in petrol to give 1-(*tert*-butyldimethylsilyloxy)hexane (**138**)[256] (1·57 g, 91%) as a colourless oil:

R_f = 0·68 (20% EtOAc in petrol); **Found** C, 66·5; H, 13·2; Si, 13·0%, $C_{12}H_{28}OSi$ requires C, 66·6; H, 13·0; Si, 13·0%; υ_{max} **(Neat)** 2965(s) 2940(s) 2865(s) 1475(m) 1465(m) 1390(w) 1365(w) 1260(s) 1105(s) 1010(w) 965(w) 840(s) 780(s) 665(w) 400(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·05 {6H, s, 1-$CH_2OSi[C(CH_3)_3](C\underline{H}_3)_2$}, 0·86-0·90 (3H, m, 6-$C\underline{H}_3$), 0·89 {9H, s, 1-$CH_2OSi[C(C\underline{H}_3)_3](CH_3)_2$}, 1·28-1·34 (6H, m, 3,4,5-$C\underline{H}_2$), 1·48-1·51 (2H, m, 2-$C\underline{H}_2$), 3·60 {2H, t, J = 6·5 Hz, 1-$C\underline{H}_2OSi[C(CH_3)_3](CH_3)_2$}; **δC (75·5 MHz, $CDCl_3$)** –5·3 {1-$CH_2OSi[C(CH_3)_3](\underline{C}H_3)_2$}, 14·1 (6-$\underline{C}H_3$), 18·3 {1-$CH_2OSi[\underline{C}(CH_3)_3](CH_3)_2$}, 22·7 (5-$\underline{C}H_2$), 25·5 (3-$\underline{C}H_2$), 26·0 {1-$CH_2OSi[C(\underline{C}H_3)_3](CH_3)_2$}, 31·7 (4-$\underline{C}H_2$), 32·9 (2-$\underline{C}H_2$), 63·4 {1-$\underline{C}H_2OSi[C(CH_3)_3](CH_3)_2$}; **m/z (Ar FAB$^+$)** 221 (55%), 207 (60%), 191 (30%), 147 (100%), 107 (30%), 105 (25%), 91 (55%), 90 (40%), 89 (60%).

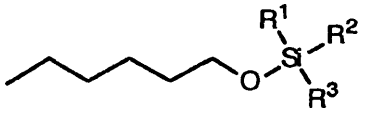
7.03: 1-(*tert*-Butyldiphenylsilyloxy)hexane ($C_{22}H_{32}OSi$, MW = 340·58) (**139**):



To a solution of n-hexanol (**136**) (0·82 g, 8·0 mmol) in dichloromethane (10 ml) was added *tert*-butylchlorodiphenylsilane (2·31 g, 8·4 mmol) and then triethylamine (1·62 g, 16·0 mmol). The resulting solution was allowed to stir at room temperature for 48 hours. The reaction mixture was concentrated *in vacuo* to give a semi-solid which was triturated three times with petrol (20 ml). The resulting solution was concentrated *in vacuo* to give an oil which was subjected to flash chromatography eluting with 0-20% ethyl acetate in petrol to give 1-(*tert*-butyldiphenylsilyloxy)hexane (**139**)[256] (2·28 g, 84%) as a colourless oil:

R_f = 0·61 (20% EtOAc in petrol); **Found** C, 78·0; H, 9·5; Si, 8·5%, $C_{22}H_{32}OSi$ requires C, 77·6; H, 9·5; Si, 8·3%; υ_{max} **(Neat)** 3075(m) 3055(m) 2970(s) 2940(s) 2865(s) 1595(w) 1480(m) 1435(s) 1395(m) 1365(w) 1195(w) 1120(s) 1010(w) 1000(w) 955(w) 830(m) 740(m) 705(s) 615(m) 510(s) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·88 (3H, t, J = 7·0 Hz, 6-$C\underline{H}_3$), 1·05 {9H, s, 1-$CH_2OSi[C(C\underline{H}_3)_3]Ph_2$}, 1·24-1·37 (6H, m, 3,4,5-$C\underline{H}_2$), 1·56 (2H, tt, *ca.* quin, J = 7·0, 6·5 Hz, 2-$C\underline{H}_2$), 3·66 {2H, t, J = 6·5 Hz, 1-$C\underline{H}_2OSi[C(CH_3)_3]Ph_2$}7·35-7·43 (6H, m, *m*-,*p*-Ar$C\underline{H}$), 7·66-7·70 (4H, m, *o*-Ar$C\underline{H}$); **δC (75·5 MHz, $CDCl_3$)** 14·0 (6-$\underline{C}H_3$), 19·1 {1-$CH_2OSi[\underline{C}(CH_3)_3]Ph_2$}, 22·6 (5-$\underline{C}H_2$), 25·4 (3-$\underline{C}H_2$), 26·8 {1-$CH_2OSi[C(\underline{C}H_3)_3]Ph_2$}, 31·5 (4-$\underline{C}H_2$), 32·5 (2-$\underline{C}H_2$), 63·9 {1-$\underline{C}H_2OSi[C(CH_3)_3]Ph_2$}, 127·5, (*m*-Ar$\underline{C}$H), 129·4 (*p*-Ar$\underline{C}$H), 134·1 (Ar *ipso*-$\underline{C}$), 135·5, (*o*-Ar$\underline{C}$H); **m/z (Ar FAB$^+$)** 283 [M$^{\bullet+}$ –$^{\bullet}C(CH_3)_3$, 90%], 263 (M$^{\bullet+}$ –Ph$^{\bullet}$, 20%), 199 ($Ph_2Si{=}OH^+$, 100%), 197 (40%), 183 (70%), 159 (30%), 137 (70%), 135 (75%), 123 (30%), 105 (30%).

7.04: General procedure for the investigation of the stability of silyl ethers with Selectfluor™:



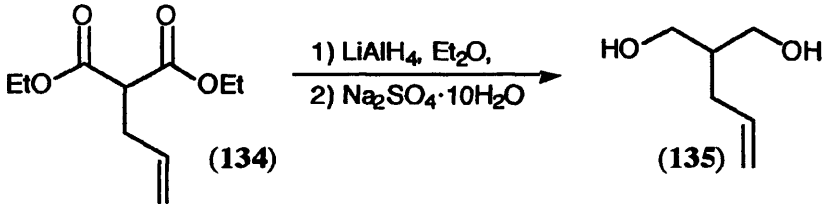
To a solution of a silyloxyhexane (57·4 μmol) in D_3-acetonitrile (0·5 ml) in a 5 mm NMR tube was added Selectfluor™ (**9**) (68·8 μmol). The tube was shaken until the Selectfluor™ had dissolved and then was allowed to stand at 20 °C or at 50 °C for 24 hours. At this point ^1H NMR (200 MHz) analysis was used to determine the percentage of the silyl ether remaining in the solution.

Silyl ether	R^1	R^2	R^3	Silyl ether present after 24 hr at 20 °C		Silyl ether present after 17 hr at 50 °C	
				Synthesised[a]	Commercial[b]	Synthesised[a]	Commercial[b]
137	CH_3	CH_3	CH_3	53%	0%	0%	0%
138	CH_3	CH_3	$C(CH_3)_3$	77%	20%	0%	0%
139	Ph	Ph	$C(CH_3)_3$	100%	100%	63%	0%

[a]Selectfluor™ which had been synthesised at UMIST. (F^- content 1·35%).
[b]Selectfluor™ which had been donated by Air Products and Chemicals Inc. (F^- content 1·85%).

3.7.2 Synthesis of 2-Fluoro-A-factor

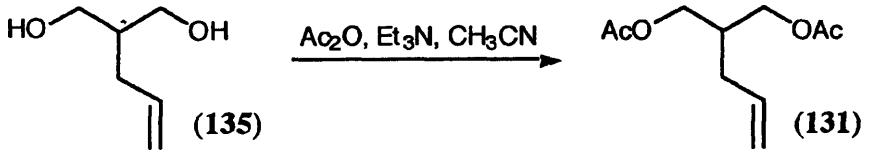
7.05: 1-Hydroxy-2-(hydroxymethyl)pent-4-ene ($C_6H_{12}O_2$, MW = 116·16) (**135**):



A solution of diethyl allylmalonate (**134**) (14·02 g, 70·0 mmol) in dry diethyl ether (125 ml) was added dropwise to a suspension of lithium aluminium hydride (3·08 g 95%, 77·0 mmol) in dry diethyl ether (100 ml) under an atmosphere of nitrogen. The addition rate was adjusted to maintain a gentle reflux. On complete addition the suspension was refluxed for 30 minutes, cooled and sodium sulfate decahydrate (25·80 g, 80 mmol) was carefully added. The resulting suspension was stirred for 15 hours, filtered, concentrated *in vacuo* to give crude 1-hydroxy-2-(hydroxymethyl)pent-4-ene (**135**)[239] (7·20 g, 89%) as a colourless oil. ^1H NMR (200 MHz, deuterochloroform) showed this material to be approximately 90% pure, thus giving a corrected crude yield of 80%. This material was used crude in subsequent reactions, but a small portion was subjected to flash chromatography to give pure **135** with a mass return of 88%:

R_f = 0·29 (EtOAc); **Found** C, 62·3; H, 10·4%, $C_6H_{12}O_2$ requires C, 62·04; H, 10·41%; υ_{max} **(Neat)** 3350(s, br) 2935(s) 2895(s) 1645(m) 1475(m) 1445(m) 1200(w) 1095(m) 1040(s) 1000(m) 975(m) 920(m) 645(m, br) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·79 [1H, dtt, J = 7·0, 7·0, 4·0 Hz, -C<u>H</u>$(CH_2OH)_2$], 2·01 (2H, dd *ca.* t, J = 7·0, 7·0 Hz, -C<u>H</u>$_2$CH=CH_2), 3·58, 3·71 [4H, ABX, J_{AB} = 11·0 Hz, J_{AX} = 4·0 Hz, J_{BX} = 7·0 Hz, -CH(C<u>H</u>$_2$OH)$_2$], 3·65 [2H, s, -CH$(CH_2O$<u>H</u>$)_2$], 5·00 (1H, dd, J = 10·0, 1·5 Hz, trans-CH_2CH=C<u>H</u>$_2$), 5·03 (1H, dd, J = 17·0, 1·5 Hz, cis-CH_2CH=C<u>H</u>$_2$), 5·75 (1H, ddt, J = 17·0, 10·0, 7·0 Hz, -CH_2C<u>H</u>=CH_2); **δC (75·5 MHz, $CDCl_3$)** 32·4 (-<u>C</u>H_2CH=CH_2), 41·8 [-<u>C</u>H$(CH_2OH)_2$], 64·6 [-CH(<u>C</u>H_2OH)$_2$], 116·5 (-CH_2CH=<u>C</u>H_2), 136·1 (-CH_2<u>C</u>H=CH_2); **m/z (Ar FAB$^+$)** 233 ($2MH^+$, 85%), 117 (MH^+, 100%), 99 (MH^+ –H_2O, 20%).

7.06: 1-Acetoxy-2-(acetoxymethyl)pent-4-ene ($C_{10}H_{16}O_4$, MW = 200·24) (**131**):

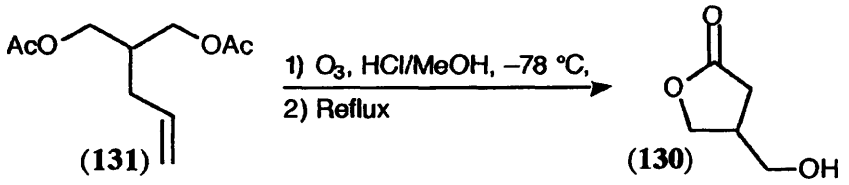


(135) **(131)**

To a solution of crude 1-hydroxy-2-(hydroxymethyl)pent-4-ene (**135**) (15·00 g 90%, 116·2 mmol) in dry acetonitrile (150 ml) was added triethylamine (37·97 g, 375·0 mmol) and then acetic anhydride (32·83 g, 322·0 mmol). The solution was then refluxed for 3 hours, cooled and concentrated *in vacuo*. The resulting semi-solid was dissolved in dichloromethane (200 ml) and washed with water (50 ml). The organic layer was then washed three times with saturated sodium bicarbonate solution (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give crude 1-acetoxy-2-(acetoxymethyl)pent-4-ene (**131**)[239] (20·20 g, 86%). This crude material was subjected to dry flash chromatography to give pure **131** (18·10 g, 78%) as a colourless oil:

R_f = 0·40 (33% EtOAc in petrol); υ_{max} **(Neat)** 3470(w) 3080(w) 2975(m, br) 1750(s) 1645(m) 1475(m) 1450(m) 1370(s) 1240(s, br) 1045(s) 1000(m) 920(m) 830(w) 640(w) 610(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 2·04-2·17 [3H, m, -C<u>H</u>$(CH_2OCOCH_3)_2$ & -C<u>H</u>$_2$CH=CH_2], 2·06 [6H, s, -CH$(CH_2OCOC$<u>H</u>$_3)_2$], 4·03, 4·08 [4H, ABX, J_{AB} = 11·0 Hz, J_{AX} = 4·5 Hz, J_{BX} = 6·0 Hz, -CH(C<u>H</u>$_2$OCOC$H_3)_2$], 5·04-5·10 (2H, m, -CH_2CH=C<u>H</u>$_2$), 5·75 (1H, ddt, J = 17·5, 9·5, 7·0 Hz, -CH_2C<u>H</u>=CH_2); **δC (75·5 MHz, $CDCl_3$)** 25·1 [-CH$(CH_2OCO$<u>C</u>H$_3)_2$], 32·6 (-<u>C</u>H_2CH=CH_2), 36·8 [<u>C</u>H$(CH_2OCOCH_3)_2$], 63·7 [-CH(<u>C</u>H_2OCOC$H_3)_2$], 117·4 (-CH_2CH=<u>C</u>H_2), 134·8 (CH_2<u>C</u>H=CH_2), 170·9 [-CH$(CH_2O$<u>C</u>OC$H_3)_2$]; **m/z (Ar FAB$^+$)** 201 (MH^+, 35%), 141 (MH^+ –CH_3CO_2H, 100%); **Found (NH_3 CI$^+$)** 201·1128 (MH^+), $C_{10}H_{17}O_4$ requires 201·1127 (MH^+).

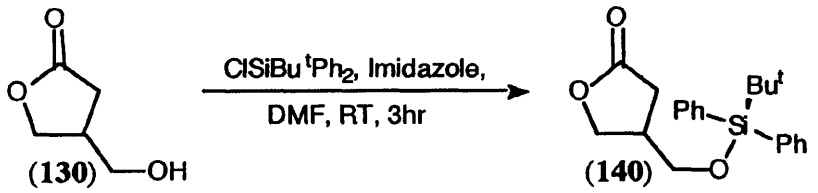
7.07: 4-Hydroxymethyl-γ-butyrolactone ($C_5H_8O_3$, MW = 116·12) (**130**):



A solution of 4·4% HCl dissolved in anhydrous methanol (20 ml) was cooled to –78 °C and 1-acetoxy-2-(acetoxymethyl)pent-4-ene (**131**) (2·00 g, 10·0 mmol) was added. The solution had oxygen bubbled through for 5 minutes whilst the temperature was kept at –78 °C with an external dry ice slush bath. Ozone was then introduced using a Fischer 501 ozone generator. The flow rate was maintained at 50 L/hr and the current supplied was kept at 0·7 A using the variable control. After about 45 minutes a blue colour appeared. Ozone was supplied for another 30 minutes, then nitrogen was bubbled through the solution until a sodium iodide test of the exhaust gas showed that there was no more ozone being off-gassed (about 45 minutes). The solution was allowed to warm to room temperature over 10 minutes, then was heated to 50 °C for 1 hour. The solution was then cooled to 10 °C and ozone was bubbled through (0·7 A, flow rate 50 L/hr) for 1 hour. The solution was then stirred under a blanket of nitrogen for 40 minutes. A solution of 4·4% HCl dissolved in anhydrous methanol (10 ml) was added and the reaction mixture was refluxed for 14 hours, cooled and solid sodium bicarbonate (5 g) was carefully added. The resulting suspension was stirred for 30 minutes, then dichloromethane (30 ml) and magnesium sulfate (5 g) was added. This was stirred for 10 minutes, filtered and the filtrate was concentrated *in vacuo*. The resulting oil (1·04 g) was subjected to flash chromatography to give pure 4-hydroxymethyl-γ-butyrolactone (**130**)[238] (0·58 g, 50%) as a colourless oil:

R_f = 0·22 (EtOAc); **υ_{max} (Neat)** 3410(s, br) 2920(m) 1770(s) 1480(w) 1420(m) 1385(m) 1265(m) 1185(s) 1025(s) 935(w) 905(w) 850(w) 690(w) 550(w) 505(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 2·39, 2·60 (2H, ABX, J_{AB} = 17·5 Hz, J_{AX} = 9·0 Hz, J_{BX} = 6·0 Hz, 3-C<u>H</u>$_2$), 2·76 (1H, dddddd, J = 9·0, 7·5, 6·5, 6·0, 5·5, 5·0 Hz, 4-C<u>H</u>CH$_2$OH), 3·64, 3·68 (2H, ABX, J_{AB} = 10·5 Hz, J_{AX} = 5·5 Hz, J_{BX} = 6·5 Hz, 4-CHC<u>H</u>$_2$OH), 3·67 (1H, s, 4-CHCH$_2$O<u>H</u>), 4·22, 4·41 (2H, ABX, J_{AB} = 9·5 Hz, J_{AX} = 7·5 Hz, J_{BX} = 5·0 Hz, 5-C<u>H</u>$_2$); **δC (75·5 MHz, $CDCl_3$)** 30·8 (3-<u>C</u>H$_2$), 36·9 (4-<u>C</u>HCH$_2$OH), 62·8 (4-CH<u>C</u>H$_2$OH), 70·8 (5-<u>C</u>H$_2$), 178·0 (2-<u>C</u>=O); **m/z (Ar FAB$^+$)** 233 ($2MH^+$, 40%), 149 (75%), 131 (25%), 117 (MH^+, 100%), 107 (40%), 91 (25%), 90 (30%), 89 (55%); **Found (NH_3 CI$^+$)** 134·0815 (MNH_4^+), $C_5H_{12}NO_3$ requires 134·0817 (MNH_4^+).

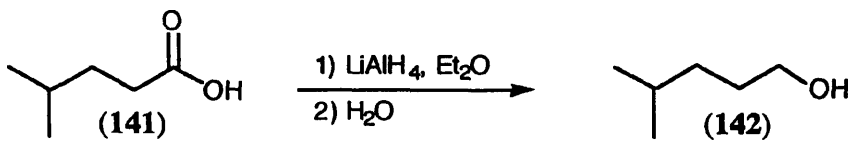
7.08: 4-[(*tert*-Butyldiphenylsilyl)oxymethyl]-γ-butyrolactone ($C_{21}H_{26}O_3Si$, MW = 354·52) (**140**):



To a well stirred solution of 4-hydroxymethyl-γ-butyrolactone (**130**) (2·11 g, 18·2 mmol) and imidazole (1·36 g, 20·0 mmol) in DMF (18 ml) was added dropwise *tert*-butylchlorodiphenylsilane (5·40 g, 19·7 mmol). On complete addition the resulting solution was stirred at room temperature for three hours. Water (150 ml) was added and the product was extracted three times into dichloromethane (100 ml). The combined organic extracts were washed four times with water (100 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil which was subjected to flash chromatography to give 4-[(*tert*-butyldiphenylsilyl)oxymethyl]-γ-butyrolactone (**140**) (5·10 g, 79%) as a white crystalline solid:

R_f = 0·30 (33% EtOAc in petrol); m.p. = 66-67 °C; **Found** C, 71·2; H, 7·6; Si 7·6%, $C_{21}H_{26}O_3Si$ requires C, 71·15; H, 7·39; Si 7·92%; υ_{max} **(KBr disk)** 3075(w) 3055(w) 2960(m) 2935(m) 2880(m) 2860(m) 1770(s) 1590(w) 1475(m) 1430(m) 1395(m) 1375(m) 1215(w) 1180(s) 1110(s) 1095(s) 1045(s) 1020(m) 1005(s) 860(w) 830(m) 815(m) 740(m) 700(s) 690(s) 620(s) 565(w) 505(s) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 1·06 {9H, s, OSi[C(C$\underline{H}_3$)$_3$]Ph$_2$}, 2·41, 2·56 (2H, ABX, J_{AB} = 17·5 Hz, J_{AX} = 9·0 Hz, J_{BX} = 6·5 Hz, 3-C$\underline{H}_2$), 2·74 (1H, dddddd, J = 9·0, 7·5, 6·5, 6·0, 5·5, 5·5 Hz, 4-C$\underline{H}$CH$_2$OSi), 3·65, 3·67 (2H, ABX, J_{AB} = 11·0 Hz, J_{AX} = 5·5 Hz, J_{BX} = 6·0 Hz, 4-CHC$\underline{H}_2$OSi), 4·23, 4·39 (2H, ABX, J_{AB} = 9·0 Hz, J_{AX} = 7·5 Hz, J_{BX} = 5·5 Hz, 5-C$\underline{H}_2$), 7·37-7·46 (6H, m, *m*-,*p*-ArC$\underline{H}$), 7·62-7·65 (4H, m, *o*-ArC$\underline{H}$); **δC (75·5 MHz, $CDCl_3$)** 19·4 {OSi[$\underline{C}$(CH$_3$)$_3$]Ph$_2$}, 26·9 {OSi[C($\underline{C}$H$_3$)$_3$]Ph$_2$}, 30·9 (3-$\underline{C}$H$_2$), 37·4 (4-$\underline{C}$HCH$_2$OSi), 64·3 (4-CH$\underline{C}$H$_2$OSi), 70·7 (5-$\underline{C}$H$_2$), 128·0, (*m*-Ar$\underline{C}$H), 130·1 (*p*-Ar$\underline{C}$H), 133·0 (Ar *ipso*-$\underline{C}$), 135·7 (*o*-Ar$\underline{C}$H), 177·2 (2-$\underline{C}$=O); **m/z (Ar FAB$^+$)** 709 ($2MH^+$, 2%), 651 {[2M –C(CH$_3$)$_3$]$^+$, 15%}, 631 [(2M –Ph)$^+$, 5%], 593 {[2M –H –2C(CH$_3$)$_3$]$^+$, 5%}, 355 (MH^+, 5%), 353 ($M^{\bullet+}$ –H$^\bullet$, 5%), 297 [$M^{\bullet+}$ –$^\bullet$C(CH$_3$)$_3$, 70%], 277 ($M^{\bullet+}$ –Ph$^\bullet$, 100%), 197 (20%), 135 (70%).

7.09: 4-Methylpentan-1-ol ($C_6H_{14}O$, MW = 102·18) (**142**):

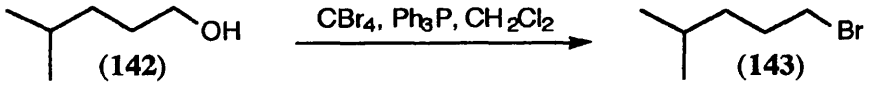


To a cooled (ice/methanol) suspension of $LiAlH_4$ (10·36 g 95%, 259 mmol) in diethyl ether (300 ml) was added dropwise a solution of 4-methylpentanoic acid (**141**) (29·4 g,

253 mmol) in diethyl ether (40 ml). On complete addition the resulting suspension was stirred at room temperature for two hours, and was then carefully quenched with water (15 ml). Diethyl ether (100 ml) was added to facilitate stirring of the resulting stiff suspension. The reaction mixture was stirred for 15 minutes, after which time $MgSO_4$ (15 g) was added. The reaction mixture was stirred a further 30 minutes and was then filtered through Celite®. The filtrate was concentrated *in vacuo* to give a colourless liquid which was distilled at ambient pressure to give 4-methylpentan-1-ol (**142**) (20·43 g, 79%) as a colourless liquid:

R_f = 0·30 (25% EtOAc in petrol); b.p.$_{760}$ 158 °C (uncorrected) (Lit.[245] b.p.$_{760}$ = 160-165 °C); υ_{max} (**Neat**) 3340(s, br) 2960(s) 2940(s) 2875(s) 1470(m) 1390(m) 1370(m) 1175(w) 1125(w) 1075(m) 1060(s) 1020(m) 900(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·88 [6H, d, J = 6·5 Hz, 4-CH($C\underline{H}_3$)$_2$], 1·18-1·26 (2H , m, 3-$C\underline{H}_2$), 1·51-1·62 [3H, m, 2-$C\underline{H}_2$ & 4-$C\underline{H}$(CH_3)$_2$], 1·67 (1H, s, 1-$CH_2O\underline{H}$), 3·62 (2H, t, J = 6·5 Hz, 1-$C\underline{H}_2$OH); **δC (75·5 MHz, $CDCl_3$)** 22·3 [4-CH($\underline{C}H_3$)$_2$], 27·7 [4-$\underline{C}$H(CH_3)$_2$], 30·4 (2-$\underline{C}H_2$), 34·7 (3-$\underline{C}H_2$), 62·8 (1-$\underline{C}H_2$OH); **m/z (Ar FAB$^+$)** 85 [MH^+ –H_2O ≡ $(CH_3)_2CHCH_2CH_2CH_2^+$, 100%].

7.10: 1-Bromo-5-methylpentane ($C_6H_{13}Br$, MW = 165·07) (**143**):

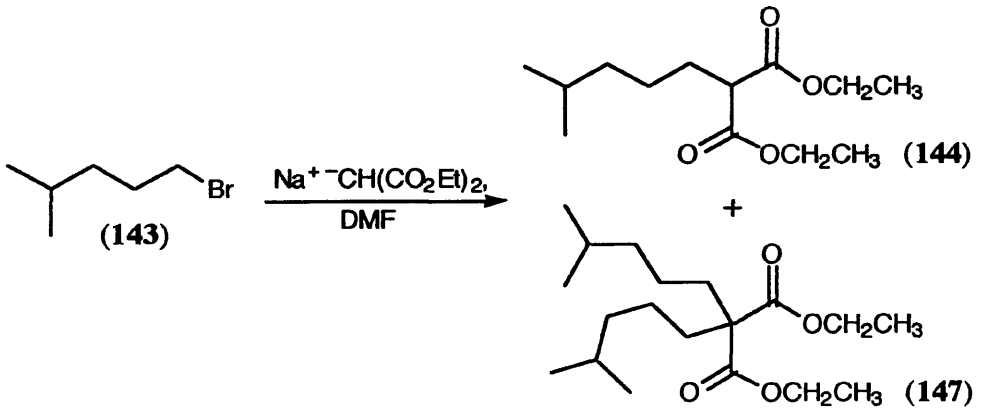


(**142**) (**143**)

To a cooled (–10 °C) solution of 4-methylpentan-1-ol (**142**) (5·00 g, 48·9 mmol) and carbon tetrabromide (20·30 g, 61·2 mmol) in dichloromethane (50 ml) was added carefully in portions triphenylphosphine (19·20 g, 73·4 mmol). On complete addition the solution was stirred at room temperature for one hour, then petrol (50 ml) was added. The resulting tacky suspension was stirred until the gum solidified, then the solid was removed by vacuum filtration and washed with petrol. The combined filtrates were concentrated *in vacuo* to give a semi-solid which was slurried in petrol (50 ml) and filtered to remove the solid. The solid was washed with petrol and the combined filtrates were concentrated *in vacuo* to give a colourless liquid which was distilled twice at ambient pressure to give 1-bromo-5-methylpentane (**143**) (7·36 g, 91%) as a colourless liquid:

R_f = 0·60 (20% EtOAc in petrol); b.p.$_{760}$ 138-142 °C (uncorrected) (Lit.[257] b.p.$_{760}$ = 142-144 °C); υ_{max} (**Neat**) 2960(s) 2935(s) 2875(s) 1470(s) 1440(m) 1390(m) 1370(m) 1305(w) 1280(w) 1260(s) 1215(m) 1175(w) 930(w) 755(w) 740(w) 645(m) 565(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·90 [6H, d, J = 6·5 Hz, 4-CH($C\underline{H}_3$)$_2$], 1·27-1·34 (2H, m, 3-$C\underline{H}_2$), 1·51-1·62 [1H, m, 4-$C\underline{H}$(CH_3)$_2$], 1·81-1·91 (2H, m, 2-$C\underline{H}_2$), 3·39 (2H, t, J = 7·0 Hz, 1-$C\underline{H}_2$Br); **δC (75·5 MHz, $CDCl_3$)** 22·5 [4-CH($\underline{C}H_3$)$_2$], 27·5 [4-$\underline{C}$H(CH_3)$_2$], 30·8 (2-$\underline{C}H_2$), 34·2 (1-$\underline{C}H_2$Br), 37·4 (3-$\underline{C}H_2$); **m/z (Ar FAB$^+$)** 251 ($3M^{\bullet+}$ –3HBr –H$^\bullet$, 95%), 167 ($2M^{\bullet+}$ –2HBr –H$^\bullet$, 25%), 167/165 (MH^+, 25%), 136 (40%), 85 ($M^{\bullet+}$ –Br$^\bullet$, 100%), 83 (70%).

7.11: Diethyl 2-(4-methylpentyl)malonate ($C_{13}H_{24}O_4$, MW = 244·33) (**144**):

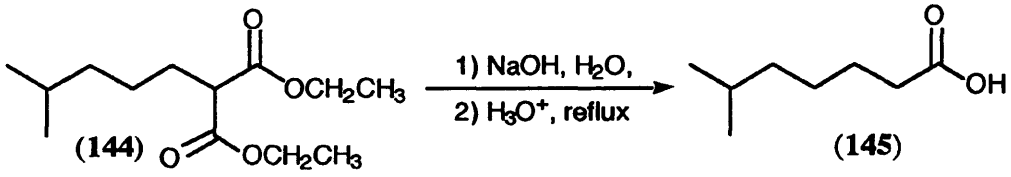


To a suspension of oil free sodium hydride (2·11 g, 88·1 mmol) cooled to –10 °C in DMF (30 ml) was added a solution of diethyl malonate (12·27 g, 76·6 mmol) in DMF (20 ml). The resulting solution was allowed to stir for 15 minutes, after which time a solution of 1-bromo-5-methylpentane (**143**) (12·64 g, 76·6 mmol) in DMF (10 ml) was added. The reaction mixture was stirred at –10 °C for 30 minutes and then at room temperature for two hours. A solution of acetic acid (0·69 g, 11·5 mmol) in water (200 ml) was added and the resulting cloudy solution was extracted three times with dichloromethane (100 ml). The combined organic extracts were washed four times with water (400 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give an oil (18·60 g, 99%) which was shown by ^1H NMR (200 MHz, $CDCl_3$) to consist of diethyl malonate, diethyl 2-(4-methylpentyl)malonate (**144**) and diethyl 2,2-[bis(4-methylpentyl)]malonate (**147**). These three components were separated by flash chromatography (eluting with 0%-25% ethyl acetate in petrol) to remove the diethyl malonate followed by distillation at reduced pressure to separate **144** and **147**. This resulted in **144** (8·19 g, 44%) and **147** (1·45 g, 6%) as colourless oils:

(**144**): R_f = 0·43 (25% EtOAc in petrol); b.p.$_{6·0}$ 122-130 °C (dec.); b.p.$_{0·7}$ 98-102 °C (Lit.[258] b.p.$_{10}$ 142-144 °C); υ_{max} **(Neat)** 2960(s, br) 2875(m) 1765(s) 1740(s) 1470(m) 1370(m) 1280(m, br) 1250(s) 1225(s) 1180(s) 1155(s) 1125(m) 1100(m) 1040(m) 865(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·85 [6H, d, J = 6·5 Hz, $(C\underline{H}_3)_2CH$], 1·14-1·34 [4H , m, $(CH_3)_2CHC\underline{H}_2C\underline{H}_2CH_2$], 1·26 [6H, t, J = 7·0 Hz, $CH(CO_2CH_2C\underline{H}_3)_2$], 1·53 [1H, hept d, *ca.* non, J = 6·5, 6·5 Hz, $(CH_3)_2C\underline{H}CH_2$], 1·86 [2H, dt, *ca.* q, J = 7·5, 7·5 Hz, $C\underline{H}_2CH(CO_2CH_2CH_3)_2$], 3·31 [1H, t, J = 7·5 Hz, $CH_2C\underline{H}(CO_2CH_2CH_3)_2$], 4·19 [4H, q, J = 7·0 Hz, $CH(CO_2C\underline{H}_2CH_3)_2$]; **δC (75·5 MHz, $CDCl_3$)** 13·9 $[CH(CO_2CH_2\underline{C}H_3)_2]$, 22·3 $[(\underline{C}H_3)_2CH]$, 24·9 $[(CH_3)_2CHCH_2\underline{C}H_2CH_2]$, 27·5 $[(CH_3)_2\underline{C}H]$, 28·8 $[(CH_3)_2CHCH_2CH_2\underline{C}H_2]$, 38·3 $[(CH_3)_2CH\underline{C}H_2CH_2CH_2]$, 51·9 $[\underline{C}H(CO_2CH_2CH_3)_2]$, 61·0 $[CH(CO_2\underline{C}H_2CH_3)_2]$, 169·4 $[CH(\underline{C}O_2CH_2CH_3)_2]$; **m/z (Ar FAB$^+$)** 245 ($MH^+$, 100%), 199 ($MH^+$ –EtOH, 10%), 181 (45%), 173 (15%), 160 (20%), 153 (MH^+ –2EtOH, 25%), 97 (20%); **Found (NH$_3$ CI$^+$)** 245·1749 (MH^+), $C_{13}H_{25}O_4$ requires 245·1753 (MH^+).

(**147**): R_f = 0·49 (25% EtOAc in petrol); b.p.$_{0.7}$ 136-146 °C; υ_{max} **(Neat)** 2960(s) 2875(m) 1735(s) 1470(m) 1390(w) 1370(m) 1300(m) 1250(s, br) 1200(s) 1150(m) 1135(m) 1100(w) 1045(w) 870(w) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·85 [12H, d, *J* = 6·5 Hz, $(C\underline{H}_3)_2CH$], 1·05-1·29 [8H , m, $(CH_3)_2CHC\underline{H}_2C\underline{H}_2CH_2$], 1·23 [6H, t, *J* = 7·0 Hz, $C(CO_2CH_2C\underline{H}_3)_2$], 1·54 [2H, hept d, *ca.* non, *J* = 6·5, 6·5 Hz, $(CH_3)_2C\underline{H}CH_2$], 1·79-1·89 [4H, m, $CH_2C\underline{H}_2)_2C(CO_2CH_2CH_3)_2$], 4·16 [4H, q, *J* = 7·0 Hz, $C(CO_2C\underline{H}_2CH_3)_2$]; **δC (75·5 MHz, $CDCl_3$)** 14·2 [$C(CO_2CH_2\underline{C}H_3)_2$], 21·7 [$(CH_3)_2CHCH_2\underline{C}H_2CH_2$], 22·6 [$(\underline{C}H_3)_2CH$], 27·6 [$(CH_3)_2\underline{C}H$], 32·4 [$(CH_2\underline{C}H_2)_2C(CO_2\underline{C}H_2CH_3)_2$], 38·9 [$(CH_3)_2CH\underline{C}H_2CH_2CH_2$], 57·7 [$\underline{C}(CO_2CH_2CH_3)_2$], 60·9 [$C(CO_2\underline{C}H_2CH_3)_2$], 172·1 [$C(\underline{C}O_2CH_2CH_3)_2$]; **m/z ($NH_3$ CI^+)** 329 (MH^+, 100%); **Found (NH_3 CI^+)** 329·2687 (MH^+), $C_{19}H_{37}O_4$ requires 329·2692 (MH^+).

7.12: 6-Methylheptanoic acid ($C_8H_{16}O_2$, MW = 144·22) (**145**):

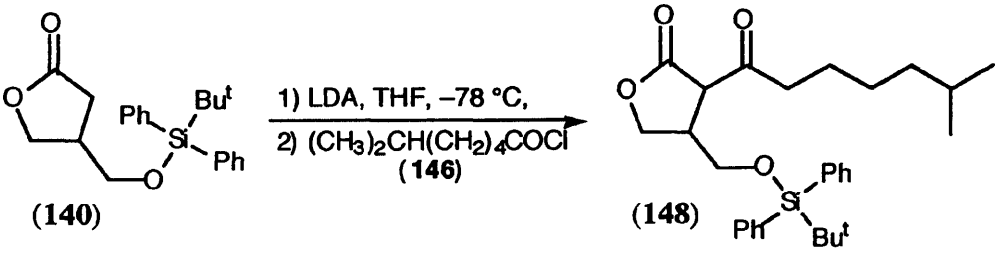


To a solution of potassium hydroxide (8·16 g, 125·5 mmol) in water (8 ml) was added a solution of 2-(4-methylpentyl)malonate (**144**) (5·11 g, 20·9 mmol) in THF (5 ml). The resulting two-phase system was heated under reflux for 30 minutes. After this time the THF was allowed to boil away over 30 minutes whilst the solution was kept at a constant volume by adding hot water. The reaction mixture was heated under reflux for a further 17 hours, after which time hot water (20 ml) was added and the ethanol was allowed to boil away over on hour whilst the solution was kept at a constant volume by adding hot water. The resulting solution was cooled by the addition of ice (5 g) and concentrated hydrochloric acid (21·3 ml, 251 mmol) was carefully added. The solution was heated under reflux for a further 22 hours, then was cooled, saturated with sodium chloride and extracted six times with ethyl acetate (20 ml). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give crude 6-methylheptanoic acid (**145**) (4·87 g, 162%) as a cloudy oil which was subjected to flash chromatography (eluting with 0%-33% ethyl acetate in petrol) to give **145** (2·99 g, 99%) as a colourless oil:

R_f = 0·35 (33% EtOAc in petrol); b.p.$_{760}$ 228-232 °C (Lit.[259] b.p.$_{760}$ 232 °C) υ_{max} **(Neat)** 3030(m, br) 2960(s) 2870(s) 2670(w, br) 1715(s) 1470(m) 1415(m) 1390(w) 1370(w) 1290(m) 1245(m) 1210(w) 1115(w) 940(w, br) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·86 [6H, d, *J* = 6·5 Hz, 6-$CH(C\underline{H}_3)_2$], 1·12-1·26 (2H , m, 4-$C\underline{H}_2$), 1·25-1·43 (2H , m, 5-$C\underline{H}_2$), 1·44-1·69 [3H , m, 6-$C\underline{H}(CH_3)_2$ & 3-$C\underline{H}_2$], 2·35 (2H, t, *J* = 7·5 Hz, 2-$C\underline{H}_2$); **δC (75·5 MHz, $CDCl_3$)** 22·6 [6-$CH(\underline{C}H_3)_2$], 24·9 (3-$C\underline{H}_2$), 26·7 (4-$C\underline{H}_2$), 27·8 [6-$\underline{C}H(CH_3)_2$], 34·2 (5-$C\underline{H}_2$), 38·6 (2-$C\underline{H}_2$) 160·7 (1-$\underline{C}O_2H$); **m/z (NH_3**

CI+) 162 (MNH_4^+, 100%), 82 (45%); **Found** (**NH_3 CI+**) 162·1493 (MNH_4^+), $C_8H_{20}NO_2$ requires 162·1494 (MNH_4^+).

7.13: 4-[(*tert*-Butyldiphenylsilyl)oxymethyl]-3-(6-methyl-1-oxoheptyl)-γ-butyrolactone ($C_{29}H_{40}O_4Si$, MW = 480·72) (**148**):

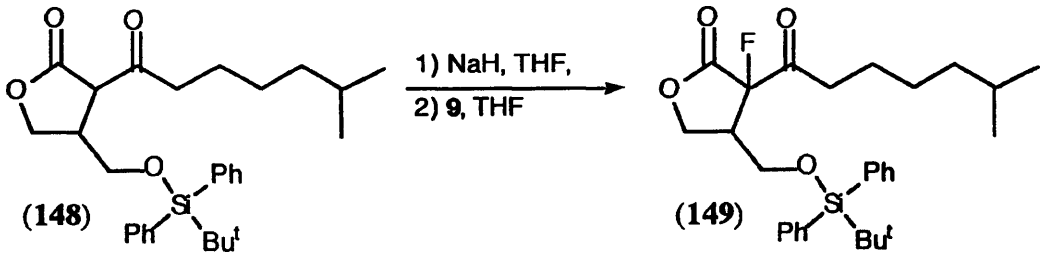


6-methylheptanoyl chloride (**146**) was prepared by heating 6-methylheptanoic acid (**145**) (0·30 g, 2·06 mmol) and a catalytic amount of DMF (1 drop) under refluxing thionyl chloride (3 ml) for two hours. The solution was cooled, toluene (5 ml) was added and the reaction mixture was concentrated *in vacuo* to give **146** as a pale yellow oil (0·33 g, 100%). A solution of diisopropylamine (0·52 g, 5·15 mmol) in THF (5 ml) under nitrogen was cooled to –78 °C and a solution of *n*-butyllithiun (2·06 ml 2·5 M in hexane, 5·15 mmol) was added dropwise, followed five minutes later by a solution of **140** (0·73 g, 2·06 mmol) in THF (2 ml). After five minutes' stirring the solution of 6-methylheptanoyl chloride (**146**) (0·33 g, 2·06 mmol) in THF (2 ml) was added dropwise. The resulting solution was allowed to warm to room temperature over 30 minutes, then was stirred at room temperature for a further 30 minutes. The reaction mixture was then poured onto an ice cold solution of acetic acid (4 ml) in water (20 ml), the layers were separated and the aqueous phase was extracted four times with dichloromethane (20 ml). The combined extracts were repeatedly washed with saturated aqueous sodium bicarbonate solution (15 ml) until no more carbon dioxide evolution was evident (about four washes). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo* to give **148** (1·03 g, 104%) as a brown oil which was subjected to flash chromatography (eluting with 0%-25% ethyl acetate in petrol) to give **148** (0·99 g, 100%) as a colourless oil:

R_f = 0·49 (33% EtOAc in petrol); **Found** C, 72·4; H, 8·7; Si, 5·6%, $C_{29}H_{40}O_4Si$ requires C, 72·46; H, 8·39; Si, 5·84%; **υ_{max} (Neat)** 2960(s) 2935(s) 2865(s) 1780(s) 1720(s) 1650(w) 1475(m) 1435(m) 1395(m) 1370(m) 1220(m) 1170(s) 1115(s) 1030(m) 1000(m) 825(m) 800(w) 745(m) 705(s) 615(m) 510(s) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·86 [6H, d, J = 6·5 Hz, 3-CHCO$(CH_2)_4$CH$(C\underline{H}_3)_2$], 1·05 {9H, s, OSi[C$(C\underline{H}_3)_3$]Ph_2}, 1·13-1·34 [4H, m, 3-CHCOCH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$(CH_3)_2$], 1·48-1·61 [3H, m, 3-CHCOCH$_2$C$\underline{H}_2(CH_2)_2$C$\underline{H}(CH_3)_2$], 2·52, 2·93 [2H, ABX_2, J_{AB} = 18·0 Hz, J_{AX} = 7·5 Hz, J_{BX} = 7·0 Hz, 3-CHCOC$\underline{H}_2(CH_2)_3$CH$(CH_3)_2$], 3·18-3·21 (1H, m, 4-C$\underline{H}$CH$_2$OSi), 3·65 (2H, d, J = 8·0 Hz, 4-CHC$\underline{H}_2$OSi), 3·67 [1H, d, J = 5·0 Hz, 3-C$\underline{H}$CO$(CH_2)_4$CH$(CH_3)_2$], 4·17, 4·39 (2H, ABX, J_{AB} = 8·5 Hz, J_{AX} = 8·5 Hz, J_{BX} =

6·0 Hz, 5-C$\underline{H}_2$), 7·37-7·48 (6H, m, *m*-,*p*-ArC$\underline{H}$), 7·59-7·61 (4H, m, *o*-ArC$\underline{H}$); δC (**75·5 MHz, $CDCl_3$**) 19·2 {OSi[$\underline{C}(CH_3)_3$]Ph_2}, 22·6 [3-CHCO$(CH_2)_4$C$\underline{H}(CH_3)_2$], 23·5 [3-CHCOC$H_2\underline{C}H_2(CH_2)_2CH(CH_3)_2$], 26·8 [3-CHCO$(CH_2)_2\underline{C}H_2CH_2CH(CH_3)_2$], 26·8 {OSi[C$(\underline{C}H_3)_3$]$Ph_2$}, 27·8 [3-CHCO$(CH_2)_4\underline{C}H(CH_3)_2$], 38·6 [3-CHCO$(CH_2)_3\underline{C}H_2CH(CH_3)_2$], 39·3 (4-$\underline{C}HCH_2$OSi), 42·6 [3-CHCO$\underline{C}H_2(CH_2)_3CH(CH_3)_2$], 55·0 [3-$\underline{C}HCO(CH_2)_4CH(CH_3)_2$], 63·1 (4-CH$\underline{C}H_2$OSi), 69·3 (5-C$\underline{H}_2$), 127·9, (*m*-ArC$\underline{H}$), 130·1 (*p*-ArC$\underline{H}$), 132·7 (Ar *ipso*-$\underline{C}$), 135·5 (*o*-ArC$\underline{H}$), 172·4 (2-$\underline{C}$=O), 202·5 [3-CH$\underline{C}O(CH_2)_4CH(CH_3)_2$]; **m/z (Ar FAB$^+$)** 481 ($MH^+$, 15%), 423 [$M^{\bullet+}$ –$^{\bullet}C(CH_3)_3$, 40%], 403 ($M^{\bullet+}$ –Ph$^{\bullet}$, 30%), 225 (30%), 199 [$(Ph_2Si{=}OH)^+$, 60%], 135 (100%), 109 (45%).

7.14: 4-[(*tert*-Butyldiphenylsilyl)oxymethyl]-3-fluoro-3-(6-methyl-1-oxoheptyl)-γ-butyrolactone ($C_{29}H_{39}FO_4Si$, MW = 498·71) (**149**):

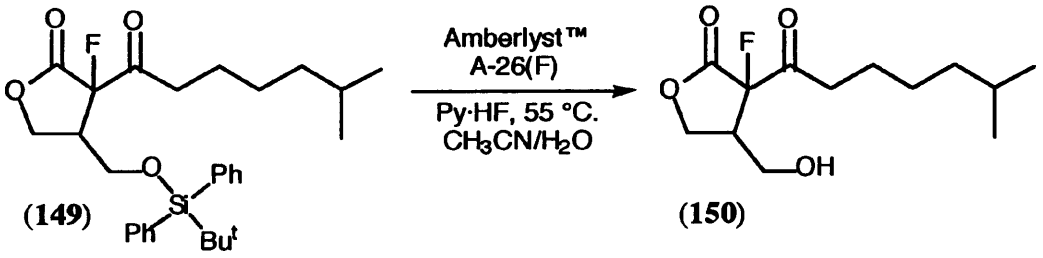


To a suspension of oil-free sodium hydride (0·102 g, 4·25 mmol) in THF (3 ml) was added a solution of **148** (1·29 g, 2·68 mmol) in THF (7 ml). After 10 minutes the solution was cooled to –10 °C and finely crushed Selectfluor™ (**9**) (1·19 g 95·6% = 1·14 g, 3·21 mmol) was added. The reaction mixture was allowed to warm to room temperature over 30 minutes, then was stirred at room temperature for a further two hours. Th resulting suspension was concentrated *in vacuo* to give a semi-solid which was partitioned between dichloromethane (30 ml) and water (20 ml). The two layers were separated and the aqueous phase was extracted with dichloromethane (30 ml). The combined organic extracts were washed twice with water (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give **149** (1·43 g, 107%) as a yellow oil. This was subjected to flash chromatography (eluting with 0%-33% ethyl acetate in petrol) to give **149** (0·88 g, 66%) as a pale yellow oil:

R_f = 0·37 (25% EtOAc in petrol); **υ_{max} (Neat)** 3570(w, br) 3080(m) 3055(m) 2950(s) 2865(s) 1960(w, br) 1895(w, br) 1800(s) 1725(s) 1630(w) 1595(m) 1470(s) 1430(s) 1395(s) 1370(s) 1205(s, br) 1115(s) 1020(s) 940(m) 830(s) 795(m, br) 745(m) 705(s) 615(m) 510(s) 495(m) cm^{-1}; **δH (300 MHz, $CDCl_3$)** 0·84, 0·85 [3H & 3H, d, J = 6·5, 6·5 Hz, 3-CFCO$(CH_2)_4$CH$(C\underline{H}_3)_2$], 1·05 {9H, s, OSi[C$(C\underline{H}_3)_3$]Ph_2}, 1·07-1·32 [4H, m, 3-CFCOC$H_2CH_2C\underline{H}_2C\underline{H}_2CH(CH_3)_2$], 1·39-1·63 [3H, m, 3-CFCOC$H_2C\underline{H}_2(CH_2)_2C\underline{H}(CH_3)_2$], 2·80-2·87 [2H, m, 3-CFCOC$\underline{H}_2(CH_2)_3$CH$(CH_3)_2$], 3·01-3·24 (1H, m, 4-C$\underline{H}$CH_2OSi), 3·68, 3·82 (2H, ABX, J_{AB} = 10·5 Hz, J_{AX} = 9·0 Hz, J_{BX} = 6·5 Hz, 4-CHC$\underline{H}_2$OSi), 4·07, 4·34 (2H, ABX, J_{AB} = 9·0 Hz, J_{AX} = 9·0 Hz,

J_{BX} = 9·0 Hz, $^4J_{H(B)F}$ = 1·5 Hz, 5-C$\underline{H}_2$), 7·37-7·49 (6H, m, *m*-,*p*-ArC$\underline{H}$), 7·57-7·64 (4H, m, *o*-ArC$\underline{H}$); **δC (75·5 MHz, CDCl$_3$)** 19·0 {OSi[$\underline{C}$(CH$_3$)$_3$]Ph$_2$}, 22·1 [3-CFCOCH$_2\underline{C}$H$_2$(CH$_2$)$_2$CH(CH$_3$)$_2$], 22·3 [3-CFCO(CH$_2$)$_4$CH($\underline{C}$H$_3$)$_2$], 26·5 [3-CFCO(CH$_2$)$_2\underline{C}$H$_2$CH$_2$CH(CH$_3$)$_2$], 26·6 {OSi[C($\underline{C}$H$_3$)$_3$]Ph$_2$}, 27·5 [3-CFCO(CH$_2$)$_4\underline{C}$H(CH$_3$)$_2$], 38·5 [3-CFCO(CH$_2$)$_3\underline{C}$H$_2$CH(CH$_3$)$_2$], 39·5 [3-CFCO$\underline{C}$H$_2$(CH$_2$)$_3$CH(CH$_3$)$_2$], 48·1 (d, J = 20·0 Hz, 4-$\underline{C}$HCH$_2$OSi), 59·5 (4-CH$\underline{C}$H$_2$OSi), 67·0 (d, J = 7·0 Hz, 5-$\underline{C}$H$_2$), 97·4 [d, J = 210·5 Hz, 3-$\underline{C}$FCO(CH$_2$)$_4$CH(CH$_3$)$_2$], 127·8, (*m*-ArCH), 130·1 (*p*-ArCH), 132·4 (Ar *ipso*-$\underline{C}$), 135·2 (*o*-ArCH), 169·4 (d, J = 24·0 Hz, 2-$\underline{C}$=O), 206·3 [d, J = 30·5 Hz, 3-CF$\underline{C}$O(CH$_2$)$_4$CH(CH$_3$)$_2$]; **δF (188 MHz, CDCl$_3$)** –85·84 [dd, $^3J_{FH}$ = 23·5 Hz, $^4J_{FH}$ = 1·5 Hz, 3-C$\underline{F}$CO(CH$_2$)$_4$CH(CH$_3$)$_2$]; **m/z (NH$_3$ CI$^+$)** 516 (MNH$_4^+$, 100%), 274 (30%), 242 {M$^{\bullet+}$ –HOSiPh$_2$[C(CH$_3$)$_3$], 50%}, 216 (25%), 196 (50%); **Found (NH$_3$ CI$^+$)** 516·2955 (MNH$_4^+$), C$_{29}$H$_{43}$FNO$_4$Si requires 516·2945 (MNH$_4^+$).

7.15: 3-Fluoro-4-(hydroxymethyl)-3-(6-methyl-1-oxoheptyl)-γ-butyrolactone (2-Fluoro-A-factor) (C$_{13}$H$_{21}$FO$_4$, MW = 260·31) (**150**):



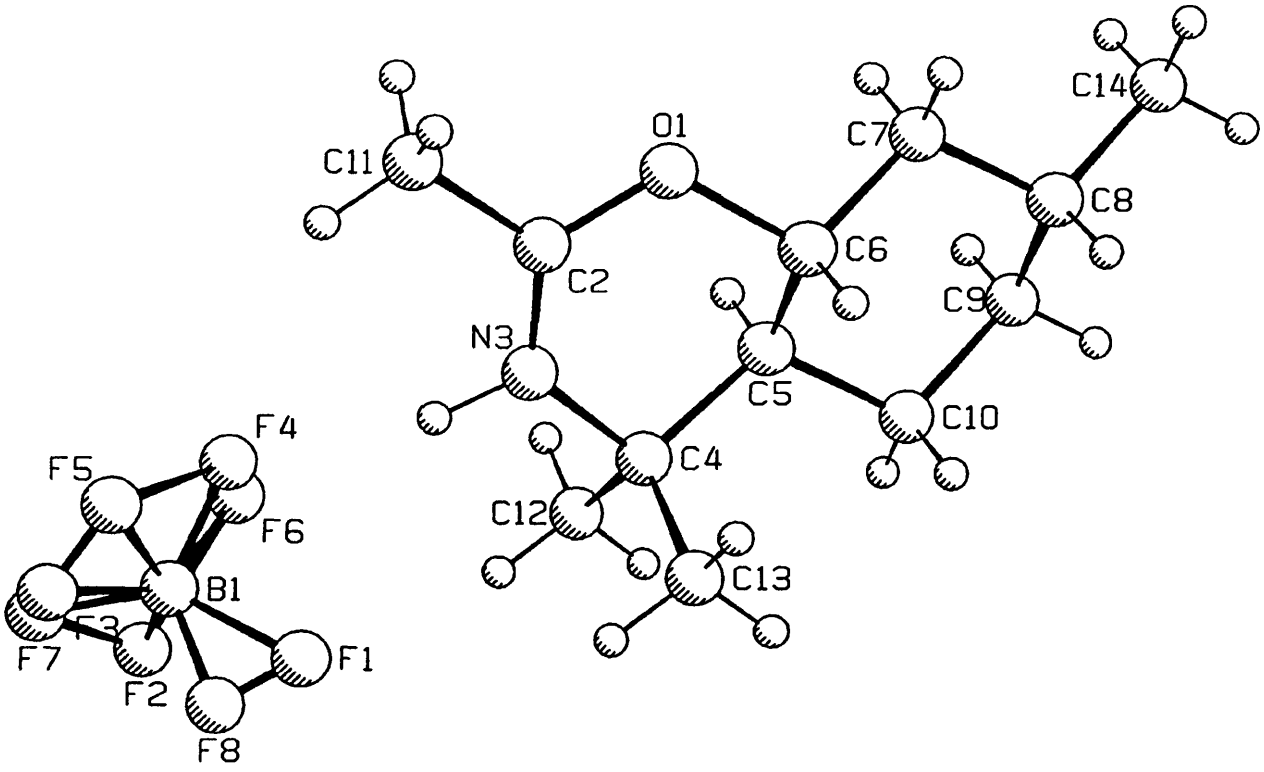
(**149**) (**150**)

To a suspension of Amberlyst™ A-26(F) ion exchange resin in acetonitrile (0·5 ml) was added water (97 mg, 5·39 mmol) and then pyridine hydrofluoride (50 mg). This was agitated and a solution of **149** (129 mg, 0·259 mmol) in acetonitrile (0·5 ml) was added. The reaction mixture was stirred for 20 hours at 55 °C under nitrogen, after which time the supernatant acetonitrile was cooled and filtered from the ion exchange resin. The resulting solution was concentrated *in vacuo* to give a two-phase system consisting of reaction products and water. This was dissolved in dichloromethane (2 ml) and dried (MgSO$_4$) before concentrating the solution *in vacuo* to givea yellow oil which was subjected to flash chromatography (eluting with 0%-47% ethyl acetate in petrol) to give **159** (19 g, 28%) as a pale yellow oil which partially solidified to a waxy solid on standing:

R_f = 0·33 (47% EtOAc in petrol); **υ_{max} (Neat)** 3425(w, br) 2965(s) 2935(s) 2875(m) 1795(s) 1785(s) 1740(m) 1620(w, br) 1475(m) 1390(m) 1370(m) 1240(s) 1130(s) 1085(s) 1055(s) 1010(s) 745(m) cm^{-1}; **δH (300 MHz, CDCl$_3$)** 0·87 [6H, d,J = 6·5 Hz, 3-CFCO(CH$_2$)$_4$CH(C$\underline{H}_3$)$_2$], 1·15-1·28 [4H, m, 3-CFCOCH$_2$CH$_2$C$\underline{H}_2\underline{C}H_2$CH(CH$_3$)$_2$], 1·29-1·43 [3H, m, 3-CFCOCH$_2$C$\underline{H}_2$(CH$_2$)$_2$C$\underline{H}$(CH$_3$)$_2$], 2·59-2·60 [2H, m, 3-CFCOC$\underline{H}_2$(CH$_2$)$_3$CH(CH$_3$)$_2$], 3·39-3·58 (1H, m, 4-C$\underline{H}$CH$_2$OH), 4·05, 4·23 (2H, ABXY, J_{AB} = 9·0 Hz, J_{AX} = 7·5 Hz, J_{BX} = 4·5 Hz, J_{AY} = 2·5 Hz, J_{BY} = 1·5 Hz, 4-CHC$\underline{H}_2$OH), 4·38, 4·58 (2H, ABX,

J_{AB} = 9·0 Hz, J_{AX} = 9·5 Hz, J_{BX} = 8·5 Hz, 5-C$\underline{H}_2$); **δC (75·5 MHz, $CDCl_3$)** 22·4 [3-CFCOCH$_2$C$\underline{H}_2$(CH$_2$)$_2$CH(CH$_3$)$_2$], 22·4 [3-CFCO(CH$_2$)$_4$CH(C$\underline{H}_3$)$_2$], 27·3 [3-CFCO(CH$_2$)$_2$C$\underline{H}_2$CH$_2$CH(CH$_3$)$_2$], 27·7 [3-CFCO(CH$_2$)$_4$C$\underline{H}$(CH$_3$)$_2$], 33·6 [3-CFCO(CH$_2$)$_3$C$\underline{H}_2$CH(CH$_3$)$_2$], 38·4 [3-CFCOC$\underline{H}_2$(CH$_2$)$_3$CH(CH$_3$)$_2$], 46·2 (d, J = 19·0 Hz, 4-C$\underline{H}$CH$_2$OH), 69·8 (d, J = 7·5 Hz, 5-C$\underline{H}_2$), 70·7 (4-CHC$\underline{H}_2$OH), 103·5 [d, J = 206·5 Hz, 3-C$\underline{F}$CO(CH$_2$)$_4$CH(CH$_3$)$_2$], 169·4 (d, J = 26·5 Hz, 2-C$\underline{=}$O), 189·7 [d, J = 31·0 Hz, 3-CFC$\underline{=}$O(CH$_2$)$_4$CH(CH$_3$)$_2$]; **δF (188 MHz, $CDCl_3$)** –92·07 [dd, $^3J_{FH}$ = 26·5 Hz, 3-C$\underline{F}$CO(CH$_2$)$_4$CH(CH$_3$)$_2$]; **m/z (NH_3 CI^+)** 278 (MNH_4^+, 40%), 260 (MNH_4^+ –H_2O, 25%), 243 (MH^+ –H_2O, 20%), 217 (MH^+ –CO_2, 25%), 127 [(CH$_3$)$_2$CH(CH$_2$)$_4$C≡O$^+$, 60%), 109 ($C_8H_{13}^+$, 100%), 82 (30%), 55 (30%); **Found (NH_3 CI^+)** 278·1767 (MNH_4^+), $C_{13}H_{25}FNO_4$ requires 278·1768 (MNH_4^+).

Appendix A: X-Ray crystallographic data for 111



EXPERIMENTAL DETAILS

1. Crystal Data

Empirical Formula	$C_{12}H_{22}NF_4BO$
Formula Weight	283.12
Crystal Colour, Habit	colourless, plate
Crystal Dimensions (mm)	0.30 X 0.30 X 0.20
Crystal System	monoclinic
No. Reflections Used for Unit Cell Determination (2θ range)	25 (12.8 - 18.3°)
Omega Scan Peak Width at Half-height	0.29
Lattice Parameters:	
	a = 8.066 (4)Å
	b = 7.116 (2)Å
	c = 12.408 (4)Å
	β = 92.61 (3)°
	V = 711.4 (8)Å^3
Space Group	$P2_1$ (#4)
Z value	2
D_{calc}	1.321 g/cm^3
F_{000}	300
$\mu_{(MoK\alpha)}$	1.11 cm^{-1}

2. Intensity Measurements

Diffractometer	UNKNO
Radiation	MoKα (λ = 0.71069 Å)
Temperature	-40°C
Take-off Angle	2.8°
Detector Aperture	2.0 - 2.5 mm horizontal 2.0 mm vertical

Crystal to Detector Distance	21 cm
Scan Type	$\omega/2\theta$
Scan Rate	2.0°/min (in omega) (3 rescans)
Scan Width	$(1.15 + 0.30 \tan\theta)°$
$2\theta_{max}$	52.1°
No. of Reflections Measured	Total: 1612 Unique: 1520 (R_{int} = .021)
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 0.10000E-05)

3. Structure Solution and Refinement

Structure Solution	Direct Methods
Hydrogen Atom Treatment	Included in calculated positions (d_{C-H} = 0.95Å)
Refinement	Full-matrix least-squares
Function Minimized	Σ w $(\|Fo\| - \|Fc\|)^2$
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.01
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1041
No. Variables	207
Reflection/Parameter Ratio	5.03
Residuals: R; R_w	0.087; 0.084
Goodness of Fit Indicator	5.31
Max Shift/Error in Final Cycle	0.52
Maximum Peak in Final Diff. Map	0.40 $e^-/Å^3$
Minimum Peak in Final Diff. Map	-0.25 $e^-/Å^3$

Positional parameters for BASH12

atom	x	y	z
F(1)	0.8671(8)	0.1357	0.5924(5)
F(2)	0.628(1)	0.065(2)	0.658(1)
F(3)	0.804(1)	0.237(3)	0.7562(6)
F(4)	0.697(2)	0.339(2)	0.6059(8)
F(5)	0.812(2)	0.347(2)	0.713(1)
F(6)	0.637(1)	0.267(3)	0.588(1)
F(7)	0.652(3)	0.143(4)	0.737(1)
F(8)	0.847(2)	0.078(3)	0.650(2)
B(1)	0.7438(8)	0.196(1)	0.6605(6)
O(1)	0.7863(4)	0.7006(7)	0.2973(3)
N(3)	0.7432(5)	0.4336(9)	0.3914(3)
C(2)	0.7597(7)	0.609(1)	0.3869(4)
C(4)	0.7396(6)	0.296(1)	0.3002(4)
C(5)	0.7098(6)	0.418(1)	0.1978(4)
C(6)	0.8162(6)	0.589(1)	0.2007(4)
C(7)	0.7822(6)	0.718(1)	0.1071(4)
C(8)	0.8010(6)	0.617(1)	0.0004(4)
C(9)	0.6984(8)	0.446(1)	-0.0033(4)
C(10)	0.7375(6)	0.313(1)	0.0937(4)
C(11)	0.7532(8)	0.733(1)	0.4819(4)
C(12)	0.5953(7)	0.168(1)	0.3147(4)
C(13)	0.9003(7)	0.193(1)	0.3056(4)
C(14)	0.7624(7)	0.748(1)	-0.0942(4)
H(5)	0.5972	0.4587	0.1957
H(6)	0.9294	0.5527	0.2022
H(7A)	0.6720	0.7644	0.1098
H(7B)	0.8581	0.8201	0.1120
H(8)	0.9137	0.5800	-0.0028
H(9A)	0.7178	0.3801	-0.0681
H(9B)	0.5848	0.4814	-0.0028
H(10A)	0.6661	0.2065	0.0887
H(10B)	0.8496	0.2724	0.0928
H(11A)	0.8540	0.8015	0.4904
H(11B)	0.7377	0.6594	0.5444
H(11C)	0.6631	0.8185	0.4717
H(12A)	0.4961	0.2405	0.3145
H(12B)	0.6099	0.1040	0.3814
H(12C)	0.5883	0.0801	0.2573
H(13A)	0.9028	0.1066	0.2475
H(13B)	0.9117	0.1271	0.3721
H(13C)	0.9890	0.2802	0.3009
H(14A)	0.8352	0.8536	-0.0896
H(14B)	0.6510	0.7904	-0.0922
H(14C)	0.7777	0.6833	-0.1598
H(3)	0.7315	0.3822	0.4614

Positional parameters and B(eq) for BASH12

atom	x	y	z	B(eq)
F(1)	0.8671(8)	0.1357	0.5924(5)	6.9(4)
F(2)	0.628(1)	0.065(2)	0.658(1)	13.6(7)
F(3)	0.804(1)	0.237(3)	0.7562(6)	13.6(8)
F(4)	0.697(2)	0.339(2)	0.6059(8)	14.8(9)
F(5)	0.812(2)	0.347(2)	0.713(1)	8.9(8)
F(6)	0.637(1)	0.267(3)	0.588(1)	10(1)
F(7)	0.652(3)	0.143(4)	0.737(1)	16(1)
F(8)	0.847(2)	0.078(3)	0.650(2)	17(1)
B(1)	0.7438(8)	0.196(1)	0.6605(6)	3.4(3)
O(1)	0.7863(4)	0.7006(7)	0.2973(3)	3.2(2)
N(3)	0.7432(5)	0.4336(9)	0.3914(3)	2.9(2)
C(2)	0.7597(7)	0.609(1)	0.3869(4)	3.2(3)
C(4)	0.7396(6)	0.296(1)	0.3002(4)	3.0(2)
C(5)	0.7098(6)	0.418(1)	0.1978(4)	2.9(2)
C(6)	0.8162(6)	0.589(1)	0.2007(4)	2.8(2)
C(7)	0.7822(6)	0.718(1)	0.1071(4)	3.4(3)
C(8)	0.8010(6)	0.617(1)	0.0004(4)	3.4(3)
C(9)	0.6984(8)	0.446(1)	-0.0033(4)	4.2(3)
C(10)	0.7375(6)	0.313(1)	0.0937(4)	3.4(3)
C(11)	0.7532(8)	0.733(1)	0.4819(4)	4.3(3)
C(12)	0.5953(7)	0.168(1)	0.3147(4)	4.2(3)
C(13)	0.9003(7)	0.193(1)	0.3056(4)	3.9(3)
C(14)	0.7624(7)	0.748(1)	-0.0942(4)	4.7(3)
H(5)	0.5972	0.4587	0.1957	3.5
H(6)	0.9294	0.5527	0.2022	3.3
H(7A)	0.6720	0.7644	0.1098	4.1
H(7B)	0.8581	0.8201	0.1120	4.1
H(8)	0.9137	0.5800	-0.0028	4.1
H(9A)	0.7178	0.3801	-0.0681	5.1
H(9B)	0.5848	0.4814	-0.0028	5.1
H(10A)	0.6661	0.2065	0.0887	4.1
H(10B)	0.8496	0.2724	0.0928	4.1
H(11A)	0.8540	0.8015	0.4904	5.2
H(11B)	0.7377	0.6594	0.5444	5.2
H(11C)	0.6631	0.8185	0.4717	5.2
H(12A)	0.4961	0.2405	0.3145	5.0
H(12B)	0.6099	0.1040	0.3814	5.0
H(12C)	0.5883	0.0801	0.2573	5.0
H(13A)	0.9028	0.1066	0.2475	4.7
H(13B)	0.9117	0.1271	0.3721	4.7
H(13C)	0.9890	0.2802	0.3009	4.7
H(14A)	0.8352	0.8536	-0.0896	5.6
H(14B)	0.6510	0.7904	-0.0922	5.6
H(14C)	0.7777	0.6833	-0.1598	5.6
H(3)	0.7315	0.3822	0.4614	3.4

U values for BASH12

ATOM	U11	U22	U33	U12	U13	U23
F(1)	0.058(3)	0.154(9)	0.052(3)	-0.004(5)	0.020(3)	-0.031(5)
F(2)	0.157(8)	0.17(1)	0.20(1)	-0.085(8)	0.095(7)	-0.05(1)
F(3)	0.135(7)	0.34(2)	0.043(4)	0.12(1)	-0.015(4)	0.006(8)
F(4)	0.41(2)	0.094(7)	0.062(5)	0.05(1)	0.052(8)	0.056(5)
F(5)	0.13(1)	0.10(1)	0.11(1)	-0.01(1)	0.001(9)	-0.065(9)
F(6)	0.043(5)	0.26(2)	0.098(9)	0.05(1)	0.003(5)	0.09(1)
F(7)	0.24(2)	0.28(2)	0.080(9)	-0.12(2)	-0.01(1)	0.10(1)
F(8)	0.24(1)	0.13(1)	0.28(2)	0.13(1)	-0.20(1)	-0.14(1)
B(1)	0.039(3)	0.042(4)	0.048(4)	-0.005(4)	0.003(3)	0.012(4)
O(1)	0.055(2)	0.030(2)	0.037(2)	0.004(2)	0.003(2)	-0.000(2)
N(3)	0.040(2)	0.038(3)	0.030(2)	0.002(2)	0.001(2)	0.005(2)
C(2)	0.043(3)	0.043(4)	0.037(3)	0.001(3)	0.007(2)	0.000(3)
C(4)	0.032(3)	0.054(4)	0.030(3)	-0.004(3)	0.004(2)	-0.008(3)
C(5)	0.029(2)	0.034(3)	0.046(3)	-0.002(3)	0.003(2)	0.004(3)
C(6)	0.027(2)	0.047(4)	0.031(3)	0.001(3)	0.000(2)	-0.003(3)
C(7)	0.041(3)	0.044(4)	0.045(3)	-0.003(3)	0.004(2)	0.010(3)
C(8)	0.028(3)	0.071(5)	0.032(3)	0.003(3)	0.004(2)	0.015(3)
C(9)	0.058(4)	0.069(5)	0.034(3)	-0.012(4)	0.005(3)	-0.011(4)
C(10)	0.039(3)	0.050(4)	0.042(3)	-0.002(3)	0.002(2)	-0.017(3)
C(11)	0.068(3)	0.053(5)	0.044(3)	0.002(4)	0.006(3)	-0.009(3)
C(12)	0.063(3)	0.046(4)	0.051(3)	-0.007(3)	0.002(3)	0.009(3)
C(13)	0.051(3)	0.046(4)	0.052(3)	0.002(4)	-0.003(3)	0.008(4)
C(14)	0.049(3)	0.085(6)	0.045(4)	0.003(4)	0.003(3)	0.012(4)
H(5)	0.0439					
H(6)	0.0420					
H(7A)	0.0517					
H(7B)	0.0517					
H(8)	0.0523					
H(9A)	0.0646					
H(9B)	0.0646					
H(10A)	0.0519					
H(10B)	0.0519					
H(11A)	0.0653					
H(11B)	0.0653					
H(11C)	0.0653					

U values for BASH12

ATOM	U11	U22	U33	U12	U13	U23
H(12A)	0.0636					
H(12B)	0.0636					
H(12C)	0.0636					
H(13A)	0.0599					
H(13B)	0.0599					
H(13C)	0.0599					
H(14A)	0.0712					
H(14B)	0.0712					
H(14C)	0.0712					
H(3)	0.0436					

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	atom	atom	distance
F(1)	F(8)	0.85(2)	O(1)	C(2)	1.313(7)
F(1)	B(1)	1.402(9)	O(1)	C(6)	1.466(7)
F(2)	F(6)	1.69(3)	N(3)	C(2)	1.26(1)
F(2)	F(7)	1.14(2)	N(3)	C(4)	1.496(8)
F(2)	B(1)	1.32(2)	C(2)	C(11)	1.474(9)
F(3)	F(5)	0.95(2)	C(4)	C(5)	1.549(8)
F(3)	F(7)	1.41(3)	C(4)	C(12)	1.493(9)
F(3)	B(1)	1.29(1)	C(4)	C(13)	1.488(8)
F(4)	F(5)	1.58(2)	C(5)	C(6)	1.489(9)
F(4)	F(6)	0.74(2)	C(5)	C(10)	1.520(8)
F(4)	B(1)	1.27(2)	C(6)	C(7)	1.493(8)
F(5)	B(1)	1.35(2)	C(7)	C(8)	1.519(8)
F(6)	B(1)	1.32(2)	C(8)	C(9)	1.47(1)
F(7)	B(1)	1.29(2)	C(8)	C(14)	1.520(9)
F(8)	B(1)	1.19(2)	C(9)	C(10)	1.553(9)

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	atom	atom	distance
N(3)	H(3)	0.951	C(11)	H(11B)	0.948
C(5)	H(5)	0.951	C(11)	H(11C)	0.952
C(6)	H(6)	0.949	C(12)	H(12A)	0.950
C(7)	H(7A)	0.951	C(12)	H(12B)	0.950
C(7)	H(7B)	0.951	C(12)	H(12C)	0.950
C(8)	H(8)	0.950	C(13)	H(13A)	0.949
C(9)	H(9A)	0.949	C(13)	H(13B)	0.950
C(9)	H(9B)	0.951	C(13)	H(13C)	0.951
C(10)	H(10A)	0.950	C(14)	H(14A)	0.951
C(10)	H(10B)	0.949	C(14)	H(14B)	0.949
C(11)	H(11A)	0.950	C(14)	H(14C)	0.950

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
F(8)	F(1)	B(1)	58(1)	F(1)	B(1)	F(8)	37(1)
F(6)	F(2)	F(7)	91(2)	F(2)	B(1)	F(3)	114(1)
F(6)	F(2)	B(1)	50.2(7)	F(2)	B(1)	F(4)	112(1)
F(7)	F(2)	B(1)	63(1)	F(2)	B(1)	F(5)	147(1)
F(5)	F(3)	F(7)	112(2)	F(2)	B(1)	F(6)	79(1)
F(5)	F(3)	B(1)	72(1)	F(2)	B(1)	F(7)	52(1)
F(7)	F(3)	B(1)	57.0(8)	F(2)	B(1)	F(8)	89(1)
F(5)	F(4)	F(6)	129(2)	F(3)	B(1)	F(4)	114(1)
F(5)	F(4)	B(1)	55.4(8)	F(3)	B(1)	F(5)	42(1)
F(6)	F(4)	B(1)	77(2)	F(3)	B(1)	F(6)	138(1)
F(3)	F(5)	F(4)	113(2)	F(3)	B(1)	F(7)	66(1)
F(3)	F(5)	B(1)	66(1)	F(3)	B(1)	F(8)	91(1)
F(4)	F(5)	B(1)	50.5(8)	F(4)	B(1)	F(5)	74(1)
F(2)	F(6)	F(4)	119(2)	F(4)	B(1)	F(6)	33(1)
F(2)	F(6)	B(1)	50.4(9)	F(4)	B(1)	F(7)	118(1)
F(4)	F(6)	B(1)	70(1)	F(4)	B(1)	F(8)	134(1)
F(2)	F(7)	F(3)	119(2)	F(5)	B(1)	F(6)	105(1)
F(2)	F(7)	B(1)	66(1)	F(5)	B(1)	F(7)	97(1)
F(3)	F(7)	B(1)	57(1)	F(5)	B(1)	F(8)	110(1)
F(1)	F(8)	B(1)	85(2)	F(6)	B(1)	F(7)	104(1)
F(1)	B(1)	F(2)	106.7(8)	F(6)	B(1)	F(8)	129(1)
F(1)	B(1)	F(3)	112.1(7)	F(7)	B(1)	F(8)	107(2)
F(1)	B(1)	F(4)	97.2(8)	C(2)	O(1)	C(6)	117.7(5)
F(1)	B(1)	F(5)	104.4(8)	C(2)	N(3)	C(4)	128.0(5)
F(1)	B(1)	F(6)	99.6(8)	O(1)	C(2)	N(3)	123.4(5)
F(1)	B(1)	F(7)	143(1)	O(1)	C(2)	C(11)	113.2(6)

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Nonhydrogen Atoms (cont)

atom	atom	atom	angle	atom	atom	atom	angle
N(3)	C(2)	C(11)	123.4(5)				
N(3)	C(4)	C(5)	104.5(5)				
N(3)	C(4)	C(12)	107.2(4)				
N(3)	C(4)	C(13)	107.5(4)				
C(5)	C(4)	C(12)	110.3(4)				
C(5)	C(4)	C(13)	114.6(4)				
C(12)	C(4)	C(13)	112.1(6)				
C(4)	C(5)	C(6)	111.8(4)				
C(4)	C(5)	C(10)	113.3(5)				
C(6)	C(5)	C(10)	108.5(5)				
O(1)	C(6)	C(5)	110.2(4)				
O(1)	C(6)	C(7)	105.9(5)				
C(5)	C(6)	C(7)	113.4(4)				
C(6)	C(7)	C(8)	111.6(6)				
C(7)	C(8)	C(9)	109.8(5)				
C(7)	C(8)	C(14)	111.1(6)				
C(9)	C(8)	C(14)	112.9(5)				
C(8)	C(9)	C(10)	112.8(5)				
C(5)	C(10)	C(9)	108.9(6)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Bond Angles Involving the Hydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	N(3)	H(3)	115.97	H(10A)	C(10)	H(10B)	109.56
C(4)	N(3)	H(3)	116.07	C(2)	C(11)	H(11A)	109.52
C(4)	C(5)	H(5)	107.71	C(2)	C(11)	H(11B)	109.57
C(6)	C(5)	H(5)	107.58	C(2)	C(11)	H(11C)	109.33
C(10)	C(5)	H(5)	107.67	H(11A)	C(11)	H(11B)	109.63
O(1)	C(6)	H(6)	109.06	H(11A)	C(11)	H(11C)	109.33
C(5)	C(6)	H(6)	109.15	H(11B)	C(11)	H(11C)	109.44
C(7)	C(6)	H(6)	109.05	C(4)	C(12)	H(12A)	109.41
C(6)	C(7)	H(7A)	108.96	C(4)	C(12)	H(12B)	109.44
C(6)	C(7)	H(7B)	108.92	C(4)	C(12)	H(12C)	109.41
C(8)	C(7)	H(7A)	109.03	H(12A)	C(12)	H(12B)	109.51
C(8)	C(7)	H(7B)	109.01	H(12A)	C(12)	H(12C)	109.51
H(7A)	C(7)	H(7B)	109.30	H(12B)	C(12)	H(12C)	109.55
C(7)	C(8)	H(8)	107.63	C(4)	C(13)	H(13A)	109.47
C(9)	C(8)	H(8)	107.68	C(4)	C(13)	H(13B)	109.45
C(14)	C(8)	H(8)	107.59	C(4)	C(13)	H(13C)	109.38
C(8)	C(9)	H(9A)	108.67	H(13A)	C(13)	H(13B)	109.62
C(8)	C(9)	H(9B)	108.58	H(13A)	C(13)	H(13C)	109.48
C(10)	C(9)	H(9A)	108.68	H(13B)	C(13)	H(13C)	109.43
C(10)	C(9)	H(9B)	108.62	C(8)	C(14)	H(14A)	109.40
H(9A)	C(9)	H(9B)	109.47	C(8)	C(14)	H(14B)	109.53
C(5)	C(10)	H(10A)	109.63	C(8)	C(14)	H(14C)	109.47
C(5)	C(10)	H(10B)	109.69	H(14A)	C(14)	H(14B)	109.45
C(9)	C(10)	H(10A)	109.49	H(14A)	C(14)	H(14C)	109.38
C(9)	C(10)	H(10B)	109.55	H(14B)	C(14)	H(14C)	109.60

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Torsion or Conformation Angles

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
F(1)	F(8)	B(1)	F(2)	119(1)	F(2)	F(7)	F(3)	B(1)	22(2)
F(1)	F(8)	B(1)	F(3)	-126(1)	F(2)	F(7)	B(1)	F(3)	-159(2)
F(1)	F(8)	B(1)	F(4)	-1(2)	F(2)	F(7)	B(1)	F(4)	96(2)
F(1)	F(8)	B(1)	F(5)	-88(2)	F(2)	F(7)	B(1)	F(5)	172(1)
F(1)	F(8)	B(1)	F(6)	44(2)	F(2)	F(7)	B(1)	F(6)	64(2)
F(1)	F(8)	B(1)	F(7)	169(1)	F(2)	F(7)	B(1)	F(8)	-75(2)
F(1)	B(1)	F(2)	F(6)	-97.0(9)	F(2)	B(1)	F(1)	F(8)	-65(2)
F(1)	B(1)	F(2)	F(7)	146(2)	F(2)	B(1)	F(3)	F(5)	-151(1)
F(1)	B(1)	F(3)	F(5)	87(1)	F(2)	B(1)	F(3)	F(7)	-18(2)
F(1)	B(1)	F(3)	F(7)	-140(1)	F(2)	B(1)	F(4)	F(5)	146(1)
F(1)	B(1)	F(4)	F(5)	-103.0(9)	F(2)	B(1)	F(4)	F(6)	-15(2)
F(1)	B(1)	F(4)	F(6)	97(2)	F(2)	B(1)	F(5)	F(3)	54(2)
F(1)	B(1)	F(5)	F(3)	-107(1)	F(2)	B(1)	F(5)	F(4)	-105(2)
F(1)	B(1)	F(5)	F(4)	94(1)	F(2)	B(1)	F(6)	F(4)	166(2)
F(1)	B(1)	F(6)	F(2)	105.4(8)	F(2)	B(1)	F(7)	F(3)	159(2)
F(1)	B(1)	F(6)	F(4)	-88(2)	F(3)	F(5)	F(4)	F(6)	4(3)
F(1)	B(1)	F(7)	F(2)	-63(2)	F(3)	F(5)	F(4)	B(1)	-21(1)
F(1)	B(1)	F(7)	F(3)	95(2)	F(3)	F(5)	B(1)	F(4)	159(1)
F(2)	F(6)	F(4)	F(5)	-9(3)	F(3)	F(5)	B(1)	F(6)	148(1)
F(2)	F(6)	F(4)	B(1)	12(2)	F(3)	F(5)	B(1)	F(7)	42(2)
F(2)	F(6)	B(1)	F(3)	-115(2)	F(3)	F(5)	B(1)	F(8)	-69(2)
F(2)	F(6)	B(1)	F(4)	-166(2)	F(3)	F(7)	F(2)	F(6)	-64(2)
F(2)	F(6)	B(1)	F(5)	-147(1)	F(3)	F(7)	F(2)	B(1)	-21(2)
F(2)	F(6)	B(1)	F(7)	-46(1)	F(3)	F(7)	B(1)	F(4)	-105(1)
F(2)	F(6)	B(1)	F(8)	80(2)	F(3)	F(7)	B(1)	F(5)	-30(1)
F(2)	F(7)	F(3)	F(5)	71(3)	F(3)	F(7)	B(1)	F(6)	-137(1)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Torsion or Conformation Angles (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
F(3)	F(7)	B(1)	F(8)	84(1)	F(5)	F(3)	B(1)	F(8)	119(2)
F(3)	B(1)	F(1)	F(8)	60(2)	F(5)	F(4)	F(6)	B(1)	-21(2)
F(3)	B(1)	F(2)	F(6)	139(1)	F(5)	F(4)	B(1)	F(6)	160(2)
F(3)	B(1)	F(2)	F(7)	21(2)	F(5)	F(4)	B(1)	F(7)	89(1)
F(3)	B(1)	F(4)	F(5)	15(1)	F(5)	F(4)	B(1)	F(8)	-103(2)
F(3)	B(1)	F(4)	F(6)	-145(1)	F(5)	B(1)	F(1)	F(8)	104(2)
F(3)	B(1)	F(5)	F(4)	-159(1)	F(5)	B(1)	F(2)	F(6)	102(2)
F(3)	B(1)	F(6)	F(4)	52(2)	F(5)	B(1)	F(2)	F(7)	-15(2)
F(4)	F(5)	F(3)	F(7)	-24(2)	F(5)	B(1)	F(3)	F(7)	133(2)
F(4)	F(5)	F(3)	B(1)	17(1)	F(5)	B(1)	F(4)	F(6)	-160(2)
F(4)	F(5)	B(1)	F(6)	-11(1)	F(6)	F(2)	F(7)	B(1)	-43.1(9)
F(4)	F(5)	B(1)	F(7)	-117(1)	F(6)	F(2)	B(1)	F(7)	117(2)
F(4)	F(5)	B(1)	F(8)	132(1)	F(6)	F(2)	B(1)	F(8)	-130(1)
F(4)	F(6)	F(2)	F(7)	38(2)	F(6)	F(4)	F(5)	B(1)	25(2)
F(4)	F(6)	F(2)	B(1)	-15(2)	F(6)	F(4)	B(1)	F(7)	-71(2)
F(4)	F(6)	B(1)	F(5)	20(2)	F(6)	F(4)	B(1)	F(8)	97(2)
F(4)	F(6)	B(1)	F(7)	120(2)	F(6)	B(1)	F(1)	F(8)	-147(2)
F(4)	F(6)	B(1)	F(8)	-113(2)	F(6)	B(1)	F(2)	F(7)	-117(2)
F(4)	B(1)	F(1)	F(8)	180(2)	F(6)	B(1)	F(3)	F(7)	83(2)
F(4)	B(1)	F(2)	F(6)	8(1)	F(7)	F(2)	F(6)	B(1)	52(1)
F(4)	B(1)	F(2)	F(7)	-109(2)	F(7)	F(2)	B(1)	F(8)	113(2)
F(4)	B(1)	F(3)	F(5)	-22(2)	F(7)	F(3)	F(5)	B(1)	-41(1)
F(4)	B(1)	F(3)	F(7)	111(2)	F(7)	F(3)	B(1)	F(8)	-108(2)
F(5)	F(3)	F(7)	B(1)	49(2)	F(7)	B(1)	F(1)	F(8)	-18(2)
F(5)	F(3)	B(1)	F(6)	-50(2)	O(1)	C(2)	N(3)	C(4)	-3.9(8)
F(5)	F(3)	B(1)	F(7)	-133(2)	O(1)	C(6)	C(5)	C(4)	-57.3(6)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Torsion or Conformation Angles (cont)

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O(1)	C(6)	C(5)	C(10)	177.0(4)					
O(1)	C(6)	C(7)	C(8)	-177.4(4)					
N(3)	C(2)	O(1)	C(6)	-6.9(7)					
N(3)	C(4)	C(5)	C(6)	44.8(5)					
N(3)	C(4)	C(5)	C(10)	167.9(4)					
C(2)	O(1)	C(6)	C(5)	37.4(6)					
C(2)	O(1)	C(6)	C(7)	160.4(4)					
C(2)	N(3)	C(4)	C(5)	-15.7(7)					
C(2)	N(3)	C(4)	C(12)	-132.8(6)					
C(2)	N(3)	C(4)	C(13)	106.4(6)					
C(4)	N(3)	C(2)	C(11)	176.8(5)					
C(4)	C(5)	C(6)	C(7)	-175.8(5)					
C(4)	C(5)	C(10)	C(9)	178.0(4)					
C(5)	C(6)	C(7)	C(8)	-56.5(6)					
C(5)	C(10)	C(9)	C(8)	58.4(6)					
C(6)	O(1)	C(2)	C(11)	172.4(4)					
C(6)	C(5)	C(4)	C(12)	159.7(5)					
C(6)	C(5)	C(4)	C(13)	-72.6(7)					
C(6)	C(5)	C(10)	C(9)	-57.1(6)					
C(6)	C(7)	C(8)	C(9)	53.2(6)					
C(6)	C(7)	C(8)	C(14)	178.7(4)					
C(7)	C(6)	C(5)	C(10)	58.5(6)					
C(7)	C(8)	C(9)	C(10)	-55.2(7)					
C(10)	C(5)	C(4)	C(12)	-77.3(6)					
C(10)	C(5)	C(4)	C(13)	50.5(7)					
C(10)	C(9)	C(8)	C(14)	-179.7(5)					

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Intermolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
F(1)	C(2)	3.015(8)	74602	F(4)	C(11)	3.24(2)	1
F(1)	O(1)	3.091(7)	74602	F(4)	C(2)	3.38(1)	1
F(1)	C(11)	3.290(8)	54501	F(4)	C(12)	3.50(2)	65602
F(1)	C(11)	3.311(9)	74602	F(5)	C(13)	3.40(2)	75602
F(1)	N(3)	3.389(7)	1	F(5)	O(1)	3.41(2)	74602
F(1)	N(3)	3.454(8)	74602	F(6)	N(3)	2.88(2)	1
F(1)	C(6)	3.554(8)	74602	F(6)	C(11)	3.23(1)	64602
F(2)	C(2)	3.17(1)	64602	F(6)	C(2)	3.42(1)	64602
F(2)	N(3)	3.17(1)	64602	F(6)	C(12)	3.46(2)	1
F(2)	C(12)	3.37(2)	64602	F(7)	C(5)	3.45(2)	64602
F(2)	C(11)	3.40(2)	54501	F(7)	O(1)	3.57(2)	64602
F(2)	C(5)	3.49(1)	64602	F(7)	C(14)	3.59(2)	54601
F(2)	O(1)	3.55(1)	64602	F(8)	O(1)	3.13(2)	74602
F(2)	C(4)	3.59(1)	64602	F(8)	C(6)	3.22(2)	74602
F(3)	C(6)	3.26(1)	74602	F(8)	C(2)	3.24(2)	74602
F(3)	O(1)	3.41(1)	74602	F(8)	C(11)	3.29(2)	54501
F(3)	C(9)	3.47(1)	55601	F(8)	C(13)	3.45(2)	74602
F(4)	N(3)	2.79(1)	1	F(8)	N(3)	3.52(2)	74602

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*)footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5,TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) +X , +Y , +Z (2) -X ,1/2+Y , -Z

Intermolecular Distances Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
F(1)	H(3)	2.599	1	F(4)	H(11C)	3.026	64602
F(1)	H(11A)	2.694	54501	F(4)	H(12B)	3.123	65602
F(1)	H(13B)	2.774	1	F(4)	H(12B)	3.299	1
F(1)	H(11A)	2.778	74602	F(4)	H(12C)	3.389	65602
F(1)	H(6)	3.027	74602	F(4)	H(12A)	3.422	65602
F(1)	H(13C)	3.060	74602	F(5)	H(9A)	2.868	55601
F(1)	H(11C)	3.134	54501	F(5)	H(14C)	2.892	55601
F(1)	H(12B)	3.273	1	F(5)	H(13A)	2.978	75602
F(1)	H(11B)	3.588	54501	F(5)	H(11B)	3.091	1
F(2)	H(12A)	2.545	64602	F(5)	H(6)	3.107	74602
F(2)	H(5)	2.732	64602	F(5)	H(3)	3.165	1
F(2)	H(11C)	2.926	54501	F(5)	H(13B)	3.206	75602
F(2)	H(11C)	3.322	64602	F(5)	H(7B)	3.367	74602
F(2)	H(11B)	3.348	54501	F(5)	H(13C)	3.487	75602
F(2)	H(11A)	3.392	54501	F(6)	H(3)	1.958	1
F(2)	H(12B)	3.442	1	F(6)	H(11C)	2.524	64602
F(2)	H(3)	3.452	64602	F(6)	H(12B)	2.812	1
F(2)	H(3)	3.456	1	F(6)	H(11B)	2.966	1
F(3)	H(9A)	2.531	55601	F(6)	H(12B)	3.150	65602
F(3)	H(6)	2.555	74602	F(6)	H(11B)	3.458	64602
F(3)	H(7B)	3.173	74602	F(6)	H(12C)	3.502	65602
F(3)	H(14A)	3.336	54601	F(6)	H(11C)	3.512	54501
F(3)	H(14C)	3.352	55601	F(6)	H(12A)	3.534	1
F(3)	H(13A)	3.541	75602	F(7)	H(5)	2.569	64602
F(4)	H(3)	1.852	1	F(7)	H(9A)	2.974	55601
F(4)	H(11B)	2.429	1	F(7)	H(12A)	3.157	64602

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
F(7)	H(14A)	3.277	54601	C(10)	H(14B)	3.137	64502
F(7)	H(14B)	3.281	54601	C(10)	H(14A)	3.462	74502
F(7)	H(7A)	3.410	64602	C(10)	H(8)	3.495	74502
F(7)	H(6)	3.485	74602	C(11)	H(12B)	3.119	56501
F(8)	H(6)	2.521	74602	C(11)	H(13B)	3.273	75602
F(8)	H(13C)	2.559	74602	C(11)	H(12A)	3.301	65602
F(8)	H(11A)	2.795	54501	C(11)	H(13C)	3.346	75602
F(8)	H(11C)	3.193	54501	C(11)	H(13B)	3.393	56501
F(8)	H(3)	3.291	1	C(11)	H(12B)	3.571	65602
F(8)	H(11B)	3.356	54501	C(12)	H(11C)	3.194	54501
F(8)	H(11A)	3.433	74602	C(12)	H(11B)	3.272	64602
F(8)	H(13B)	3.530	1	C(12)	H(14B)	3.438	64502
B(1)	H(3)	2.799	1	C(12)	H(14C)	3.497	64502
B(1)	H(6)	3.239	74602	C(13)	H(14C)	3.233	74502
B(1)	H(11B)	3.595	1	C(13)	H(11A)	3.236	74602
O(1)	H(13A)	3.109	56501	C(13)	H(11B)	3.399	74602
O(1)	H(12C)	3.165	56501	C(13)	H(7B)	3.585	54501
O(1)	H(13B)	3.318	56501	C(14)	H(10B)	3.133	75502
O(1)	H(12B)	3.389	56501	C(14)	H(13C)	3.334	75502
C(5)	H(14B)	3.266	64502	C(14)	H(12A)	3.362	65502
C(7)	H(13A)	3.388	56501	C(14)	H(5)	3.451	65502
C(7)	H(12C)	3.582	56501	C(14)	H(10A)	3.473	65502
C(8)	H(10B)	3.285	75502	C(14)	H(9B)	3.514	65502
C(9)	H(14B)	3.297	64502	C(14)	H(13A)	3.521	75502
C(9)	H(7A)	3.461	64502	H(5)	H(14B)	2.619	64502
C(9)	H(10A)	3.595	65502	H(6)	H(14A)	2.794	74502

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

Intermolecular Distances Involving the Hydrogen Atoms (cont)

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(6)	H(14C)	3.589	74502	H(11A)	H(3)	3.418	75602
H(7A)	H(9B)	2.862	65502	H(11B)	H(12A)	2.695	65602
H(7A)	H(12C)	2.994	56501	H(11B)	H(13B)	2.976	75602
H(7A)	H(10A)	3.157	56501	H(11B)	H(13C)	2.983	75602
H(7A)	H(9A)	3.269	65502	H(11B)	H(12B)	3.017	65602
H(7A)	H(13A)	3.467	56501	H(11C)	H(12B)	2.350	56501
H(7B)	H(13A)	2.657	56501	H(11C)	H(12A)	3.050	65602
H(7B)	H(8)	2.978	75502	H(11C)	H(13B)	3.256	56501
H(7B)	H(10A)	3.162	56501	H(11C)	H(12C)	3.281	56501
H(7B)	H(10B)	3.228	56501	H(11C)	H(12B)	3.296	65602
H(7B)	H(12C)	3.430	56501	H(11C)	H(3)	3.356	65602
H(7B)	H(9A)	3.515	75502	H(12A)	H(14C)	2.887	64502
H(7B)	H(10B)	3.560	75502	H(12A)	H(14B)	2.973	64502
H(8)	H(10B)	2.638	75502	H(12C)	H(14B)	3.131	64502
H(8)	H(14A)	2.793	74502	H(12C)	H(14C)	3.224	64502
H(8)	H(13A)	3.442	75502	H(13A)	H(14C)	2.895	74502
H(9B)	H(14B)	2.657	64502	H(13A)	H(14A)	3.431	74502
H(9B)	H(10A)	2.757	65502	H(13C)	H(14C)	2.717	74502
H(9B)	H(12C)	3.467	65502	H(13C)	H(14A)	3.082	74502
H(10A)	H(14B)	2.628	64502				
H(10B)	H(14A)	2.610	74502				
H(10B)	H(14C)	3.147	74502				
H(11A)	H(13B)	2.780	75602				
H(11A)	H(13B)	2.793	56501				
H(11A)	H(13C)	2.835	75602				
H(11A)	H(12B)	3.178	56501				

Contacts out to 3.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*)footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5,TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) +X , +Y , +Z (2) -X ,1/2+Y , -Z

Special Contacts Involving the Hydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
H(3)	N(3)	0.951	1	H(3)	F(6)	1.958	1
H(3)	F(4)	1.852	1	H(3)	F(1)	2.599	1
H(3)	C(2)	1.881	1				

Contacts out to 2.60 angstroms. Estimated standard deviations in the least significant figure are given in parentheses.

(*)footnote

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one digit numbers and one two digit number: TA(1st digit) + TB(2nd digit) + TC(3rd digit) + SN(4th and 5th digit). TA, TB, & TC are the crystal lattice translation digits along cell edges a, b, and c. A translation digit of 5 indicates the origin unit cell. If TA=4, this indicates a translation of one unit cell length along the a axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus (+/-)4 lattice translations from the origin (TA=5,TB=5,TC=5) can be represented.

The SN or symmetry operator number refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of the symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell (TA=5,TB=5,TC=5) and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always ADC=55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of that atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (i.e.cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1) +X , +Y , +Z (2) -X ,1/2+Y , -Z

Special Angles Involving the Hydrogen Atoms

atom	atom	atom	angle	atom	atom	atom	angle
N(3)	H(3)	F(4)	166.63	F(4)	H(3)	F(6)	22.11
N(3)	H(3)	C(2)	36.99	F(4)	H(3)	F(1)	50.19
N(3)	H(3)	F(6)	162.26	C(2)	H(3)	F(6)	144.54
N(3)	H(3)	F(1)	140.76	C(2)	H(3)	F(1)	146.15
F(4)	H(3)	C(2)	130.10	F(6)	H(3)	F(1)	51.98

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
O2	C1	C2	C3	-69(5)	C2	C1	C8	F14	-68(6)
O2	C1	C2	F6	47(5)	C2	C1	C8	F12	-179(4)
O2	C1	C2	F5	167(4)	C2	C1	C8	F13	59(7)
O2	C1	C8	F14	173(4)	C2	C3	C4	F1	175(4)
O2	C1	C8	F12	62(5)	C2	C3	C4	F2	-75(5)
O2	C1	C8	F13	-59(7)	C1	C2	C3	F3	75(5)
O2	C1	N1	C5	60(5)	C1	C2	C3	F4	-173(4)
O1	C5	C4	C3	64(6)	C1	N1	C5	C6	176(4)
O1	C5	C4	F1	-51(4)	C3	C4	C5	C6	-173(4)
O1	C5	C4	F2	-161(4)	C3	C4	C5	N1	-60(5)
O1	C5	C6	F7	57(5)	C3	C2	C1	C8	174(4)
O1	C5	C6	F9	177(4)	C3	C2	C1	N1	51(5)
O1	C5	C6	F8	-59(5)	C6	C5	C4	F1	72(4)
O1	C5	N1	C1	-63(5)	C6	C5	C4	F2	-38(6)
C4	C5	C6	F7	-68(5)	C8	C1	C2	F6	-70(5)
C4	C5	C6	F9	52(5)	C8	C1	C2	F5	49(5)
C4	C5	C6	F8	176(4)	F3	C3	C4	F1	51(6)
C4	C5	N1	C1	62(5)	F3	C3	C4	F2	162(4)
C4	C3	C2	C1	-54(5)	F3	C3	C2	F6	-42(5)
C4	C3	C2	F6	-171(4)	F3	C3	C2	F5	-162(3)
C4	C3	C2	F5	70(5)	F6	C2	C1	N1	167(4)
C5	C4	C3	C2	59(5)	F6	C2	C3	F4	71(4)
C5	C4	C3	F3	-65(6)	F1	C4	C5	N1	-176(3)
C5	C4	C3	F4	172(4)	F1	C4	C3	F4	-72(5)
C5	N1	C1	C2	-59(5)	F2	C4	C5	N1	75(5)
C5	N1	C1	C8	180(5)	F2	C4	C3	F4	39(6)

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

(1)	(2)	(3)	(4)	angle	(1)	(2)	(3)	(4)	angle
F5	C2	C1	N1	-73(5)					
F5	C2	C3	F4	-49(5)					
N1	C5	C6	F7	179(4)					
N1	C5	C6	F9	-62(5)					
N1	C5	C6	F8	62(5)					
N1	C1	C8	F14	53(7)					
N1	C1	C8	F12	-58(6)					
N1	C1	C8	F13	-180(5)					

The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

Appendix B: Publications

J. Chem. Soc., Chem. Commun., 1994, 343

Synlett, 1994, 831

J. Chem. Soc., Chem. Commun., 1996, 1629

J. CHEM. SOC., CHEM. COMMUN., 1994

Efficient Electrophilic Fluorination of β-Dicarbonyl Compounds with the Selectfluor Reagent F-TEDA-BF_4 {1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}

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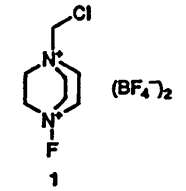
1,3-Dicarbonyl compounds (acyclic and cyclic 1,3-diketones, β-ketoesters, β-ketoamides) are converted efficiently to 2-monofluoro derivatives, and thence to 2,2-difluoro derivatives, with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

Although the site-selective introduction of fluorine into biologically active molecules is now well-established as an invaluable stratagem in medicinal chemistry,[1] progress is still hampered by the lack of more generally acceptable fluorinating agents of both the F^- and F^+ delivery classes.[2] The situation in the latter case has improved markedly recently with the discovery of easily-handled 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts,[3-5] especially since the cost-effective bis(tetrafluoroborate) **1** [F-TEDA-BF_4 (TEDA = triethylenediamine)] has rapidly become a commercial chemical[6] with established applications in the pharmaceutical industry.[7] The great research potential of **1** and its congeners[3] has been revealed in but a few publications so far (fluorination of resonance stabilized carbanions;[8] of styrene and related olefins;[8] of substituted benzenes;[3,8] of steroidal enol acetates and silyl enol ethers;[7] of enamines;[3,4,8] and of compounds containing carbon–metal[8,9,10] or carbon–sulfur[8] bonds).



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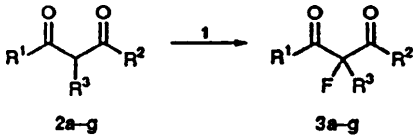


2a–g **3a–g**

	R^1	R^2	R^3
a	$-(CH_2)_3-$		Me
b	Ph	Ph	H
c	Ph	OEt	H
d	Me	OEt	H
e	OEt	OEt	Ph
f	Ph	NMe_2	H
g	Ph	NMeCH(Ph)Me	H

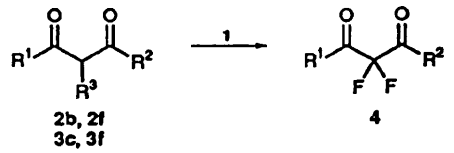
Scheme 1

The present report aims to establish the important case of selective monofluorination of 1,3-diketones and related substrates (including β-ketoamides) under neutral conditions—a synthetic manipulation which best precedes *gem*-difluorination *via* sodium salts; also revealed is the first example of fluorination α to a cyano group with F-TEDA-BF_4 **1**. The results reveal that Selectfluor reagent **1** is just as effective a fluorinating agent as the DesMarteau reagent $(CF_3SO_2)_2NF$,[11] which is not available commercially and is both costly and hazardous to prepare.[12]

The reaction of 1,3-diketones **2a** and **2b** with one equivalent of F-TEDA-BF_4 **1** under neutral† conditions in acetonitrile at room temp. proceeds smoothly to give α-fluoro derivatives in very good yields (Scheme 1 and Table 1). Under the same conditions fluorination of the ketoesters **2c** and **2d** is a little slower, but after two days the monofluoro derivatives **3c** and **3d** can be obtained (these resist further fluorination under neutral conditions); the diethyl ester **2e** is not attacked by **1** under neutral conditions, but its sodium derivative‡ gives the fluorodiester **3e** in excellent yield.

Monofluorination of the *N*,*N*-dimethylketoamide **2f**§ occurs rapidly under neutral conditions to give the monofluoro derivative. Its *N*-methyl-*N*-(α-methylbenzyl)amide analogue **2g**¶ suffers fluorination under neutral conditions to give, perhaps not surprisingly, an equal mixture of diastereoisomeric monofluoroamides **3g**. Even if the initial fluorination is stereoselective, the monofluoro derivative might epimerize under the reaction conditions. These are the first examples of the α-fluorination of secondary amides with F-TEDA-BF_4 **1**.

Nitriles seem compatible with F-TEDA-BF_4 **1**, as indicated by conversion of the cyanoester $PhCH(CN)CO_2Et$ to the corresponding α-fluoro product $PhCF(CN)CO_2Et$ under neutral conditions (1.5 equiv. **1**, at 40 °C) in excellent yield (92%). Significant applications in synthesis stem from this result, and examples will be reported in due course.



2b, 2f **4**
3c, 3f

Scheme 2

Table 1 Conversion of 1,3-dicarbonyl substrates **2** to monofluorides **3** with **1**, at room temp.

2	R^1	R^2	R^3	Method[a]	Time/h	Yield (%) (crude product)[b]	Purif. method[c]	Yield (%) (pure 3)
a	$-(CH_2)_3-$		Me	n	19	—	Tritur.	84
b	Ph	Ph	H	n	5	100	Recryst.	84
c	Ph	OEt	H	n	54	88	Chrom.	22
d	Me	OEt	H	n	120	57	—	—
e	OEt	OEt	Ph	b	20	96	Chrom.	93
f	Ph	NMe_2	H	n	3	96	Recryst.	87
g	Ph	(±)-N(Me)CH(Ph)Me	H	n	67	87	Chrom.	80

[a] n = neutral conditons, b = basic conditions. [b] Crude yields were estimated from percentage conversions judged by ^1H NMR analysis. [c] Recryst. = recrystallisation; Chrom. = flash or dry flash chromatography; Tritur. = trituration.

Table 2 Synthesis of *gem*-difluorocarbonyl compounds 4 from 2 or 3

	R^1	R^2	R^3	Method[a]	Reactant ratio [molar, 1:2 (or 3)]	Temp/°C	Time/h	Yield (%) (crude)[c]	Purif. method[d]	Yield (pure)
2b	Ph	Ph	H	n	2.1	RT[b]	192	96	Recryst.	78
3c	Ph	OEt	F	b	1.1	RT	24	95	—	95
2f	Ph	NMe_2	H	n	3.2	40	647	93	Chrom.	91
3f	Ph	NMe_2	F	b	1.2	RT	27	84	Chrom.	73

[a] n = neutral conditions, b = basic conditions. [b] RT = room temp. [c] Crude yields were estimated from percentage conversions judged by ^{1}H NMR analysis. [d] Recryst. = recrystallisation; Chrom. = flash or dry flash chromatography.

Prompted by the increasing utility of biologically-active compounds containing difluoromethylene groups,[13–16] difluorination of dicarbonyl compounds with F-TEDA-BF_4 was studied (Table 2). Difluorination of 2b under neutral conditions proved extremely slow; when treated with two equivalents of 1, a near-quantitative yield of the corresponding α,α-difluorodiketone was obtained, but only after an eight day reaction period at room temp. Difluorination of 2c occurred even more slowly. However, the sodium enolate of 3c reacted rapidly to give the difluoro derivative 4c in excellent yield. Difluorination of the amide 2f proceeded only slowly, but nevertheless gave the difluoroamide 4f when treated with an excess of 1 for 27 days at 40 °C in acetonitrile. Alternatively, and more conveniently, the sodium derivative of the monofluoride 3f can be converted cleanly to 4f after only one day.

In summary, electrophilic fluorination of all the dicarbonyl compounds studied, except for diester 2e, proceeds efficiently at 20 °C under neutral conditions with F-TEDA-BF_4. The monofluoro derivatives 3 resist attack under these conditions, as indicated by their extremely slow difluorination when the reagent is present in excess. Fluorination occurs more rapidly with those compounds which exist (at least in part) in enolic form (as measured by ^{1}H NMR in $CDCl_3$). For example, 2f and 2g have keto:enol contents of 2:1 and 2.4:1, respectively. The monofluoro derivatives exist solely as their keto forms and consequently are not easily fluorinated further by 1. This appears to indicate that the reaction is occurring *via* the enol or enolate and is ionic in nature.

We thank Dr Ray Fisher (Peakdale Fine Chemicals, Glossop) for helpful discussions and financial support.

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Footnotes

† *Neutral conditions*: The substrate (1 mmol) was stirred with F-TEDA-BF_4 1 (1 mmol) in acetonitrile (10 cm^3) at room temp. When fluorination was complete (as judged by TLC), the reaction solution was concentrated *in vacuo*, and the residue was partitioned between water and dichloromethane. The organic layer was washed twice with water, dried ($MgSO_4$) and evaporated *in vacuo*. Residues were purified further as indicated in Tables 1 and 2.

‡ *Basic conditions*: A solution of the substrate (1 mmol) in dry tetrahydrofuran (THF) (15 cm^3) was added to an oil-free suspension of NaH (1.22 mmol) in THF (2 cm^3). The resulting suspension (or solution) was stirred at room temp. until no more hydrogen was evolved (*ca.* 15 min). F-TEDA-BF_4 1 reagent (equiv. as stated) was then added and the resulting suspension stirred at room temp. until the reaction was complete (as judged by TLC). The solvent was removed *in vacuo* and the residues purified as stated in Tables 1 and 2.

§ Made by Claisen condensation of *N*,*N*-dimethylacetamide with methyl benzoate.

¶ Made by Claisen condensation of *N*-methyl-*N*-(α-methylbenzyl)-acetamide with methyl benzoate.

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Oxidation of Benzylic Alcohols and Benzaldehydes with the Selectfluor™ Reagent F-TEDA-BF4 {1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}

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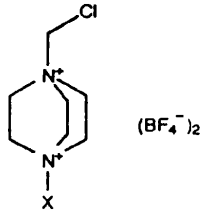
Abstract: Substituted benzylic alcohols and aromatic aldehydes can be oxidised efficiently to substituted benzaldehydes and benzoic acids respectively with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate); the latter conversion proceeds via acid fluorides, which enables aldehydes to function as acylating agents in a one-pot procedure.

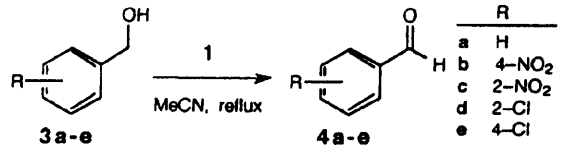
The site-selective introduction of fluorine into biologically-active molecules is now well-established as an invaluable stratagem in medicinal chemistry.[1] Progress has been aided by many recently discovered fluorinating agents of both the F^- and F^+ delivery classes,[2] including the easily-handled 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts.[3, 4, 5] One member of this remarkable class of electrophilic fluorinating agents, the bis(tetrafluoroborate) **1** [F-TEDA-BF_4 (TEDA = triethylenediamine)], has rapidly become a commercial chemical[6] with established applications in the pharmaceutical industry.[7] The great research potential of **1** and its congeners[3] has been revealed in relatively few publications so far (fluorination of resonance stabilized carbanions;[8] of styrene and related olefins;[8,9] of substituted benzenes;[3,8] of steroidal enol acetates and silyl enol ethers;[7] of enamines;[3,4,8] of 1,3-dicarbonyl compounds;[10] of aralkyl *tert*-alcohols;[11] vinylstannanes;[12] and of compounds containing carbon-metal[8,9,10] or carbon sulfur[8] bonds), and the present report is the first to deal with the oxidation of alcohols.



1 (X = F)
2 (X = H)

Treatment of benzylic alcohols **3a–e** with F-TEDA-BF_4 **1** in boiling acetonitrile slowly produces benzaldehydes **4a–e** (Eqn. 1 and Table 1).[13] A nitro group, especially when positioned *ortho* to the hydroxymethyl function, retards the oxidation process; and an *ortho*-effect is noticeable with a chloro substituent. These and other factors bearing on the reaction mechanism will be discussed later when current investigations have been completed; at present we favour an SET-initiated radical-mode benzylic fluorination culminating in the expected rapid dehydrofluorination of the α-fluoroalcohol thus generated [$ArCH_2OH$ + **1** → $(ArCH_2OH)^{+\bullet}(F\text{–}N^+)^{-\bullet}$ → **2** + ArCHFOH → ArCHO + 2.HF].

Use of a 50–100% excess of the oxidant **1** in the cases of the *o*- and *p*-chlorobenzyl alcohol (Table 1) produced detectable (<10%) quantities of a benzoic acid except in the case of the *ortho* nitro-



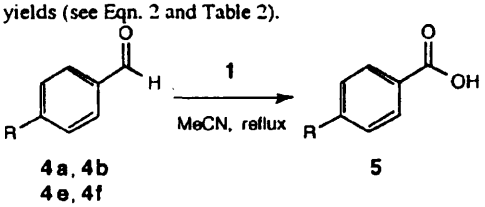
3a-e **4a-e** Eqn. 1

Table 1. Reaction of benzylic alcohols **3** with Selectfluor™ **1**.[13]

3	R	Molar Ratio 1 : 3	Time (h)	Yield (%)[a] of 4
a	H	1.05	18	43
b	4-NO_2	1.10	65	62
c	2-NO_2	1.10	435	56
d	2-Cl	2.00	45	42
e	4-Cl	1.50	15	37[b]

a. Pure isolated material; b. Some *p*-$ClC_6H_4CO_2H$ was detected in the crude product.

substrate **3c**. By contrast, benzoic acid itself was isolated in 87% yield following treatment of benzyl alcohol with an excess of F-TEDA-BF_4 (**3a** : **1** = 1.0 : 2.2) at 82 °C for 48 h in acetonitrile. Separate oxidation of benzaldehyde **4a** and its *para*-substituted derivatives **4b**, **4e**, and **4f** with a 1.2–1.4 molar proportion of **1** provided the corresponding benzoic acids **5a–f** in fair-to-excellent yields (see Eqn. 2 and Table 2).



4a, 4b
4e, 4f **5** Eqn. 2

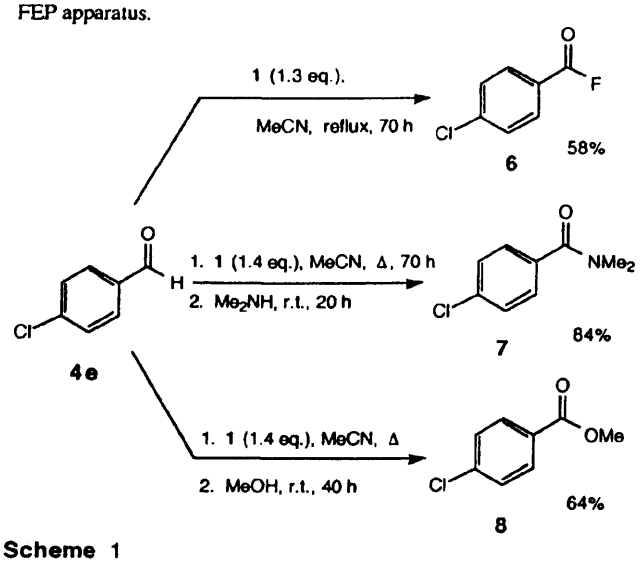
Table 2. Reaction of benzaldehydes **4** with Selectfluor™ **1**.[14]

4	R	Molar Ratio 1 : 4[a]	Time (h)	Yield (%) of 5
a	H	1.2	31	46
b	NO_2	1.2	384	50[b]
e	Cl	1.4	66	93
f	CN	1.2	80	87

a. Pure isolated material; b. Determined by ^1H nmr analysis, which revealed the presence of *ca.* 50% unchanged **4b**.

The reactions proceed *via* benzoyl fluorides, as established by ^{19}F nmr analysis of reaction mixtures and by one-pot derivatisation reactions involving dimethylamine or methanol (Scheme 1). The related direct transformations of an aldehyde to an acid chloride or bromide appear to be quite rare.[15] Isolation of the benzoyl fluorides proved troublesome owing to inadvertent hydrolysis and attack on glass, but

was achieved in the case of *p*–chlorobenzoyl fluoride using Teflon® FEP apparatus.



Scheme 1

F–TEDA–BF_4 is only one of numerous electrophilic fluorinating agents, including N–F compounds,[16] that are known to be strong oxidising agents. Caesium fluoroxysulfate rapidly oxidizes both aromatic and aliphatic aldehydes to the corresponding acid fluorides *via* a mechanism analogous to the SET–initiated radical–type process we favour with **1**.[17] Nevertheless, we recommend the use of the readily-available, easy-to-use, storable reagent **1** for this process since $CsSO_4F$ is not commercially available and its use is hazardous.[18] Interestingly, the well–known commercial electrophilic fluorinating reagent xenon difluoride reacts with benzylic alcohols in a very different manner from **1** to give fluoromethoxy-benzenes.[19]

In conclusion, we have demonstrated that benzylic alcohols and benzaldehydes are oxidised by the Selectfluor™ reagent **1** in moderate yield. Although this method is only likely to compete with established oxidising agents under special circumstances, the intermediacy of acyl fluorides will offer potential advantages should acyl derivatives be the ultimate target molecules. Our results also indicate that if oxidation of a substrate by Selectfluor™ possessing a benzylic alcohol is to be avoided, protection will be required.

We thank Dr Ray Fisher (Peakdale Fine Chemicals, Glossop) for helpful discussion and financial support.

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13 The substrate (1 mmol) was stirred with F-TEDA-BF_4 (**1**) (eq. as stated) in boiling acetonitrile (10 ml; nitrogen atomsphere) until oxidation was complete (as judged by TLC). The reaction solution was then concentrated *in vacuo*, and the residue was partitioned between water and dichloromethane. The organic layer was washed twice with water, dried ($MgSO_4$) then evaporated *in vacuo* and the residue purified by recrystallisation or chromatography.

14 A stirred solution of the substrate (5 mmol) and F-TEDA-BF_4 (**1**) (eq. as stated) in acetonitrile (50 cm^3) was heated under reflux (nitrogen atmosphere) until fluorination was complete (as judged by TLC). Water (10 ml) was then added and the resulting solution was stirred for 20 h, concentrated *in vacuo*, diluted with water (20 ml). The mixture was stirred for 30 min., cooled to 5 °C, and finally filtered. The precipitate was washed with cold water and purified by recrystallisation or chromatography.

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Remote functionalization of (−)-menthol—synthesis of 4a,5,6,7,8,8a-hexahydro-4*H*-benzo[1,3]oxazine derivatives with the Selectfluor™ reagent F–TEDA–BF_4

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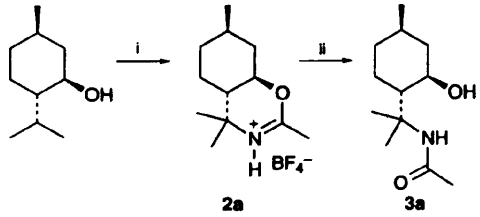
An unprecedented synthesis of 4a,5,6,7,8,8a-hexahydro-4*H*- benzo[1,3]oxazine derivatives involving the remote functionalization of alcohols using the Selectfluor™ reagent F–TEDA–BF_4 and an organonitrile is disclosed; X-ray crystallographic data for the oxazinium tetrafluoroborate derived from (−)-menthol and acetonitrile is presented.

Many new reagents for the site-selective fluorination of organic compounds have recently been developed.[1] Of these, the Selectfluor™ reagent F–TEDA–BF_4 **1**† is one of the foremost, and since its introduction in 1992[2,3] has been used to fluorinate in electrophilic mode a wide variety of organic substrates.

As part of a programme to discover new uses for F–TEDA–BF_4 **1**, we are actively seeking one-pot transformation leading to non-fluorinated final products. The present report concerns a chance discovery—a novel synthesis of benzo[1,3]oxazine derivatives—made whilst extending work on the oxidation of benzylic alcohols to benzaldehydes and hence (*via* benzoyl fluorides) benzoic acid esters and amides.[4]

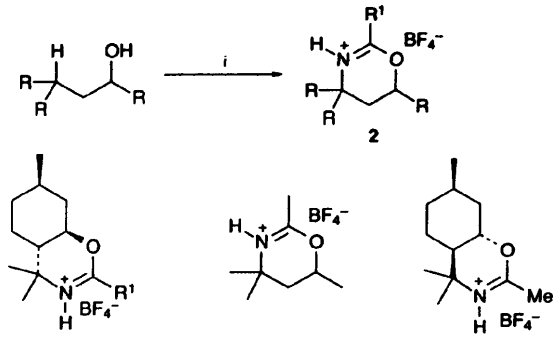
Treatment of (−)-menthol with 2 equiv. of F–TEDA–BF_4 **1** in refluxing acetonitrile did not result in its oxidation to (−)-menthone, as expected, but gave a crystalline salt of composition $C_{12}H_{21}NO{\cdot}HBF_4$ (50% yield), formation of which clearly had involved the incorporation of the reaction solvent.‡,§ ^{1}H NMR ($CDCl_3$) analysis revealed that the menthol cyclohexyl ring had remained intact, with a triple doublet at δ 4.31 (1 H, td, *J* 11.0 and 4.5 Hz) indicating no change in the relative stereochemistry at the Pr^{i}C–COH moiety.¶ A new signal was present at δ 2.42 (3 H, s) corresponding to a methyl group of an imidate moiety. The ^{19}F NMR spectrum ($CDCl_3$) of the product comprised a singlet at δ_{TFA} −71·8, characteristic of a tetrafluoroborate group. Clinching evidence that the product was the oxazinium tetrafluoroborate **2a** was provided by X-ray crystallographic analysis (Fig. 1).‖ This is the first reported crystal structure of a *trans*-4a,5,6,7,8,8a-hezahydro-4*H*-benzo[1,3]oxazine ring nucleus. The *cis* ring system[5] has a short C=N bond of 1.238(4) Å compared to 1.259(8) Å in **2a** in which the nitrogen atom is protonated. Although the BF_4^- anion is disordered two short non-bonded contacts to the proton reveal the presence of hydrogen bonding [F···H 1.85(2) and 1.96(2) Å]. This new salt is remarkably stable in air, and shows little to no signs of decomposition when stored in dry Pyrex for several weeks. The reaction is a remarkable example of remote functionalisation, a particularly difficult process to effect.

Preliminary results indicate that the reaction is not restricted to that between (−)-menthol and acetonitrile. The acetonitrile can be replaced by propionitrile or butyronitrile, leading to progressively lower yields of the homologous 1,3-oxazine salts **2b** (30%) and **2c** (21%), respectively. Use of 4-methylpentan-2-ol instead of (−)-menthol gives the monocyclic adduct **2d** in 49% yield, while (+)-isomenthol, under standard reaction conditions in acetonitrile, gives the 1,3-oxazine salt **2e** in 20% yield. Poor yields are believed to stem, in part, from ready hydrolysis of the oxazinium salts and incomplete conversion of the alcohols. In the case of **2e** the NMR spectrum of the crude product indicated a yield of 62%.** Also, when the crude



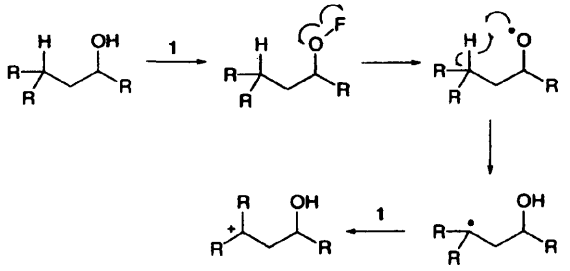
2a **3a**

Scheme 1 *Reagents and conditions*: i, Selectfluor™ **1** (2.2 equiv.), MeCN, 16 h, reflux; ii, NaOH, H_2O–CH_2Cl_2, 16 h room temp.

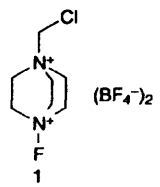


2a R^1 = Me, 50% **2d** 49% **2e** 20%
b R^1 = Et, 30%
c R^1 = Pr, 21%

Scheme 2 *Reagents and conditions*: i, Selectfluor™ **1** (2.2 equiv.), R^{1}CN, 16 h, reflux



Scheme 3 Possible mechanism for the formation of a γ-hydroxy carbenium ion



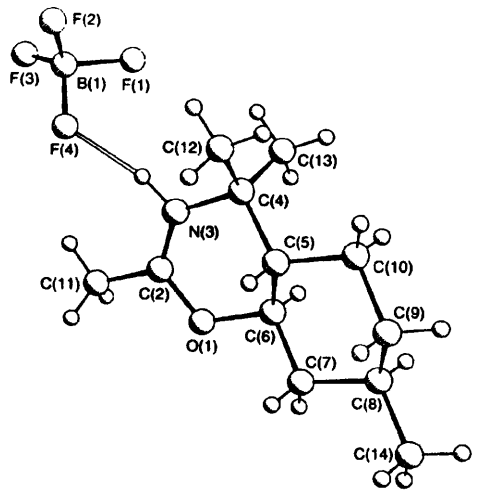


Fig. 1 X-Ray crystal structure of oxazinium tetrafluoroborate **2a**

reaction product from (−)-menthol, F–TEDA–BF_4 and acetonitrile was treated directly with aq. sodium hydroxide [NaOH (10%), room temp., 16 h], the hydroxy amide **3** was isolated in 83% yield, a clear improvement over the yield of isolated **2a** (50%). The amide was further hydrolysed to the hydroxyamine **4** (51%, isolated as the maleate salt) by more rigorous treatment with aq. sodium hydroxide [NaOH (10%), reflux, 15 h].

No reaction of the type alcohol → **2** was evident with 2-methylbutan-1-ol, pentan-2-ol and 4-phenylbutan-2-ol. This supports a reaction pathway involving formation of a tertiary carbenium ion at the position to the hydroxy function of the substrate. Generation of a tertiary carbenium ion would provide a route to the oxazinium salt *via* Ritter-like involvement of the organonitrile solvent.[6] The origin of such a carbenium ion is currently under investigation, two possibilities being solvolysis of the tertiary alkyl fluoride $R_2CFCH_2CH(OH)R$ formed first or SET conversion of a tertiary alkyl radical *via* decomposition of a hypofluorite produced initially (see Scheme 3).

We thank Dr Ray Fisher (Peakdale Fine Chemicals, Glossop) for financial support and Air Products and Chemicals, Inc., for samples of Selectfluor™.

Footnotes

† An MSDS (Material Safety Data Sheet) is available from Dr Helen M. Marsden, Air Products PLC, European Technology Group, Chineham, Basingstoke, Hampshire RG24 0FE, UK or Dr G. P. Pez, Air Products and Chemicals Inc., 7201 Hamilton Boulevard, Allentown, PA 18195-1501, USA.

‡ All compounds were fully characterised and gave the expected spectral and analytical data.

§ *Preparation of* **2a**: A stirred solution of the alcohol **2** (5.0 mmol) and F–TEDA–BF_4 **1** (11.0 mmol) in dry nitrile (50 cm^3) was refluxed under nitrogen. After the alcohol had been consumed (as judged by TLC in ethyl acetate–hexane with ammonium molybdate stain) the reaction was allowed to cool to room temp. The mixture was concentrated *in vacuo* to give a semi-solid which was triturated three times into dichloromethane (40 cm^3). The organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a crude material which was recrystallised from ethyl acetate–hexane to give **2a** as a solid.

¶ *Selected physical and spectroscopic data* for **2a**: R_f = 0.06 (67% ethyl acetate in hexane); mp 176–177 °C; ν_{max}(KBr disk)/cm^{-1} 3260(m), 3180(w), 3085(w), 2940(s), 2870(m), 2785(m), 2730(m), 1660(s), 1550(m), 1465(m), 1440(m), 1400(m), 1380(m), 1365(m), 1320(m), 1295(m), 1230(m), 1205(m), 1175(m), 1080 (s, br), 920(m), 840(m), 615(w), 535(w) and 520(w); δ_H(300 MHz, $CDCl_3$) 1.02 (3 H, d, *J* 6.5 Hz, 6-CHCH_3), 1.07–2.17 (7 H, m, 5-,6-,7-,8-C*H* and CH_2), 1.34 (3 H, s, 10-CH_{3ax}), 1.48 (3 H, s, 10-CH_{3eq}), 2.28–2.38 (1 H, m, *ca.* dt, 9-CH), 2.42 (3 H, s, 2-CH_3), 4.31 (1 H, td, *J* 11.0, 4.5 Hz, 4-CH) and 10.05 (1 H, br s, 1-NH); δ_C (75.5 MHz, $CDCl_3$) 19.9 (10-CH_{3ax}), 21.5 (10-CH_{3eq}), 23.3, 30.7 (6-*C*H and 6-CHCH_3), 23.6, 33.0, 38.6 (5-,7-,8-CH_2), 25.5 (2-CH_3), 44.0 (9-CH), 55.8 [10-*C*$(CH_3)_2$], 79.5 (4-CH) and 172.7 [2-(C=N)O]; δ_F (188 MHz, $CDCl_3$) −71.8 (s, BF_4^-); *m/z* (Ar FAB$^+$) 479 (2M − BF_4^-, 10%), 196 (M − BF_4^-, 100%).

‖ *Crystal data* for **2a**. A colourless plate shaped crystal of **2a** having approximate dimensions of 0.30 × 0.30 × 0.20 mm was mounted on a glass fibre. All measurements were made on a Siemens R3m/v diffractometer with graphite-monochromated Mo-Kα X-radiation. The data were collected at a temperature of −40 ± 1 °C using the $\omega/2\Theta$ scanning technique to a maximum 2Θ value of 52.1°. The structure was solved by direct methods using SHELXS-86[7] and DIRDIF.[8] Full-matrix least-squares refinement using TEXSAN,[9] in which each of the disordered F atoms occupied two semi-occupied sites, yielded final residuals of R = 0.087 and R' = 0.084 with $w = 1/[\sigma^2(F_o) + 0.03F_o^2]$. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/129.

** Based on diagnostic oxazine and alcohol NMR signals ($CDCl_3$, 200 MHz) present of the crude reaction mixture.

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"We are like dwarves on the shoulders of giants, so that we can see more than they, and things at a greater distance, not by virtue of any sharpness of sight on our part, or any physical distinction, but because we are carried high and raised up by their giant size."
-Bernard of Chartres.

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