# Fluoroalkyl Radical Cyclisation Reactions

A thesis presented by

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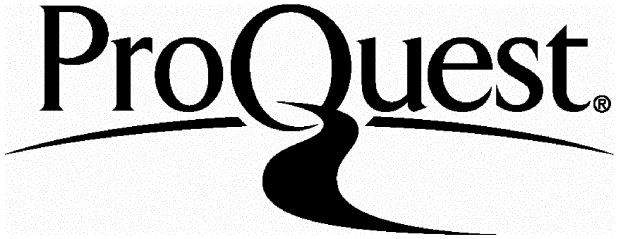

"I was a young man under the discipline of a system, so I had no real choice....."

Prof. R.J.P.Williams

"We as chemists are sitting between the dog and the lamppost."

Prof. S.V.Ley

# Abstract

This thesis is divided into four chapters.

Chapter one contains three different introductory sections of relevance to the research carried out and opens with a short account of the applications of fluorinated organic molecules and materials. As the complexity of the molecules increases, some of the typical reagents and methods for fluorination are introduced. The effects which fluorination can have are explained by reference to the modes of action of appropriate biologically active molecules. The second part of the introduction contains material relating to the concept of "philicity" of radicals which is required for a full understanding of chapter two. Finally, a literature survey of 5-*exo*-trig cyclisation reactions of $\alpha$-heteroatom substituted radicals is presented together with the objectives of our own research.

Chapter two consists of research in the area of fluoroalkyl radical cyclisation chemistry. An account of the novel use of dibromofluoromethane as an alkylating agent to prepare fluoroalkyl radical precursors is followed by a description of their 5-*exo*-trig cyclisation reactions. Results from the use of tri(*n*-butyl)tin hydride / AIBN conditions are discussed with regard to the efficiency of cyclisation and the stereochemistry of the resultant cyclopentanoids produced as a function of the character of the radical. Samarium diiodide and cobalt mediated cyclisations are also demonstrated.

The synthesis of a chiral building block intended as an intermediate to allow our methodology to provide nucleoside analogues appears towards the end of chapter two, as does an account of preliminary attempts to perform atom transfer cyclisation reactions involving difluoroalkyl radicals.

Chapter three provides a formal description of the experimental results and the procedures used to obtain them.

# Contents

## Acknowledgements

I would like to put on record my gratitude to Prof. Willie Motherwell for his guidance and patience over the last three years, and for giving me the opportunity to work in such a stimulating field. Thanks, Willie; it has been a privilege to share a project with you.

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At a personal level I thank my parents for their support throughout my extended education; Alf, Pierre & Isabelle, Amy & Mike, Shaun, Matt, Kazza and everyone else who put a roof over my head while I was finishing off. Also to Michelle (wouldn't be here without you); Jean-Marc and Letitia (for helping me get settled in a tough first year); Mark ("Always something there to remind me") and K.D. (a friend to cross the road for); David (the best flatmate in the whole of SW17); The Tabor group, in particular Al, Pickup, Martin and Sheady (for your valued friendship and trusted support): Ian, Mike S., Rich, Mike E., Pateman, Maria, Ann, Quentin and Jane.

# Abbreviations

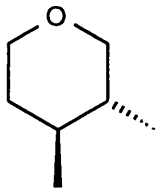
| | |
|---|---|
| Ac | Acetyl substituent |
| AIBN | Azo*bis*(*iso*butyronitrile) |
| APT | Attached proton test |
| ATP | Adenosine triphosphate |
| BDE | Bond dissociation energy |
| Bn | Benzyl substituent |
| b.p. | Boiling point |
| Bu | Butyl substituent |
| Bz | Benzoyl substituent |
| c. | Concentrated |
| *c*- | Cyclo- |
| cat. | Catalytic |
| COSY | Correlation spectroscopy |
| DAST | Diethylaminosulphur trifluoride |
| DCM | Dichloromethane |
| DEC | *N,N*-diethylcarbamoyl substituent |
| DIPA | Di(*iso*propyl)amine |
| DIPEA | Di(*iso*propyl)ethylamine |
| DMAP | 4-(*N,N*-dimethylamino)pyridine |
| DME | 1,2-Dimethoxyethane |
| DMF | *N,N*-dimethyl formamide |
| dmgH | Dimethylglyoximato (monoanion) |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidone |
| Δ | Heat |
| E.A. | Electron affinity |

| | |
|---|---|
| EI | Electron impact mass spectrometry |
| Enz | Enzyme fragment |
| Et | Ethyl substituent |
| FAB | Fast atom bombardment mass spectrometry |
| G.P. | Gas phase |
| High Res. | High Resolution mass spectrometry |
| HOMO | Highest occupied molecular orbital |
| I.P. | Ionisation potential |
| LDA | Lithium di(*iso*propyl)amide |
| LUMO | Lowest unoccupied molecular orbital |
| Me | Methyl substituent |
| MEM | (2-Methoxyethoxy)methyl substituent |
| MO | Molecular orbital |
| m.p. | Melting point |
| Ms | Methanesulphonyl substituent |
| $N^A$ | Adenine substituent |
| NIS | *N*-iodosuccinimide |
| NMR | Nuclear magnetic resonance spectroscopy |
| $N^T$ | Thymine substituent |
| $N^U$ | Uracil substituent |
| petrol | Petroleum spirit, b.p. 40°C-60°C |
| PMB | *p*-Methoxybenzyl substituent |
| ppm | Parts per million |
| Pr | Propyl substituent |
| py | Pyridine |
| Pyr | Pyridoxal phosphate ring system |
| sat. | Saturated |
| SET | Single electron transfer |

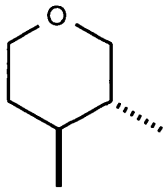
| | |
|---|---|
| SOMO | Singly occupied molecular orbital |
| TBAF | Tetrabutylammonium fluoride |
| TBS | Tributylsilyl substituent |
| TES | Triethylsilyl substituent |
| Tf | Trifluoromethylsulphonyl substituent |
| TFA | Trifluoacetic acid |
| THF | Tetrahydrofuran |
| tlc | Thin layer chromatography |
| TMS | Trimethylsilyl substituent |
| *p*-Tol | *p*-Toluyl substituent |
| Tr | Triphenylmethyl substituent |
| Ts | *p*-Toluenesulphonyl substituent |
| TS | Thermospray mass spectroscopy |
| VB | Valence bond |

## Stereochemical Notation

The graphical representation of stereochemistry within this thesis follows the conventions of Maehr[1]. Solid and broken lines indicate racemates while solid and broken wedges denote absolute configuration. For the latter, narrowing of the wedges indicates increasing distance from the viewpoint.



single enantiomer



racemate

# Preface

The present thesis is concerned with research in the area of fluoroalkyl radical chemistry. The generation and cyclisation reactions are studied in depth and observed trends in the efficiency and diastereoselectivity of the reactions discussed. For this reason, by way of introduction it is appropriate to highlight various concepts and previous research studies which are of direct relevance to our study. The introductory chapter is therefore divided into four sections. In the first part, the reasons why we are interested in fluoroalkyl radical cyclisation reactions and the molecules which potentially could be synthesised by them are demonstrated by reference to the utility of fluorinated molecules and materials and some of the methods used in their synthesis. In the second section, the concept of radical philicity is introduced. This is a concept which has been used to aid rationalisation of regioselectivity of radical addition reactions. Appreciation of this concept, its basis and implications is desirable for the discussion of results contained in chapter two. Thirdly, a review of previous research into 5-*exo*-trig cyclisation reactions of $\alpha$-heteroatom substituted alkyl radicals with the emphasis on diastereoselectivity is presented. Such reactions are related to the fluoroalkyl radical cyclisation reactions which we have studied, and thus this material is a logical introductory review. A formal statement of the objectives of the present study completes the introduction.

# Chapter 1

# Introduction

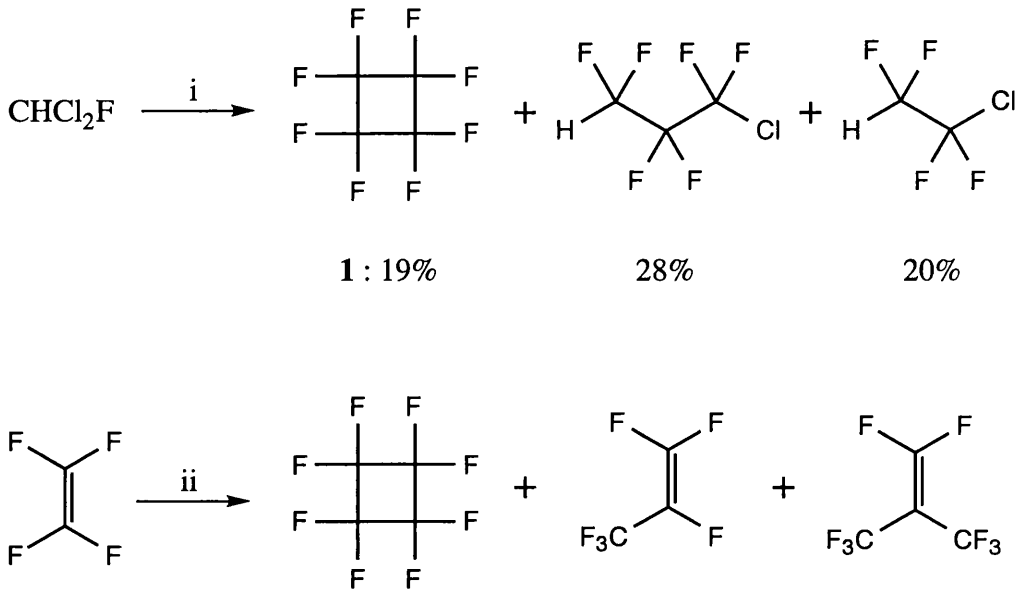
## 1.1 Applications of Fluorinated Organic Molecules

### 1.1.1 Introduction

Fluorinated organic molecules posses a diverse range of physical and chemical properties. They are suited to numerous applications in areas as wide-ranging as materials, pharmaceuticals, pest control and bio-medicinal research. This part of the introduction outlines many of those uses, and in some cases interesting modes of action are highlighted. In recent decades an increased research effort in the field of organofluorine chemistry and in fluorination[2] has enabled a rich supply of such molecules to be maintained. Such is the depth of knowledge in the field of fluorination that recent reviews may now concentrate on a given type of target molecule or on a particular reagent or method of fluorination[3,4,5]. Useful addition to such comprehensive coverage is beyond the scope of the current work, although a brief overview of fluorination methods is relevant. Thus the synthesis of some of the featured molecules is given as a basic introduction to fluorination chemistry.

### 1.1.2 Perfluorinated Materials

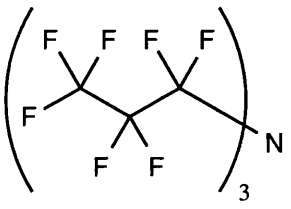
Perfluorinated molecules have found a variety of uses. Most of these rely on the physical rather than chemical properties of the molecules. The use of polytetrafluoroethene (PTFE) as a "non-stick" coating for cookware and as a substitute for oil or graphite mechanical lubricants and water repellents is an obvious example. Many other less well known examples can be found, their unfamiliarity probably being due to the highly technical functions for which they are employed. Perfluorocyclobutane (1) is used as a refrigerant and heat transfer medium, and may be synthesised in various ways[6,7,8], two of which are shown (scheme 1).




i) 700°C; ii) 600°C

**Scheme 1**

Even though the conditions are quite brutal and yields low this type of synthesis is fine for perfluorinated materials because of the absence of other reactive groups. Some functionality can be tolerated, for example simple tertiary amines may be perfluorinated by metal fluorides. The most important example is that of perfluorotripropylamine (2), which can be prepared from tripropylamine and cobalt trifluoride at 300°C[9]. Perfluorotripropylamine and perfluorodecalin (3) make up "Fluosol DA", a blood substitute which makes use of the high solubility of oxygen in many fluorinated solvents and the biological inertness of its perfluorinated constituents.



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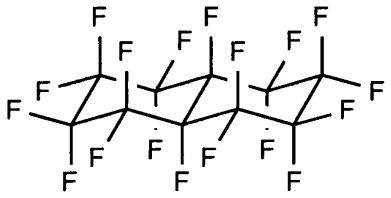

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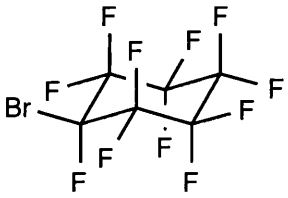
### 1.1.3 Haloperfluorinated Molecules and Halofluoroethers

The scope of perfluorinated molecules is essentially limited and many more properties are discovered when a few other atoms are introduced. Use of chlorofluorocarbons as refrigerants has been highlighted recently following environmental concerns. 1-Bromoperfluorooctane (Perflubron) and related molecules (*e.g.* 4) have found application as radiopaque biomedical contrast media[10]. This means they can be taken as an alternative to a "barium meal" when the gastrointestinal tract is being searched by X-ray for ulcers or tumours. Naturally, the chemical and biological inertness is again crucial, but the oxygen solvating capability has also allowed bronchial tracts to be studied using these materials.



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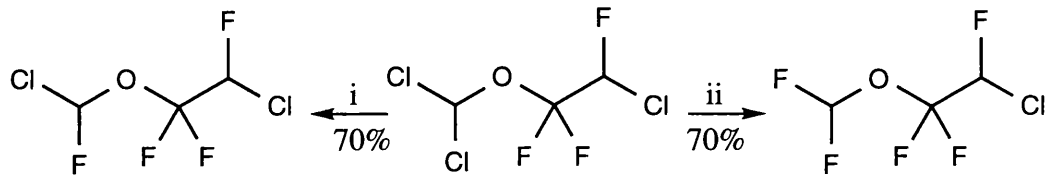
Many halogenated fluorinated ethers are good anaesthetics: it is found that the most suitable for medical applications are those with at least one hydrogen atom. The synthesis of two such ethers is shown (scheme 2)[11] and these also serve as an example of the specificity of fluorination which is possible by careful choice of

conditions. This type of ether has also been synthesised by selective photochlorination or photobromination.

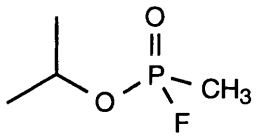



i) HF, cat.$SbCl_5$, -20°C; ii) $SbF_3$, cat.$SbCl_5$, 70°C

**Scheme 2**

So far we have seen that the physical properties dominate the useful attributes of molecules containing a large number of fluorine atoms. More interesting chemical properties result in cases where the extent of fluorination is limited. Fluorine and hydrogen have small van der Waals radii (1.4Å and 1.0Å respectively), and the C-F bond is typically 1.3Å in length which is comparable with that of a C-H bond (usually 1.1Å). Many monofluoro- derivatives are accepted by enzymes and receptors in the same way as the non-fluorinated molecule, although inclusion of a fluorine atom instead of a hydrogen atom gives the molecule a very different electronic structure. The carbon-fluorine bond has also been considered to behave like a carbon-hydroxyl bond since they have similar dipole moments and are of similar length. Both fluorine and hydroxyl groups may act as hydrogen bond acceptors[12]. Substitution of either a hydroxyl group or a hydrogen atom by a fluorine atom can dramatically alter the physiochemical properties of that molecule.

### 1.1.4 Fluorinated Organophosphates and Organophosphonates



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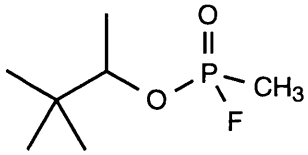

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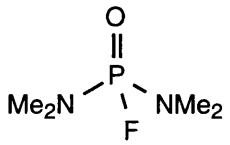

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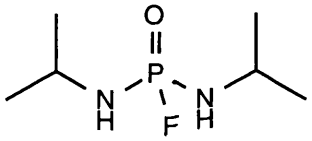

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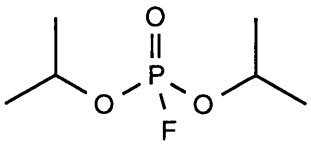

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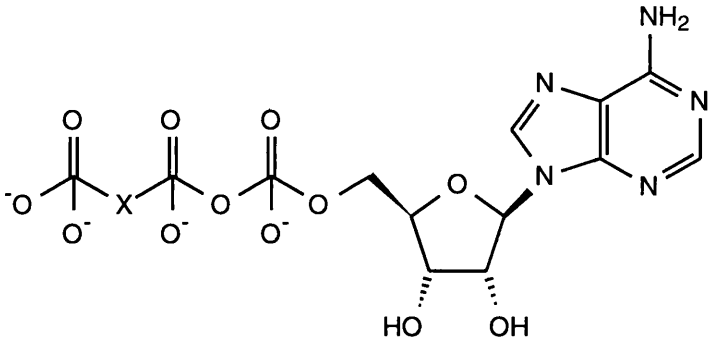
Organic fluorophosphonates show potent anticholinergic activity[13]. Sarin (5) and Sorran (6) are known chemical warfare agents. Fluorophosphates are cholinesterase inhibitors[14,15] although Dimefox (7), Mypafox (8) and Isofluorophate (9) find more civilised uses as an acaracide, an insecticide, and as a miotic respectively. Nucleophilic substitution of the corresponding chloride allows straightforward synthesis of these compounds.

Phosphate esters are of central importance to many biological processes. Modification of ATP (10) (fig. 1)[16] demonstrates another important feature of organofluorine compounds. Fluorine-containing groups can be added to biologically active molecules to modify properties of nearby functional groups. A difluoromethylene group can be used to replace an oxygen atom, and will affect the electron density of nearby functionality (revealed by the relative pKa values of (10), (11), and (12)).

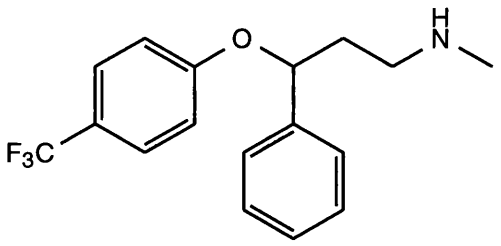


| | X | pKa |
|---|---|---|
| **10** | O | 6.63 |
| **11** | $CH_2$ | 8.09 |
| **12** | $CF_2$ | 6.4 |

**Figure 1**

### 1.1.5 Rational Drug Design

Rational drug design allows for routine incorporation of fluorinated groups into molecules. The effects of fluorine atoms and trifluoromethyl groups are well known and such entities may be added to a molecule to modify a specific property. As an example, inclusion of a trifluoromethyl group is known to increase lipophilicity and alter bioavailablity of a molecule. The antidepressant Fluoxetine (13)[17] is particularly notable for the recent controversy surrounding liberal prescription of its hydrochloride salt, Prozac. Disinfectant Fluorosalan (14)[17] and neuroprotective / anticonvulsant Riluzole (15)[18] are other examples of useful trifluoromethylated molecules. 4-Nitro-3-(trifluoromethyl)phenol (Lamprecid, 16) is used to control parasitic sea lamprey *Petromyzan marinus* which prey upon commercial fish stocks of the Great Lakes[19]. Part of the reason for the use of fluorine in this manner is undoubtedly the ease with which these groups can be added. Often no actual fluorination is required as a carbon fragment containing all the necessary fluorine



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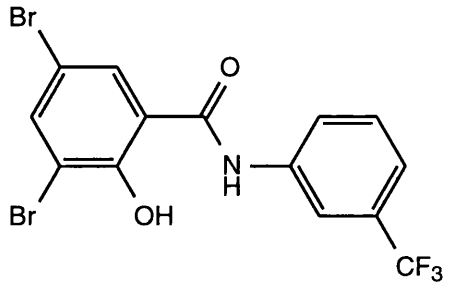

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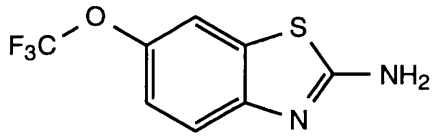

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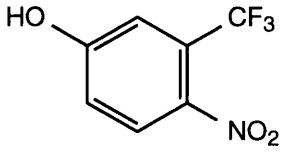

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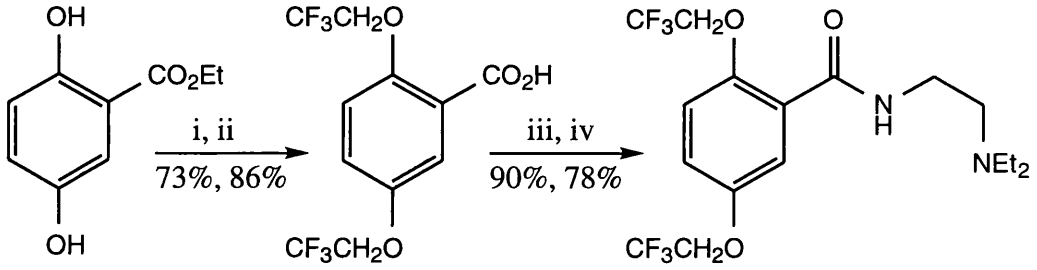
atoms can usually be added *via* a basic transformation. This is shown (scheme 3) for *N*-(2-diethylamino)ethyl 2,5-*bis*(2,2,2-trifluoroethoxy)benzamide (17), one of a family of antiarrhythmic benzamides and naphthamides for which activity is related to the number and position of the trifluoroethoxy groups[20].



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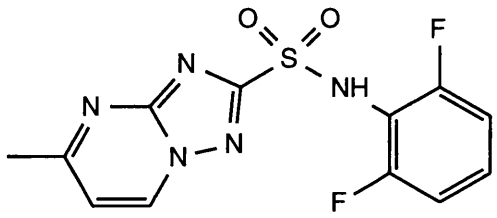
i) $CF_3CH_2OTf$, $K_2CO_3$, acetone, reflux, 72h; ii) NaOH, $H_2O$, reflux, 24h;
iii) $SOCl_2$, DMF, reflux, 1h; iv) $Et_2NCH_2CH_2NH_2$, $Et_3N$, 2-butanone, 0°C-RT

**Scheme 3**

In the case of Flumetsulam (18) fluorination of the aniline ring is crucial to function even though the fluorine atoms have little direct effect on the active portion of the molecule.

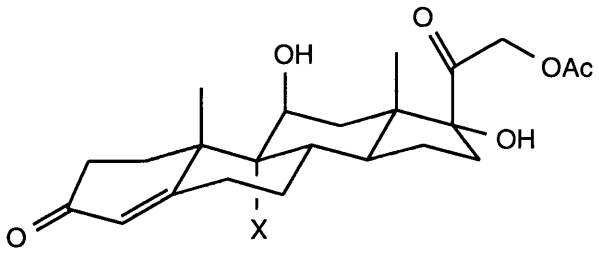



**18**

Flumetsulam is used as a herbicide against broad leaf weeds, particularly in maize and soybean crops[21]. The selectivity is associated with differing rates of metabolism, which occurs *via* oxidation of the aniline ring to a 4-hydroxy derivative[22]. The fluorine atoms apparently make this process more difficult for weeds, rendering efficient detoxification impossible.

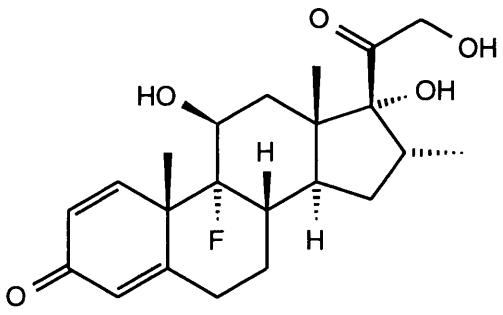
### 1.1.6 Fluorinated Steroids

Powerful electron withdrawal such as that described above can influence the active site of a molecule as well. The case of 6-$\alpha$- and 9-$\alpha$-fluoroglucocorticoids is well documented. 9-$\alpha$-Fluorohydrocortisone acetate (19b) is a suitable example. Hydrocortisone acetate (19a) is an anti-inflammatory steroid, made in the adrenal cortex, which fits into a receptor site in the liver. The recognition depends on formation of a hydrogen bond between a hydrogen bond acceptor of part of the receptor and the 11'-hydroxyl group of the steroid. It was found that the fluorinated analogue (19b) showed increased activity[23] and this has been explained by the inductive effect of the fluorine on the adjacent hydroxyl group[24]; the fluorine atom polarises the molecule, drawing electron density away




**19a** : X=H
**19b** : X=F

from the 11'-hydroxyl group. This polarisation makes the hydroxyl group more acidic, thus increasing its hydrogen-bond donating ability and making the steroid more active than its naturally occurring analogue. This is particularly useful because anti-inflammatory steroids can have undesirable side effects, such as causing excretion of potassium ions and retention of sodium ions (thus disturbing the ionic balance). These are avoided because of the specificity of the fluorinated versions for the appropriate receptor, and the lower doses needed for these molecules. Dexamethasone (20) and Betamethasone (21) are two such drugs which are actually currently in use.

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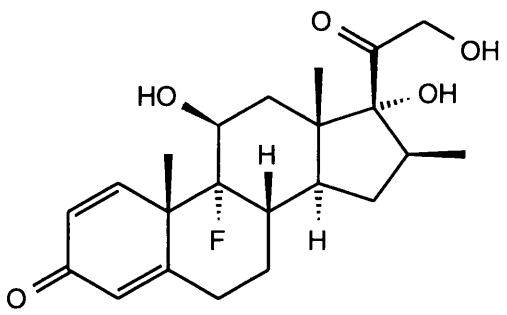
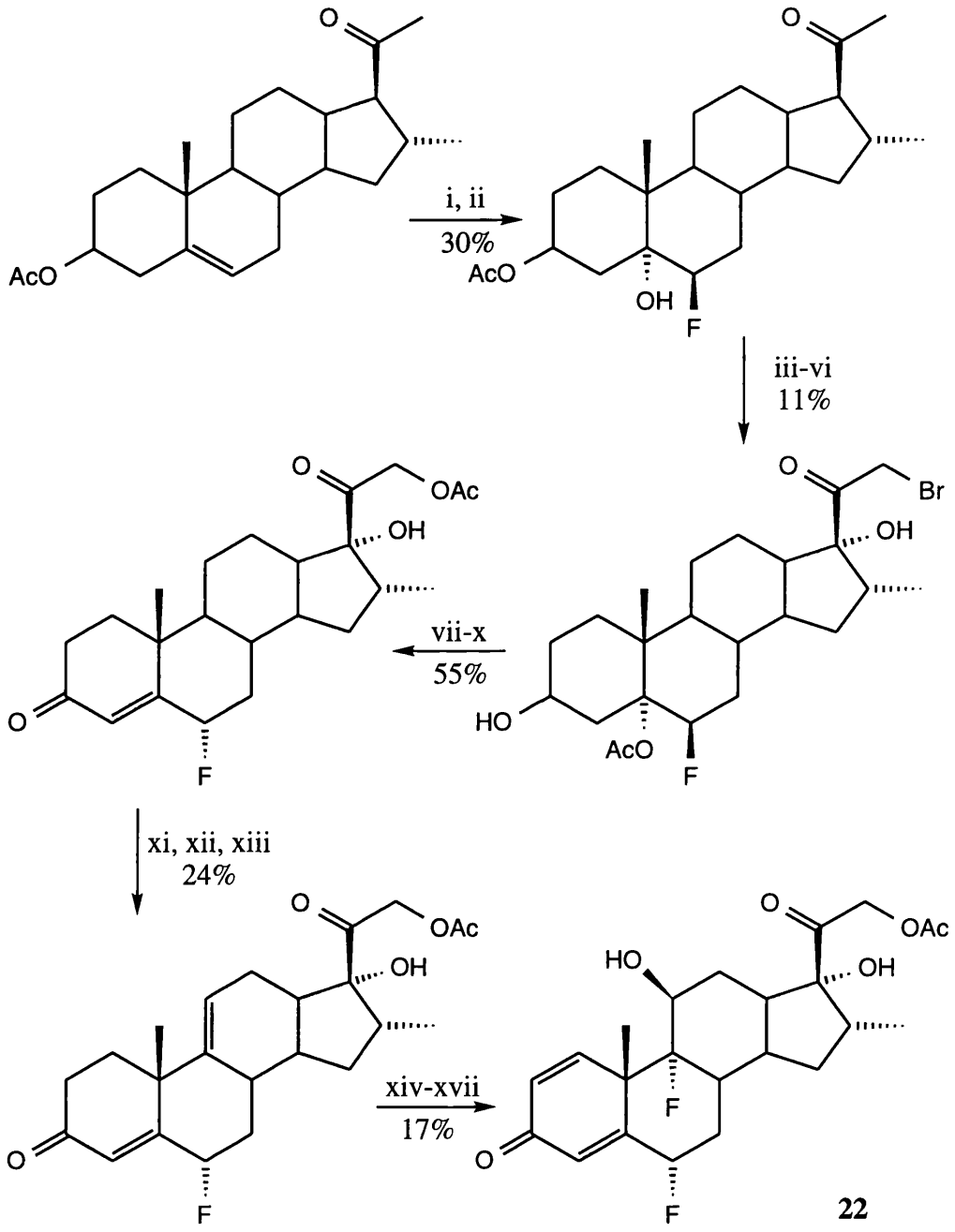



**21**

The synthesis of Flumethasone (22) (scheme 4)[25] provides a good example of the type of procedure used for this family of drugs. Flumethasone is 300 times more active as an anti-inflammatory than is hydrocortisone.

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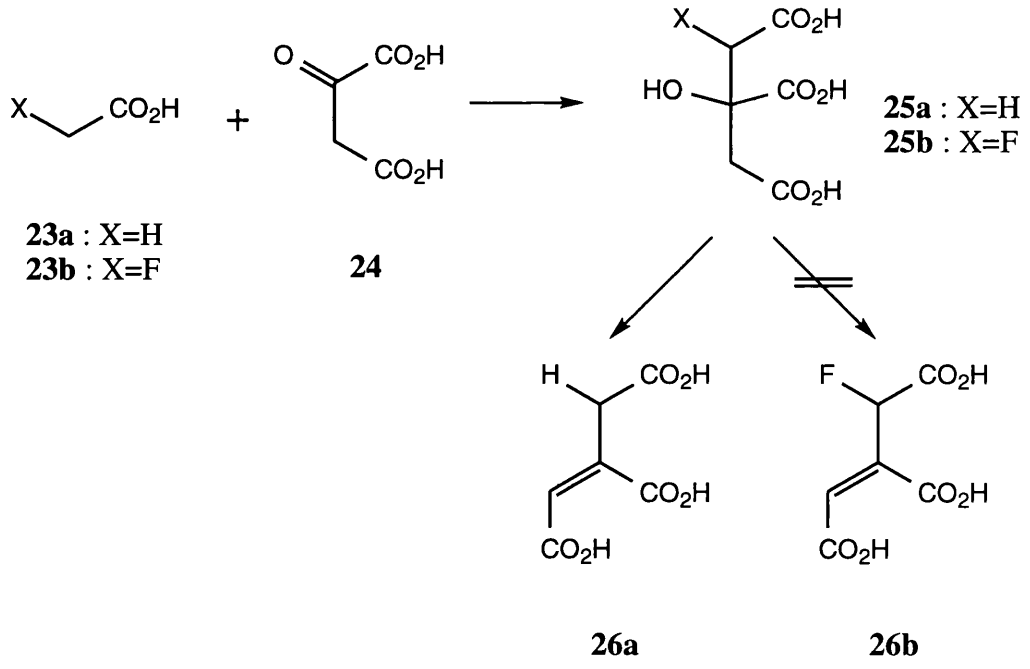
i) NaOAc, *o*-$HO_2CC_6H_4CO_3H$, $Et_2O$, RT, 12h; ii) $BF_3$-$Et_2O$, $Et_2O$, PhH, RT, 24h; iii) $Ac_2O$, AcCl, reflux, 96h; iv) *o*-$HO_2CC_6H_4CO_3H$, $Et_2O$, PhH, overnight; v) KOH, $H_2O$, MeOH, RT, 1h; vi) $Br_2$, dioxane, 0.5h; vii) NaI, acetone, reflux, 1h; viii) KOAc, acetone, reflux, 20h; ix) "$CrO_3$", acetone, 0°C; x) AcOH, HCl, RT, 6h; xi) KOH, MeOH, $H_2O$, 5°C, 1h; xii) bovine adrenals, buffer, 30°C, 3h; xiii) MsCl, py, DMF, Δ, 3h; xiv) $HClO_4$, AcNHBr, dioxane, 2h; xv) KOAc, acetone, reflux, 17h; xvi) HF, THF, DCM, -70°C to -10°C, 6h; xvii) $SeO_2$, *t*-BuOH, py, reflux, 62h

**Scheme 4**

### 1.1.7 Enzyme Inhibition

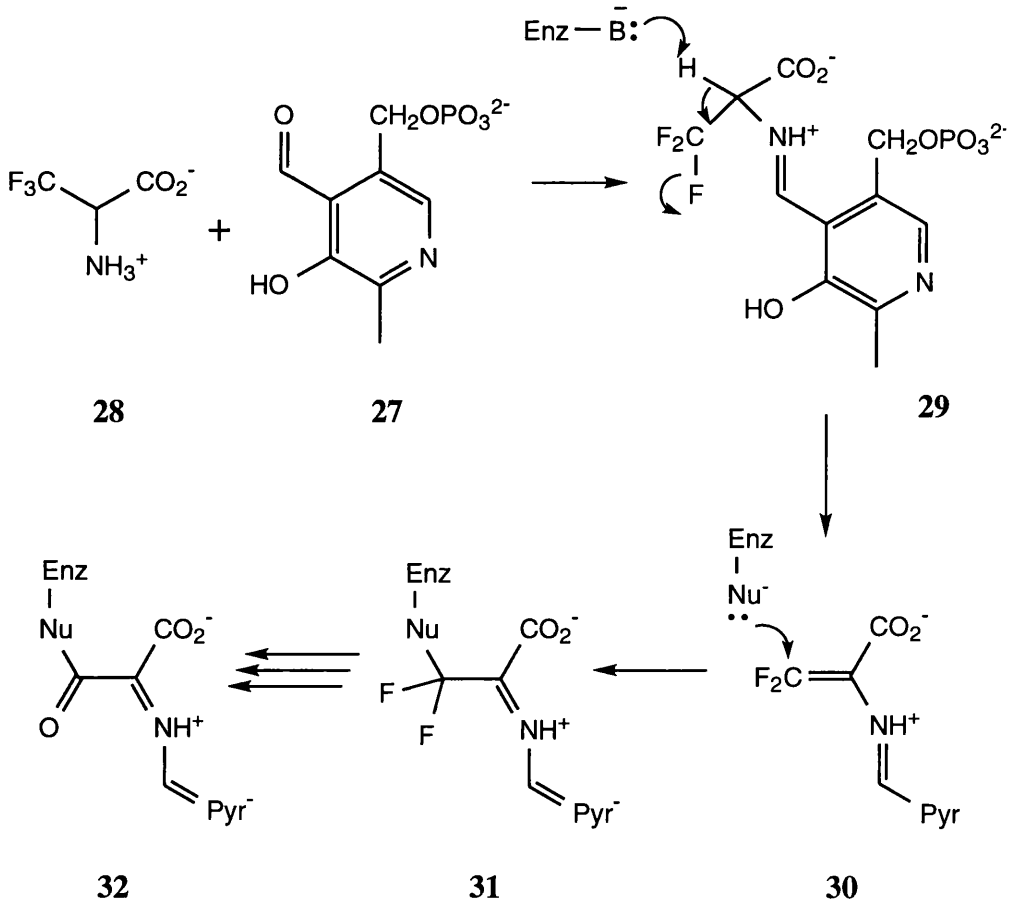
In addition to subtle modifications of activity, fluorination of molecules may have very destructive effects on biological systems. A classic example is fluoroacetic acid (23b), which Marais first isolated as its potassium salt from the African plant "Gifblaar" (*Dichapetalum cymosum*)[26]. The plant's toxicity is due to this particular antimetabolite, which interferes with the Krebs cycle, a key metabolic pathway necessary for aerobic respiration in higher organisms. In a cell operating normally, acetic acid (in the form of acetyl coenzyme A) is combined with oxaloacetic acid (24) to form citric acid (25a). Citric acid is then dehydrated in a reaction catalysed by aconitase to give aconitic acid (26a); this is shown formally in scheme 5. In a series of subsequent reactions the aconitic acid is transformed back into oxaloacetic acid by a process which liberates carbon dioxide and hydrogen (in the form of reduced flavoproteins), and provides energy for ATP formation. When fluoroacetic acid is incorporated into the cycle, 2-fluorocitric acid (25b) is formed and binds to aconitase.




**Scheme 5**

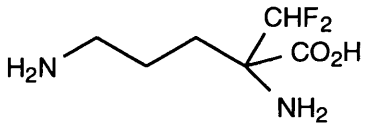
Elimination of water is repressed by the powerful electron withdrawing effect of the fluorine atom, making 2-fluorocitrate a competitive inhibitor of aconitase[27,28]. The sodium salt of fluoroacetic acid has an oral lethal dose of approximately $2mgkg^{-1}$ to $5mgkg^{-1}$ and is used as a rodenticide.

Fluorinated amino acids have been used as inhibitors of pyridoxal phosphate dependent decarboxylase enzymes. Pyridoxal phosphate (27) is a cofactor derived from vitamin $B_6$. A proposed mode of action is shown (scheme 6)[29]. Condensation of (enzyme bound) (27) with trifluoroalanine (28) to form (29) followed by elimination of HF (catalysed by an enzyme bound base) modifies the amino acid fragment into a Michael acceptor (30). Addition of some nearby nucleophilic portion of the enzyme follows to give (31). Loss of a fluoride ion is




**Scheme 6**

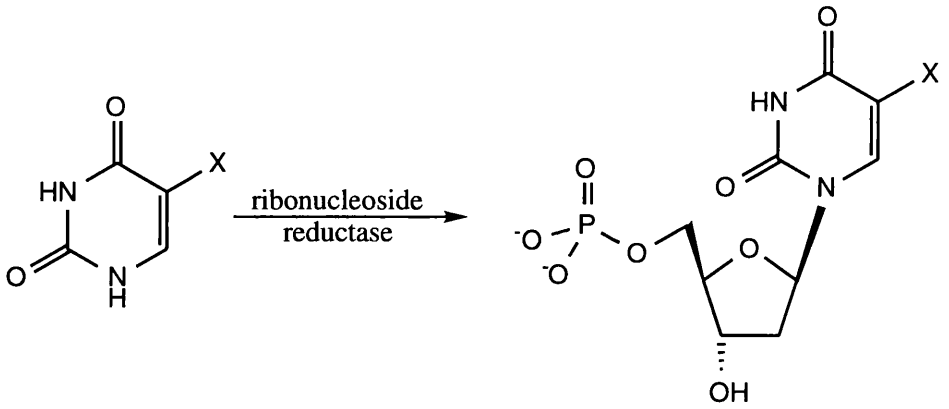
followed by addition of water, loss of another fluoride ion and another addition of water. This leaves the amino acid fragment covalently attached to the enzyme (32), blocking the active site. $\alpha$-Difluoromethylornithine (33) acts in a similar fashion on ornithine decarboxylase. Thus it is an inhibitor of polyamine synthesis[30,31], shows antiproliferative effects on cultured tumour cells[32], and antitrypanosomal activity in mice[33].




**33**

## 1.1.8 Fluorinated Nucleosides

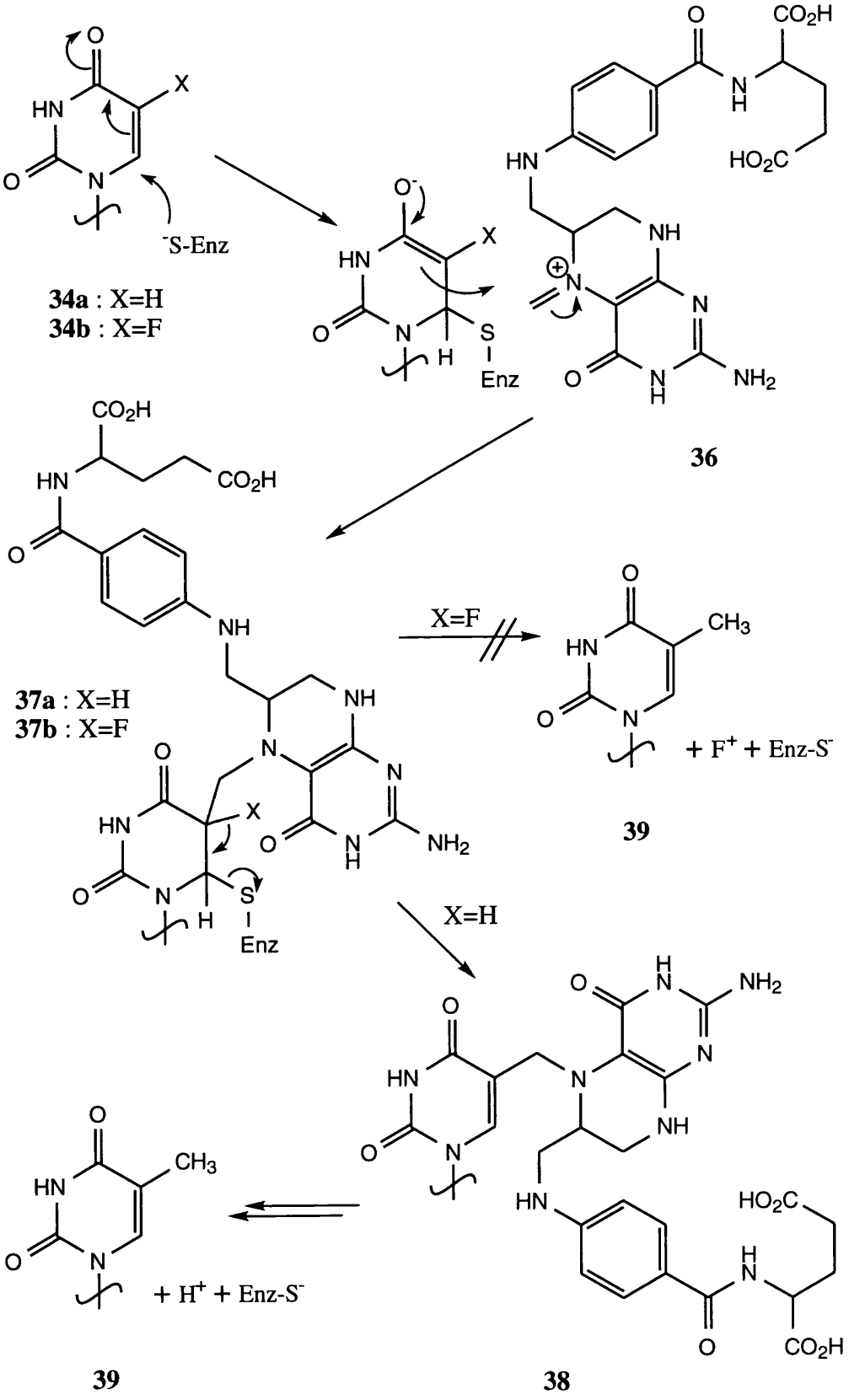
The drug 5-fluoro-2'-deoxyuridinemonophosphate (F-dUMP, 34b), an antimetabolite for thymidylate synthase, works on the principle[34] of suicide inhibition. Pro-drug 5-fluorouracil (5-FU, 35b) is converted into F-dUMP (scheme 7). The action of F-dUMP is shown in scheme 8[35].




**35a** : X=H
**35b** : X=F

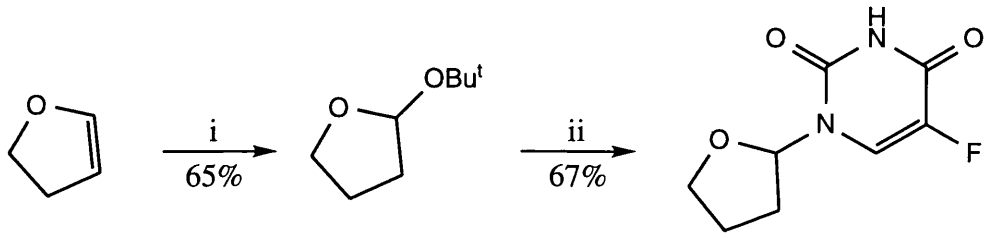
**34a** : X=H
**34b** : X=F

**Scheme 7**




**Scheme 8**

Normally, thymidylate synthase effects a Michael-type addition to 2'-deoxyuridinemonophosphate (dUMP, 34a), and the resulting intermediate adds an electrophile (36) derived from $N^5$,$N^{10}$-methylenetetrahydrofolate to give (37a). Subsequent reductive cleavage and elimination of the enzyme furnishes 2'-deoxythymidine (39). When F-dUMP acts as a substrate the elimination step cannot proceed ("$F^+$" would need to be eliminated) and the thymidylate synthase is trapped in the bound form (37b). 5-FU is used in cancer chemotherapy. A less toxic alternative[36,37], Tegafur (40) is also readily available from 5-FU (scheme 9)[38].

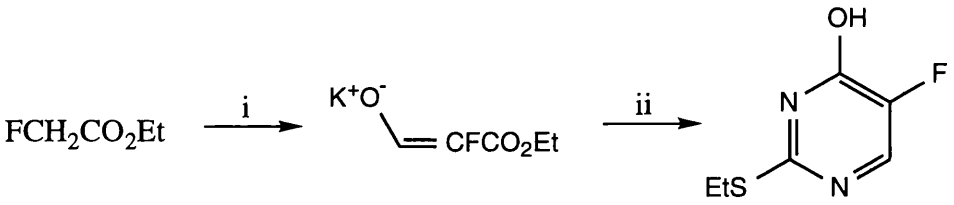



**40**

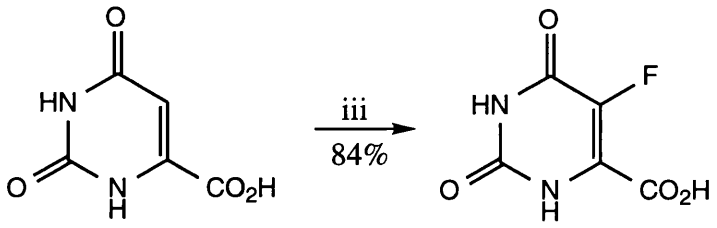
i) *t*-BuOH, *p*-TsOH, THF, reflux, 1h; ii) 5-FU (35b), DMF, 160°C, 5h

**Scheme 9**

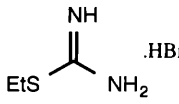
Scheme 10 shows two contrasting synthetic methods available for fluorinated pyrimidines[39,40]. First, the fluorinated synthon approach starting from ethyl fluoroacetate is fairly straightforward taking just two steps and using a standard pyrimidine disconnection. The second involves the use of a fluorinating agent on orotic acid (42) and proceeds in high yield.




**41** : 24%

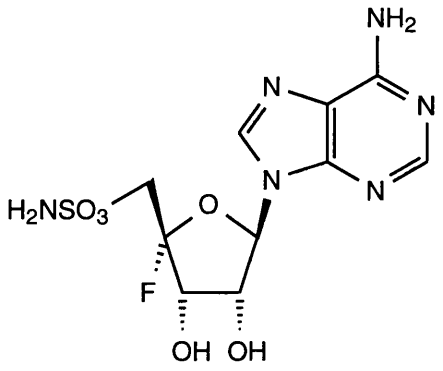



**42** **43**

i) $HCO_2Me$, KOEt, PhMe, 0°C-RT, 16h; ii)  , NaOMe, EtOH, reflux, 2h;
iii) $CF_3OF$, $CFCl_3$, TFA, $H_2O$, RT, 4h

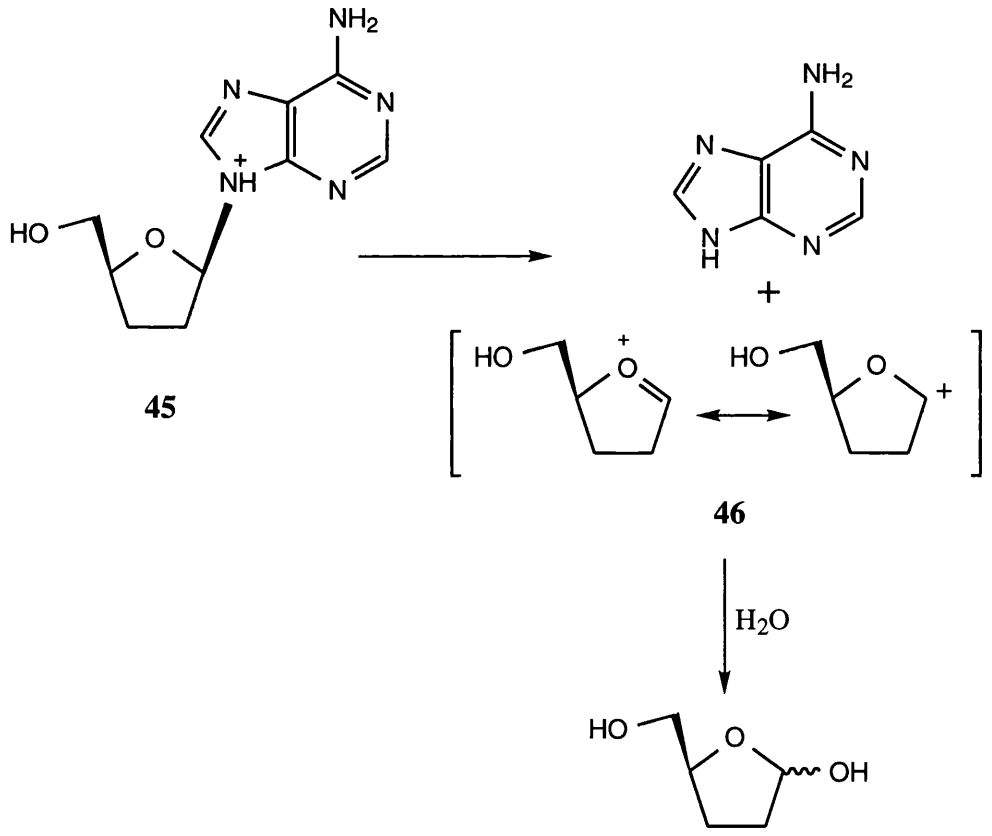
**Scheme 10**

Nucleoside analogues which are fluorinated in the ribosyl ring have been found to show antiviral properties[3]. One of the few naturally occurring organofluorine compounds is the antibiotic 4'-fluoro-5'-sulfamoyladenosine (Nucleocidin, 44)[41].




**44**

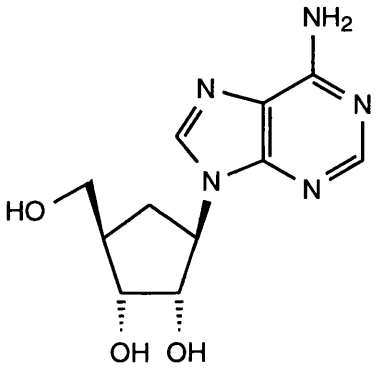
Nucleosides contain a glycosidic bond which joins the base to the sugar portion of the molecule. The use of any drug is made much easier if it can be administered orally, but in the case of drugs based on nucleosides the hydrolytic instability of the glycosidic bond can preclude this. The mechanism of hydrolysis is thought to be an E1 elimination of the protonated base[42] followed by nucleophilic attack of water on the resulting glycosyl cation (46). This is shown (scheme 11) for dideoxyadenosine (ddA, 45), which has a half life of about 30 seconds under conditions similar to those found in the human stomach[43].



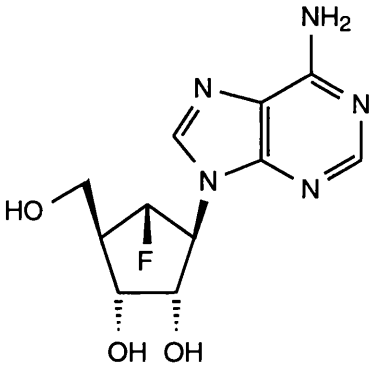

**Scheme 11**

When the 2'-methylene or the oxygen atom of the ribosyl ring is substituted for a fluoromethylene or difluoromethylene group the resulting nucleoside analogue is more stable to acid hydrolysis because the carbonium ion produced as the purine or pyrimidine leaves is not as stable. Thus attempts have

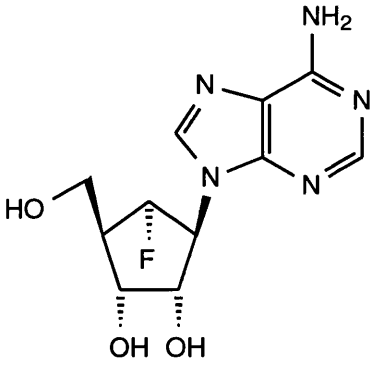
been made to increase the stability of known therapeutic agents by fluorination. Aristeromycin (47) is a naturally occurring carbocyclic nucleoside analogue of this genre which shows antibacterial and antifungal activity[44,45]. Both of the 6-fluoro analogues (48)[46,47] and (49)[48] have been synthesised. The anti-HIV agent 3'-azido-dideoxythymidine (AZT, 50) has also been modified in the same way[49].



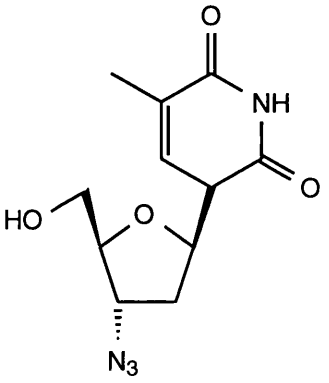

**47**




**48**

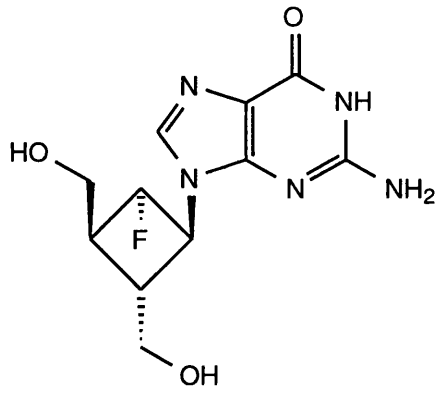



**49**



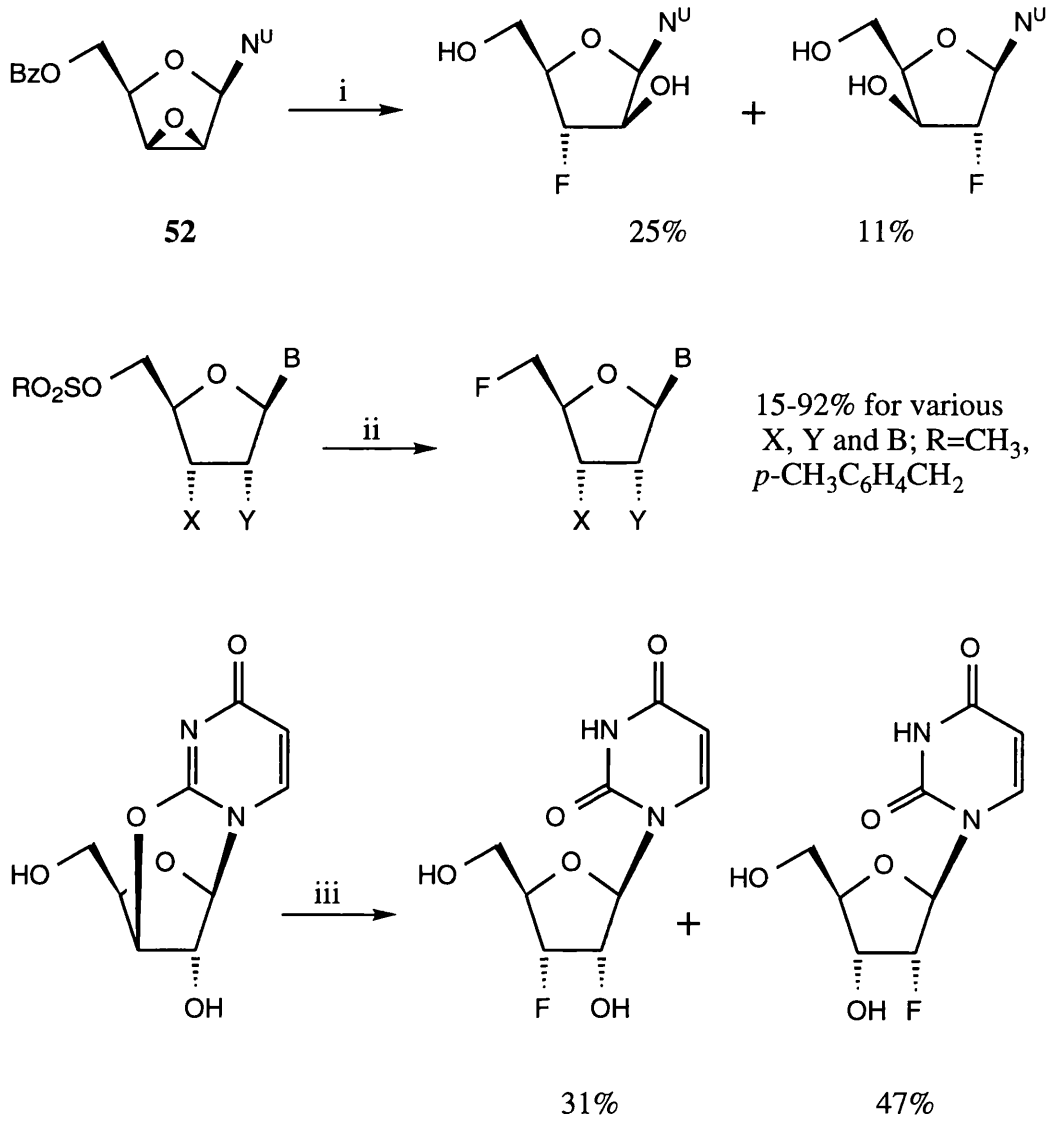

**50**

A series of nucleoside analogues containing a fluorinated cyclobutane ring instead of the ribosyl ring have been synthesised[50]. (51) was found to be as active as the commercially available drug acyclovir against herpes (HSV-1 and HSV-2) and the "chicken pox" virus, VZV.




**51**

As a direct consequence of the importance of selective fluorine incorporation into nucleosides there has been a vast body of research into synthesis of nucleosides which are fluorinated in the ribosyl ring. A collection of some of the more popular methods is illustrative of the limitations and strengths of late stage ionic fluorination (the most important method of producing fluorinated nucleosides). The formal process of displacing a leaving group with a fluoride ion has been done in many ways, some of which are shown (scheme 12).

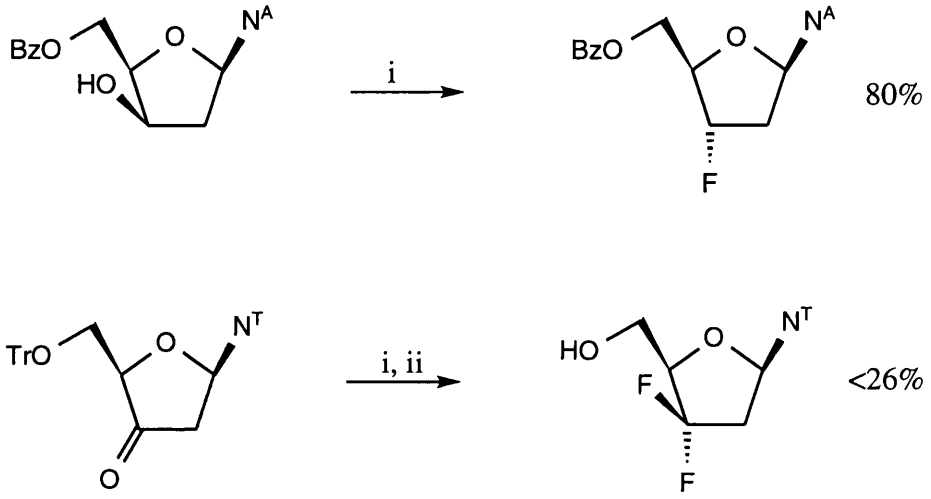



i) HF, dioxan; ii) KF, $HOCH_2CH_2OH$, 130-150°C
or TBAF, DMF, 50°C; iii) HF, $AlF_3$, dioxan

**Scheme 12**

Opening an epoxide (*e.g.* 52) with HF[51] gives only *trans* products, in poor yields, with regioisomerism possible. The 5'-carbon, being primary, is the easiest place for $S_N2$ fluorination with KF[12] or TBAF[12]. Nevertheless, because of the $\beta$-oxygen atom effect good leaving groups are essential and yields can be variable. Another method, specific to pyrimidine nucleosides, displacement of an "anhydro" bond

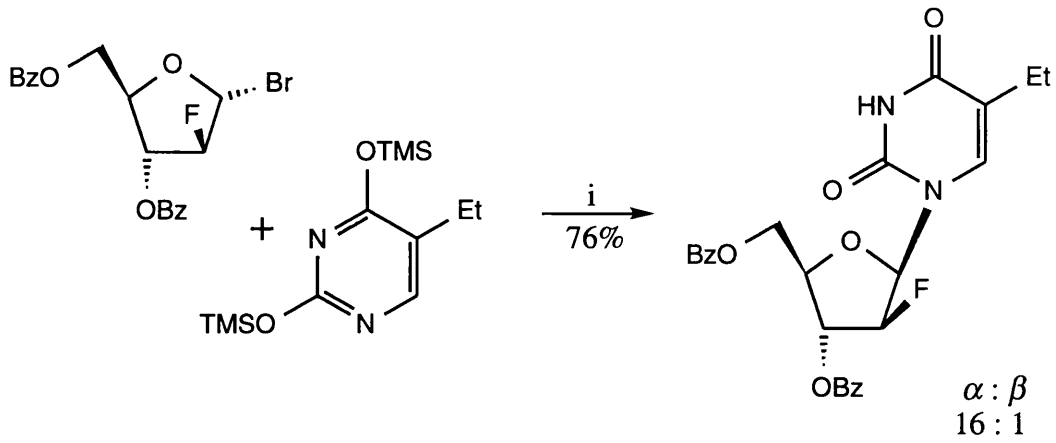
by HF / $AlF_3$[52], can also lead to regiochemical problems. Of the more recent methods of fluorination (scheme 13), the reagent DAST has been of great importance. Displacement of a leaving group or substitution of a hydroxyl group by DAST[12], and fluorination of ketones by DAST[53] can both be effective methods of fluorination, but poor yields with appalling regiochemical and / or stereochemical outcomes are commonplace and as a result research continues into alternative methods of fluorination.




i) DAST; ii) AcOH

**Scheme 13**

Nucleoside synthesis using fluorinated carbohydrate derivatives has been demonstrated[54] (scheme 14). Late formation of the glycosidic bond gives good yields but the anomeric ratios can be a problem. Synthesis of the appropriate carbohydrate, which may not be trivial, must also be achieved.

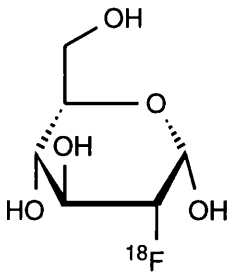



i) $CHCl_3$, reflux, 20h

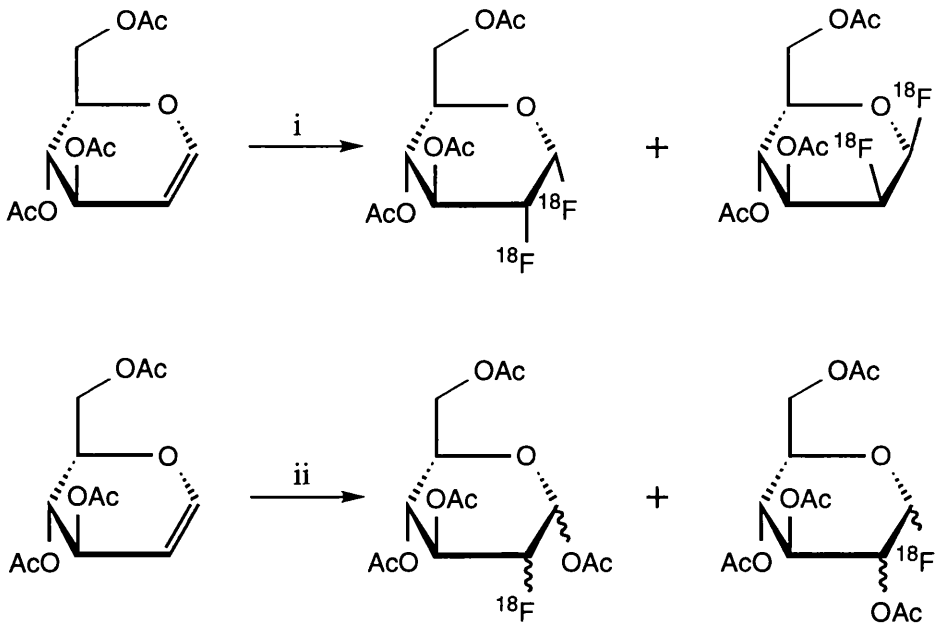
**Scheme 14**

### 1.1.9 Fluorinated Carbohydrates

2-deoxy-2-(fluoro-$^{18}$F)-(D)-glucose (53) has been used as a radioactive imaging agent in evaluation of the effect of certain diseases and conditions on glucose metabolism. The required isotope of fluorine confers a need for a simple source of fluorine atoms, and unusually fluorination at a double bond has been used (scheme 15)[55,56]. Peracetyl fluoride is the most often used reagent, whilst the most efficient method requires complexed potassium fluoride (scheme 16)[57].

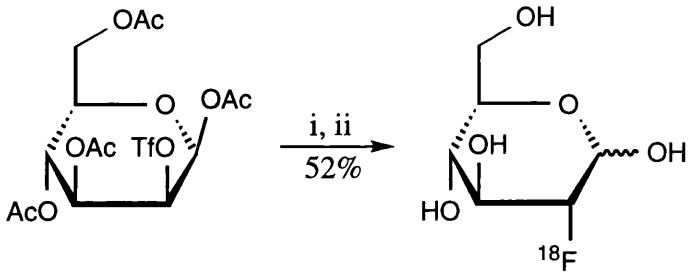



**53**




i) $^{18}F_2$; ii) AcOF, AcOH

**Scheme 15**



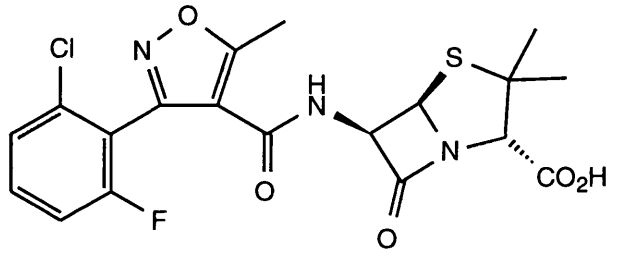

i) K$^{18}$F / 2,2,2-Kryptofix; ii) HCl

**Scheme 16**

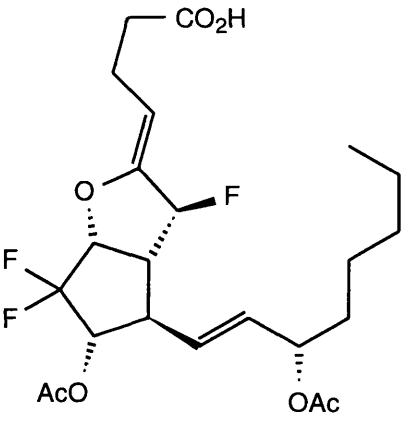
## 1.1.10 Conclusion

There can be few classes of biologically active molecule which remain to be fluorinated. In addition to those above, $\beta$-lactams (*e.g.* antibacterial

Floxacillin, 54)[58], prostaglandins (*e.g.* 7-fluoro $PGI_2$, 55)[59], terpenes (*e.g.* 20,20,20-trifluororetinal, 56)[60] and alkaloids (*e.g.* bronchodilator Flutropium bromide, 57)[61] have all received attention. However, new methods for their synthesis is still a potentially fruitful area of research.




**54**

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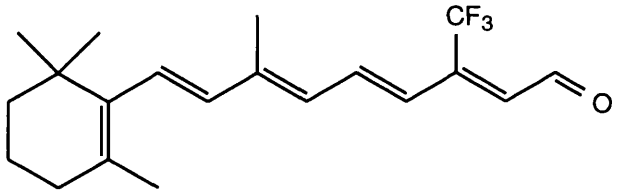
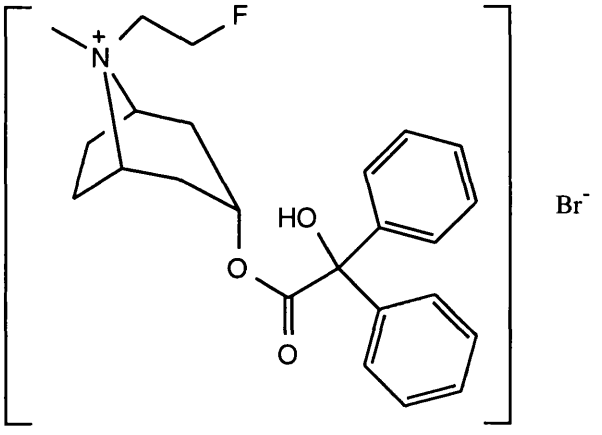



**56**




**57**

## 1.2 Nucleophilic and Electrophilic Radicals

This section contains a brief summary of an important concept which will be used in discussing the meaning of our results; that of radical philicity.

### 1.2.1 Introduction

The character of a carbon centred radical is affected by the nature of the substituents. Before using the addition of a radical to a radical acceptor as a synthetic method, the affinity of the radical for a given type of acceptor should be considered as it can make a difference to the course or efficiency of the reaction. This affinity can be measured by the rate of addition of the radical to an appropriate alkene. Radicals are said to be nucleophilic if they react faster with electron deficient alkenes than with electron rich ones. If a radical reacts faster with an electron rich alkene, it may be described as electrophilic. The data in table 1 show the relative rate constants for addition of the nucleophilic cyclohexyl radical to some substituted alkenes $CH_2$=CHX[62].

| Alkene X | CHO | $CO_2Me$ | Cl | OAc | *n*-Bu |
|---|---|---|---|---|---|
| $k_{rel}$ | 8500 | 1700 | 30 | 4 | 1 |

**Table 1**

The reaction of the trifluoromethyl radical with various alkenes demonstrates the effect for electrophilic radicals: that a radical with a low SOMO reacts faster with methyl substituted, hence more electron rich alkenes (table 2)[63]. ($k_e$=rate of addition to ethene, $k_a$=rate of addition to the least substituted carbon).

| | $CH_2=CH_2$ | $CH_2=CHMe$ | $CH_2=CMe_2$ |
|---|---|---|---|
| $2k_a/k_e$ ($CF_3\cdot$) | 1 | 2.3 | 6.0 |

**Table 2**

The difference in behaviour of nucleophilic and electrophilic radicals can in part be rationalised by frontier molecular orbital theory (figs. 2a, 2b).

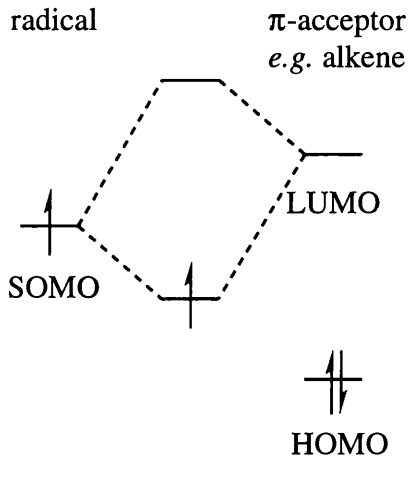



**Figure 2a**

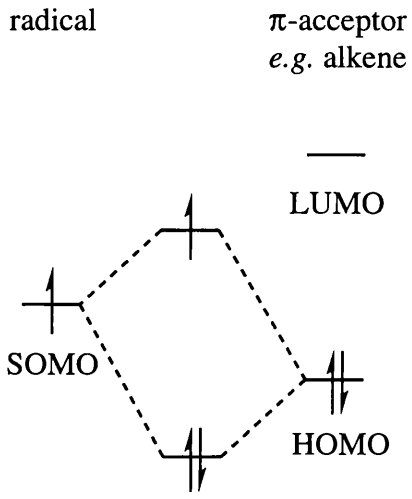



**Figure 2b**

In figure 2a, the dominant interaction is between the singly occupied molecular orbital (SOMO) of the radical and the lowest unoccupied molecular orbital (LUMO) of the acceptor. This diagram is associated with what would usually be described as a nucleophilic radical. In figure 2b the radical SOMO, which is much lower in energy than that of figure 2a, can interact with the highest occupied molecular orbital (HOMO) of the alkene. The SOMO always lies between the HOMO and LUMO, therefore for a radical with a low SOMO increasing the energy of the HOMO and LUMO will lead to an increase in rate of reaction. For a radical with a high SOMO the rate would decrease. It should be noted that the orbitals shown in the centre of each diagram are not the final orbitals of the

addition product, but a set of orbitals which are evolving as the reactants approach each other.

The pre-exponential factor of similar reactions is approximately constant, thus in this rationalisation we are taking the strength of the initial favourable interaction between the reactive elements to be indicative of the energy of the transition state. This turns out to be a good assumption for many radicals and alkenes, but can fail in certain cases.

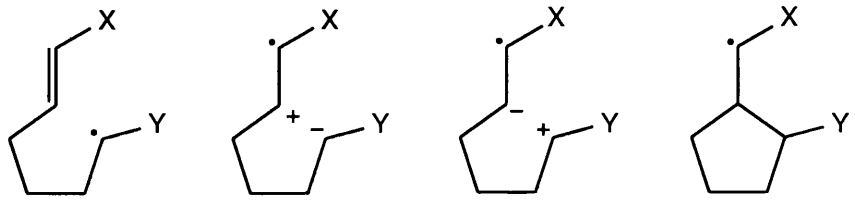
The definition of philicity for any radical or set of radicals is limited to a stated type of acceptor because a nucleophilic radical with one acceptor can become an electrophilic radical with a different acceptor. This is clearly shown by the rate constants for addition of electrophilic $CF_3\cdot$ and nucleophilic $CH_3\cdot$ to alkenes. ($k_e$=rate constant for addition to ethene, $k_a$=rate constant for addition to the least substituted carbon). Allowing for statistically more likely attack on ethene, chloroethene reacts faster with both radicals than either radical reacts with ethene (table 3).

| | $CH_2=CH_2$ | $CH_2=CHMe$ | $CH_2=CHCl$ |
|---|---|---|---|
| $2k_a / k_e$ ($CH_3\cdot$) | 1 | 0.7[64] | 4.2[65] |
| $2k_a / k_e$ ($CF_3\cdot$) | 1 | 2.3[66] | 1.3[67] |

**Table 3**

These results can be intuitively rationalised by considering that the product chloroalkyl radical is more stable than the primary alkyl radical formed during the reaction with ethene. The valence-bond description of the transition state takes this into account. In this model, the four structures (58-61), which represent a prototypical cyclisation reaction, are assumed to be the major contributors to the transition state.

Structures (58) and (61) are immediately recognisable as the initial and final radicals. Structures (59) and (60) are contributors which involve charge separation. It is the relative contributions to the transition state of these two structures which is most important in explaining radical addition rates.




**58** **59** **60** **61**

In (59), an electron has been transferred to the radical centre: the contribution of this transition state structure is determined by the ionisation potential of the alkene and the electron affinity of the radical. This structure contributes more when the radical is electrophilic, *i.e.* when it can stabilise a negative charge effectively. Conversely, when the radical can stabilise a positive charge effectively (*i.e.* has a low ionisation potential; a nucleophilic radical), then structure (60) becomes more important and hence an alkene which has a high electron affinity will increase the rate of cyclisation. Notice that in using ionisation potentials and electron affinities of the alkenes, both the effects of the substituent X (on the stability of the radical formed and on the accommodation of charge by the alkene) are taken into account.

### 1.2.2 Effect of Fluorination on Radical Philicity

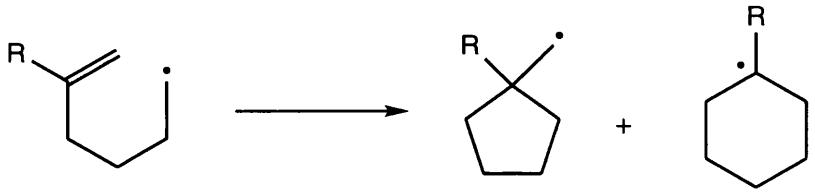
Fluorination of a radical changes the philicity. While unsubstituted alkyl radicals are nucleophilic[68] perfluorination leads to electrophilic character. The trifluoromethyl radical ($CF_3\cdot$) has been called electrophilic[69] and studies on the perfluoropropyl radical ($n$-$C_3F_7\cdot$)[70] suggest that this is of an electrophilic

nature. The radical ($n$-$C_5F_{11}(CF_3)CF\cdot$) is formally a perfluoroalkyl radical, though unlike the previous radicals it has only one $\alpha$-F substituent. This too, is said to be electrophilic[71]. When partially fluorinated radicals are considered, the distinction of character becomes more difficult. The difluoroalkyl radical ($RCF_2\cdot$) has been called nucleophilic[72], the difluoromethyl radical ($HCF_2\cdot$) both nucleophilic[73] and electrophilic[74] and there may be some justification for the term "ambiphilic" being used here. The fluoromethyl radical ($FCH_2\cdot$) is apparently slightly nucleophilic[63], as may be the fluoroalkyl radical ($RCHF\cdot$)[74].

## 1.3 Stereochemical Aspects of Radical Cyclisation Reactions

### 1.3.1 Introduction

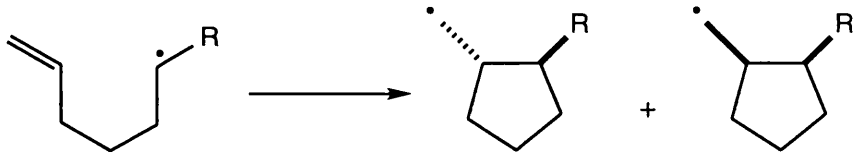
A 5-hexenyl radical can cyclise to generate a six or a five membered ring. Usually the cyclopentanoid product is observed, but the cyclohexanoid can occur (scheme 17)[75].




| | | |
|---|---|---|
| **62** : R=H | 98% | 2% |
| **63** : R=Me | 33% | 66% |

**Scheme 17**

The cyclohexanoid structures are usually seen when there is a substituent on the 5-position and so are not of major concern to us. However, the cyclisation of a monofluoroalkyl radical to form a five membered ring will generate two new stereocentres, and the product could be either of two diastereomers, or a mixture of both. Previous results indicate that in practice a mixture is usually obtained, and although it is not always obvious what the major product is going to be (scheme 18)[76,77] in the vast majority of cases the *cis* product is obtained in greatest yield for alkyl substituted carbon centred radicals. The stereochemical outcome is so dependable that generation of *cis* products has been cited as evidence for the operation of a radical mechanism in alkyl zinc iodide-palladium mediated cyclisations[78].




| | | | |
|---|---|---|---|
| **64** : R=$CH_3$ | 27 | : | 73 |
| **65** : R=$CF_3CF_2CF_2CH_2$ | 79 | : | 21 |

**Scheme 18**

The transition state for a cyclisation reaction of this kind has been modelled by Spellmeyer and Houk[75]. They assumed the reactive site geometry and dimensions of figure 3 for their model, and using those parameters they found that the lowest energy transition states for closure to a five membered ring are those shown (fig. 4).

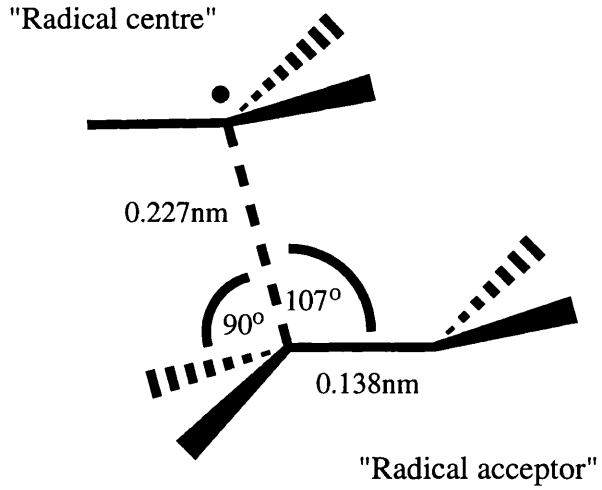
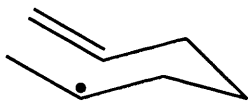



**Figure 3**

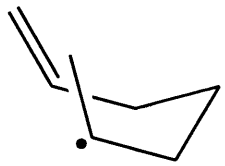
The transition states are geometrically similar to the lowest energy conformations of cyclohexane; Beckwith[79] has also suggested that this is the case. The radical for which the transition states are shown is the best one in terms of fitting calculated products to experimental observations. The difference in energy between the boat and chair transition states is 2.0kJmol$^{-1}$, much less than the difference between boat and chair forms of cyclohexane (27.5kJmol$^{-1}$). The transition states (66a) and (66b) lead to the *cis* product whilst (66c) and (66d) give the *trans* product.

Chair-like transition states

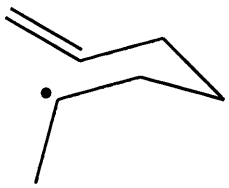


**66a**

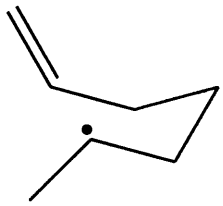
Boat-like transition states



**66b**



**66c**



**66d**

**Figure 4**

The model predicts regiochemical and stereochemical results which are in broad agreement with published experimental results for a variety of different radicals[80,81]. The cyclisation of the 1-methyl-5-hexenyl radical (64) is typical of many simple radicals in occurring through the sterically more hindered transition

states (66a) and / or (66b) to give *cis* products. There must be some stabilising effect to make either or both of these transition states lower in energy than the two which afford *trans* disubstituted products. Beckwith[76] suggested that the primary orbital interaction is between the half-full p-orbital of the radical and the vacant $\pi^*$ of the acceptor. A secondary interaction, at the opposite end of the alkene bond, occurs between the $\sigma$-orbitals of the radical substituent and the vacant $\pi^*$ of the acceptor. Such an interaction is only possible when the radical substituent is lying approximately parallel to the alkene bond (fig. 5).

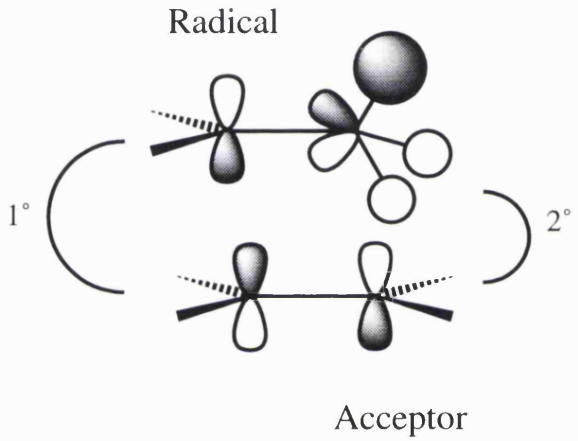


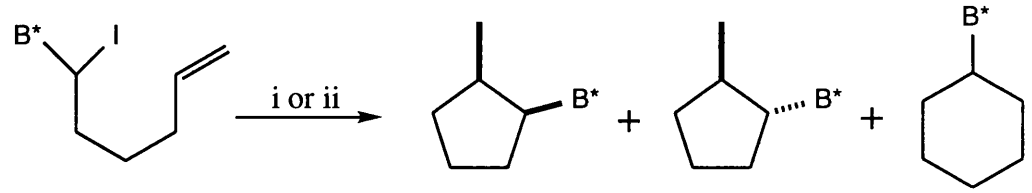

**Figure 5**

### 1.3.2 α-Heteroalkyl Radical Cyclisation Reactions

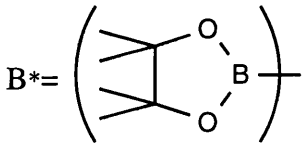
Despite the interest surrounding diastereoselective ring closure of alkyl substituted radicals there have been no published studies specifically designed to assess the effect of swapping the alkyl group for an heteroatom in determining the diastereoselectivity of a 5-*exo*-trig radical cyclisation. In fact reactions containing this type of process are quite rare and a survey of those which have been published is only just large enough to allow some trends to become visible.

### 1.3.2.1 α-Boroalkyl Radicals

Only one example of cyclisation of a boron substituted carbon centred radical is known. Photolytic and thermal initiation do not give appreciable differences in product ratios (scheme 19)[82].




| | | | | |
|---|---|---|---|---|
| **67** | Conditions i | 43% | 34% | 8% |
| | Conditions ii | 36% | 38% | 11% |



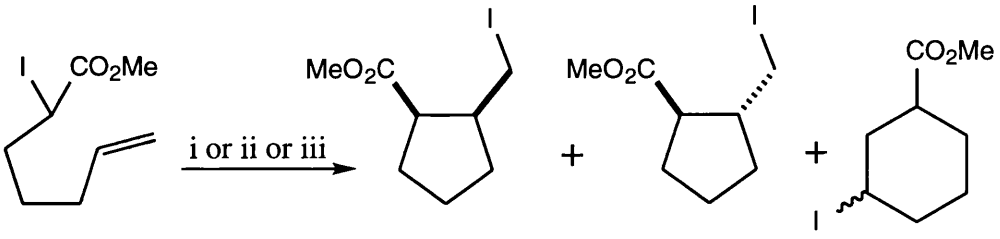

i) 1.1eq.*n*-$Bu_3SnH$, 0.05eq.AIBN, hν, PhMe, 25°C, slow addition; ii) 1.1eq.*n*-$Bu_3SnH$, 0.05eq.AIBN, PhMe, 90°C, slow addition

**Scheme 19**

Homolysis of a carbon-iodine bond gives the desired radical. Diastereoselectivity is low and the major product depends on the method used to carry out the reaction. The transition states appear to be close enough in energy that the entropic contribution to that energy can overturn the stereochemical preference even over the small range of 25°C to 90°C. This effect of close transition state energies is enhanced because the boron atom stabilises the radical very effectively[83], so the activation energy will be relatively high for this reaction. Small differences between the transition state energies become unimportant as the overall activation energy becomes large. The proportion of material which cyclises to a six membered ring is significant. The boron apparently reduces the rate of 5-*exo*-trig cyclisation to a level where 6-*endo*-trig can compete effectively. Given that Baldwin's rules predict the former process to be favoured on the

grounds of orbital interactions, it is not entirely surprising that we can see some of the cyclohexanoid product. In common with all boranes the alkyl dialkoxyborane (67) has a vacant $p_z$ orbital on the boron which can interact with the $p_z$ orbital of the radical centre (*i.e.* the SOMO) when it is created. The radical centre would thus be more planar than the corresponding alkyl substituted radical and the geometry of the transition states for cyclisation may be significantly disrupted. Theoretical calculations on various radicals with boron substituents give planar ground states[84]. The effect of the boron substituents is an interesting one. Both s and p effects of those substituents could alter the ability of the boron to accept the SOMO electron density and thus affect the electronic character and geometry of the radical. Arguments which have been used to rationalise diastereoselectivity of alkyl radical ring closure cannot be applied to the cyclisation in scheme 19.

### 1.3.2.2 α-Carbonylalkyl Radicals




| 68 | | | | |
|---|---|---|---|---|
| | Conditions i | 23% | 22% | 3% |
| | Conditions ii | 38% | 36% | 6% |
| | Conditions iii | 44% | 33% | 6% |

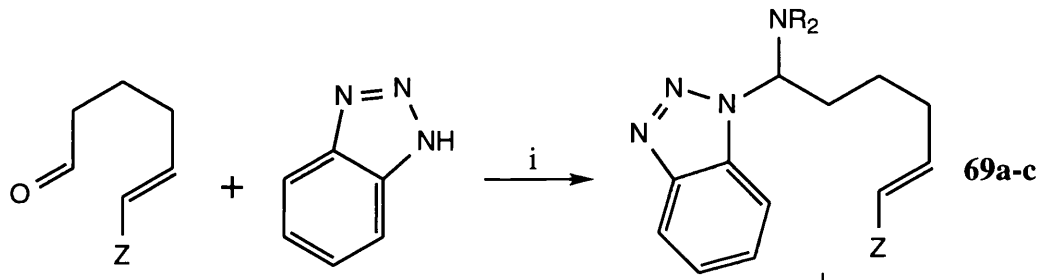
i) 0.1eq.*n*-$Bu_3SnH$, 0.1eq.AIBN, PhH, reflux, 5h; ii) 0.1eq.AIBN, PhH, reflux, 24h; iii) 0.1eq.AIBN, 0.1eq.$(Me_3Sn)_2$, PhH, Δ, 16h

**Scheme 20**

Although not an $\alpha$-heteroatom radical, the situation of having an $\alpha$-carbonyl substituent is worth considering. The effect of the methoxycarbonyl group on a radical centre is to reduce the SOMO energy and stabilise the planar structure, the same situation as in the above case for (dialkoxyboro)alkyl radical. Taking some atom transfer cyclisations[85] (scheme 20) as examples we see again a lack of stereoselectivity, the best case being a 3 : 4 ratio in favour of the *cis* product. In terms of overall yield, diastereomeric ratio and ratio of 5-*exo* to 6-*endo* the results of cyclisation are rather similar for the (dialkoxyboro)alkyl and the (methoxycarbonyl)alkyl radicals.

### 1.3.2.3 α-Nitrogen Substituted Alkyl Radicals

Results obtained from the cyclisation of $\alpha$-aminoalkyl radicals have demonstrated that the reaction favours *cis* products (scheme 21)[86].

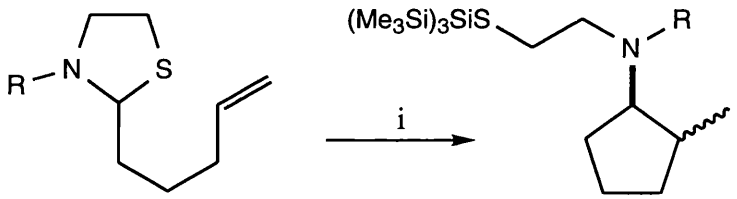



| | R | Z | yield | *cis* : *trans* |
|---|---|---|---|---|
| **69a** | $PhCH_2$ | $CO_2Et$ | 39% | 81 : 19 |
| **69b** | $PhCH_2$ | CN | 63% | 67 : 33 |
| **69c** | $CH_2$=$CHCH_2$ | CN | 65% | 70 : 30 |

i) $R_2NH$, sieves, 25°C; ii) $SmI_2$, THF, 0°C

**Scheme 21**

The selectivity is dependent on both the substitution pattern of the nitrogen and the acceptor. The yields shown in scheme 21 cannot be related to the cyclisation process because they are for two steps, but the diastereomeric ratio varies from 1 : 2 to 1 : 4. Another example (scheme 22)[87] shows that the diastereoselectivity can be maintained at the higher temperatures required for AIBN initiation. The ratios given in scheme 22 fall within the range of those of the cyclisations above (scheme 21). In this case there is different substitution on the amine, which might have a bearing on the outcome. In both cases (70a) and (70b) direct reduction rather than cyclisation accounts for approximately half of the isolated products.




**70a,b**

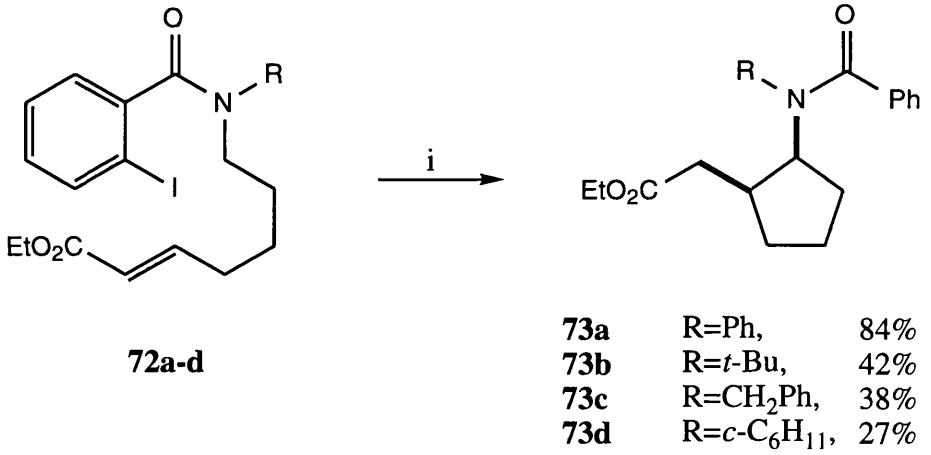
| | | |
|---|---|---|
| **71a** | R=$CO_2$Et, | 42% *cis* : *trans* 2.3 : 1 |
| **71b** | R=COMe, | 41% *cis* : *trans* 2.5 : 1 |

i) 1.2eq.$(Me_3Si)_3SiH$, 0.05eq.AIBN, PhMe, 88-90°C

**Scheme 22**

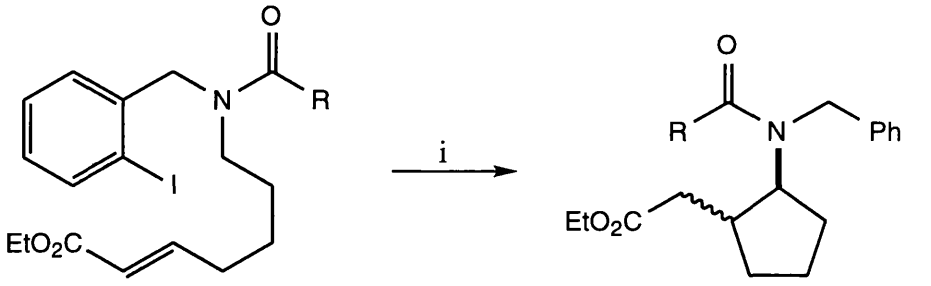
The greatest diastereoselectivity has been observed by Curran[88] (scheme 23) in his work on $\alpha$-amidoalkyl radicals. 100% *cis* diastereospecificity was found for amides (72a-d). The yields are dependent on the nitrogen substituent but there is evidence to suggest that this is due to the conformation of the amide during the translocation step rather than being related to the cyclisation. The stereochemical outcome is particular to benzamides as is shown by the results of cyclisation of (74a) and (74b). The acetamide (74a) gives low diastereoselectivity, whilst benzamide (74b) (which forms an intermediate

common with that formed in reaction of (72c)) shows total diastereoselectivity. In all of these cyclisations, an $\alpha,\beta$-unsaturated ester was necessary to obtain any cyclised product, use of an unsubstituted alkene (e.g. 76) giving simply reduction of the translocated radical.




**72a-d**

| | | |
|---|---|---|
| **73a** | R=Ph, | 84% |
| **73b** | R=*t*-Bu, | 42% |
| **73c** | R=$CH_2Ph$, | 38% |
| **73d** | R=*c*-$C_6H_{11}$, | 27% |



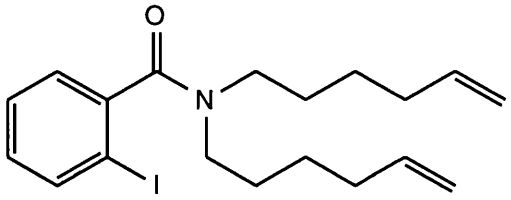

**74a** : R=Me

**74b** : R=Ph

| | | |
|---|---|---|
| **75** : R=Me, | 61% *cis* : *trans* 1.4 : 1 |
| **73c** : R=Ph, | 51% pure *cis* |

i) 2eq.*n*-$Bu_3SnH$, 0.05eq.AIBN, PhH, reflux, 8h

**Scheme 23**

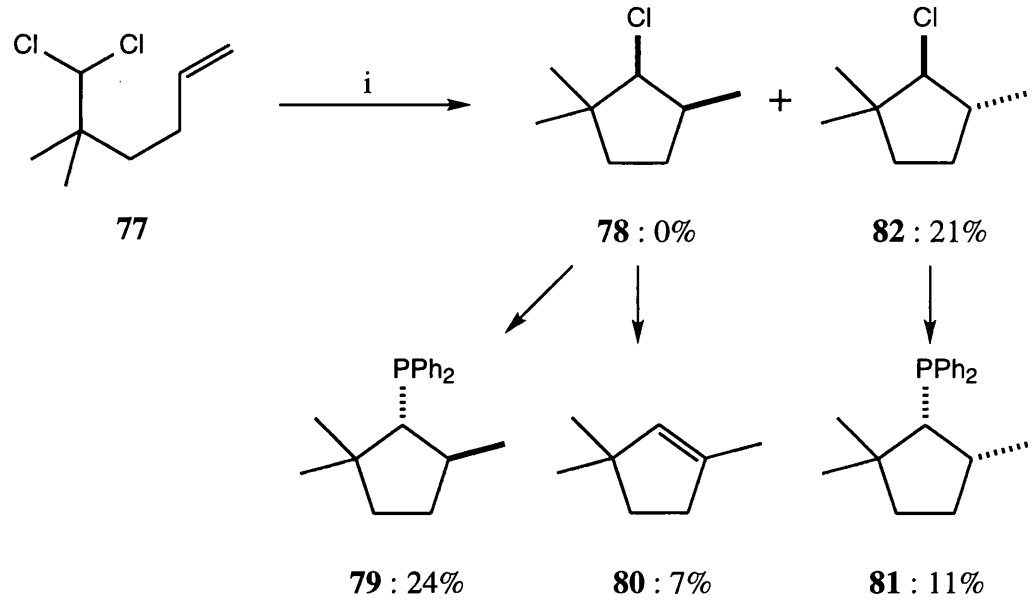


**76**

The cyclisation of all of the radicals with a nitrogen substituent can be summarised as being of poor to moderate diastereoselectivity, although total selectivity is possible in some exceptional circumstances. Most yields are in the range 40%-50%, though again there are some exceptions.

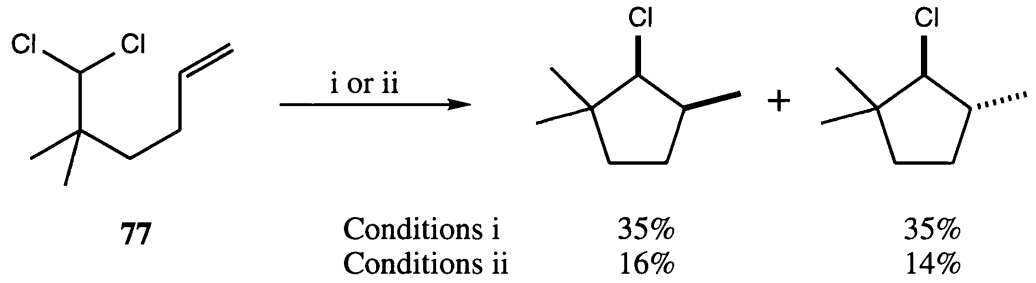
### 1.3.2.4 α-Chloroalkyl Radicals

*Gem*-dichlorides can be reduced to chloroalkyl radicals by electron transfer followed by loss of a chloride ion. Although this is not a synthetically useful method of producing α-chloroalkyl radicals it has provided most of the examples of such species being involved in cyclisation. Sodium diphenylphosphide can achieve the transformation[89], though in this case the products can react further (scheme 24) and other reactions do occur. Since products (79-81) are derived from the cyclised material, adding the yields of (78-80) and comparing to the total yield of (81) and (82) gives the ratio of *cis* : *trans* cyclisation, which turns out to be 31 : 32. To demonstrate that the products (79-81) were derived from radical cyclisation products, two conventional methods for generating a radical from a carbon-chlorine bond were used to carry out the cyclisation of (77)[89,90] (scheme 25).




i) 5eq.$NaPPh_2$, THF, 25°C, 40h

**Scheme 24**




| 77 | Conditions i | 35% | 35% |
|---|---|---|---|
| | Conditions ii | 16% | 14% |

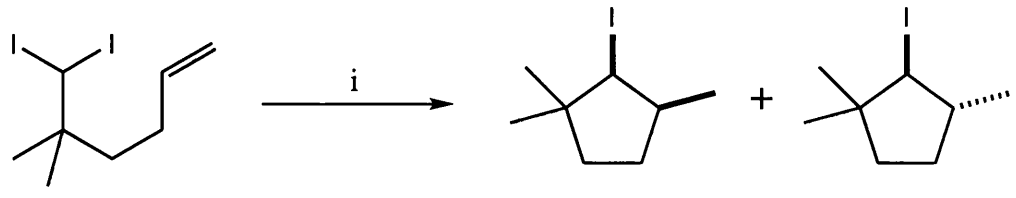
i) 7eq.$LiAlH_4$, THF, 25°C, 30h; ii) 10eq.*n*-$Bu_3SnH$, AIBN, 25°C, THF

**Scheme 25**

The 1 : 1 ratio occurs again. Reaction of (77) with sodium trimethyltin at 0°C also gives 1 : 1 stereochemistry[91]. Even at temperatures below those of thermally initiated reactions there is absolutely no diastereoselectivity in cyclisation of the $\alpha$-chloroalkyl radical.

### 1.3.2.5 α-Iodoalkyl Radicals

The production of the α-iodoalkyl radical may be achieved in similar fashion to the chlorine analogue, and the only examples of cyclisation have been published by the same researchers responsible for the work on chlorinated substrates. Complicated mixtures are again obtained when diiodides are treated with electron transfer agents such as LDA[92], magnesium[93], $NaSnMe_3$[91], and $NaPPh_2$[89]. Scheme 26 shows an example where the reaction is monitored before the initially formed cyclised products have had time to react further. After one minute, the other products which *may* have been derived from the cyclised material totalled less than 6%. Even assuming that all 6% were derived from the *trans* cyclised product there is still a clear preference for *cis* diastereoselectivity. This stereoselectivity was compared to that of the 6-hepten-2-yl radical closure (*cis* selective), and that of the corresponding 6-hepten-2-yl anion (*trans* selective) and this used as evidence for the SET / radical cyclisation mechanism. The fact that diastereoselectivity is possible at all is curious, and one might imagine that an atom as large as iodine would favour *trans* products if any. Little can be learned from this isolated example except that the cyclisation of α-iodoalkyl radicals appears to deserve more thorough investigation.



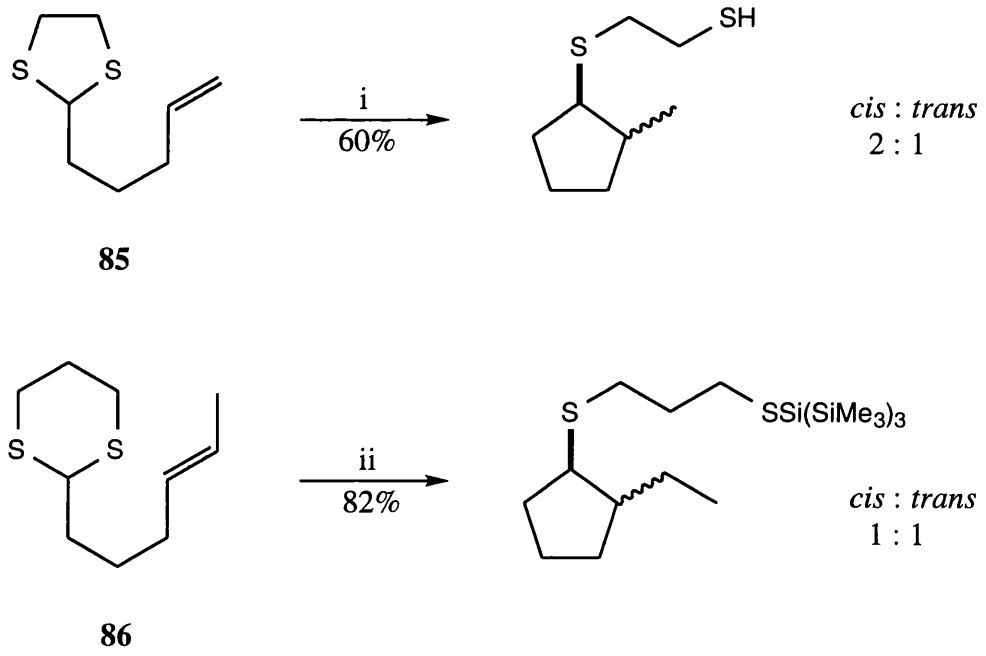

**83** ***cis*-84** : 43% ***trans*-84** : 25%

i) 3eq.Mg, THF, 25°C, sonicate, 1min

**Scheme 26**

### 1.3.2.6 α-Thioalkyl Radicals

There have been two examples of this type of cyclisation (scheme 27). In the case of the dithiolane (85)[94] moderate *cis* diastereoselectivity was observed at the temperature of refluxing benzene. Given the similarity of the starting materials it is difficult to rationalise why in the second case, at only 5°C higher temperature, the dithiane (86) gives a 1 : 1 mixture of cyclised products[95]. The stereochemistry of the reaction is fixed after the thioacetal is cleaved, so the methyl group on the alkene is apparently responsible for the difference. These two examples show the difficulty involved in attempting to predict the degree of diastereoselectivity of this type of reaction.

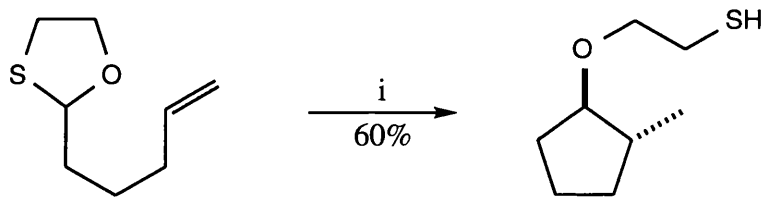



i) 1.2eq.*n*-$Bu_3SnH$, 0.04eq.AIBN, PhH, 80°C, 24h;
ii) 1.2eq.$(Me_3Si)_3SiH$, AIBN, PhMe, 85°C, 2.5h

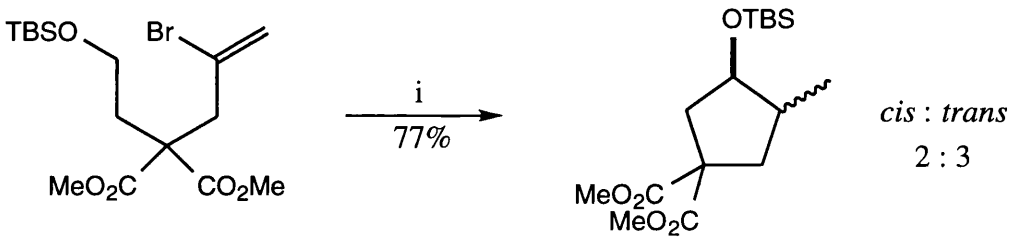
**Scheme 27**

### 1.3.2.7 α-Oxygen Substituted Alkyl Radicals

In this case, *trans* products are found to predominate. This marks an important difference to the cyclisation of alkyl-, thio-, iodo- and nitrogen-substituted radicals. The first example[94] is directly comparable to the cyclisation of the sulphur analogue ((85), scheme 27). Translocation of a radical has been used in the second example[96]. The yield is good in both cases. It is fortunate that a number of these cyclisations have been performed since this reversal of diastereoselectivity will, as we shall see, be useful for comparison with fluoroalkyl radical cyclisations.




**87**



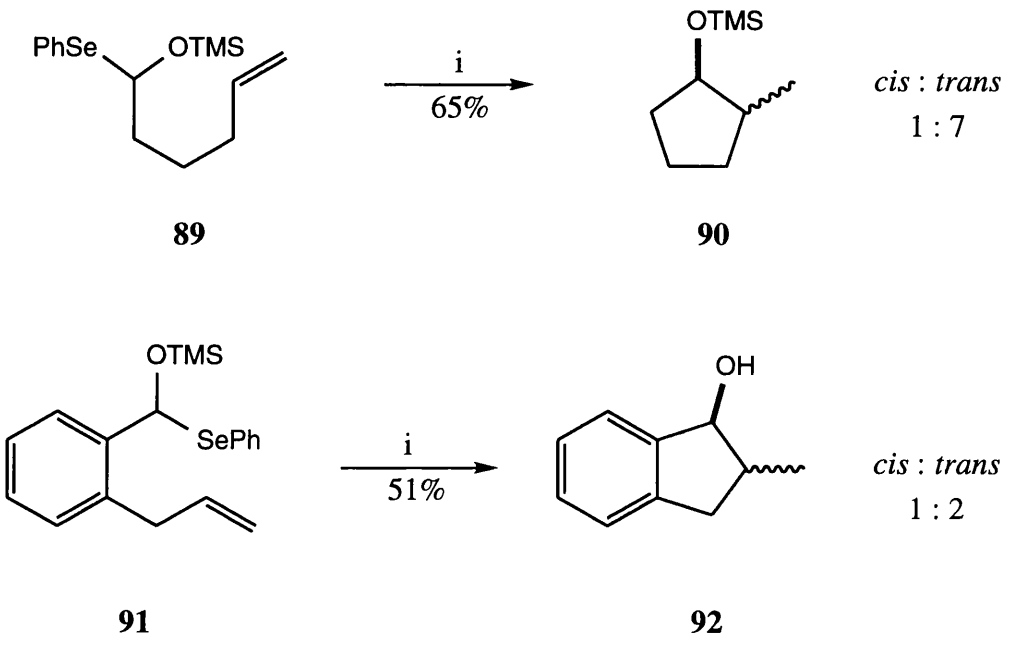

**88**

i) 1.2eq.*n*-$Bu_3SnH$, 0.04eq.AIBN, PhH, reflux, 24h;
ii) 0.1eq.*n*-$Bu_3SnCl$, 2eq.$NaCNBH_3$, *t*-BuOH, reflux

**Scheme 28**

Further examples (scheme 29) with the same diastereoselectivity were accompanied by a possible rationalisation[97]. Electrostatic repulsion of the oxygen atom and the developing negative charge of the new radical centre (fig. 6) was

proposed. Such an interaction would disfavour the *cis* product and is accentuated in this case because of the early transition state for cyclisation of an $\alpha$-silyloxy radical onto an alkene. In the case of (91), the diastereomeric ratio may be lower because the stability of the intermediate benzylic radical means the reaction could be reversible.




i) 2eq.*n*-$Bu_3SnH$, 0.1eq.AIBN, PhH, reflux, slow addition

**Scheme 29**

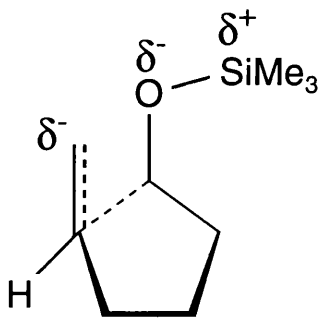


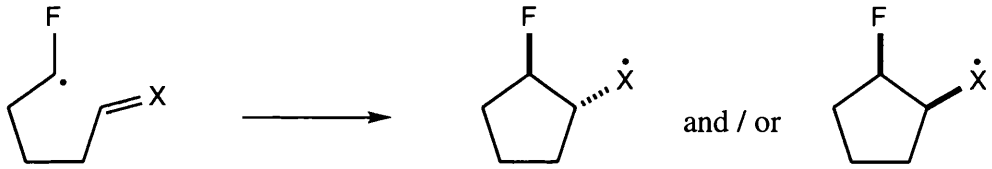

**Figure 6**

### 1.3.2.8 Summary

With the small sample of reactions at our disposal it is difficult to draw conclusions or suggest trends in the diastereoselectivity of the above reactions. We could suggest that good *trans* selectivity is seen for small, hard, highly electronegative substituents *i.e.* oxygen, whilst relatively poor *cis* selectivity is seen for other substituents which may be considered as $\pi$-donors. The $\pi$-acceptors seem to destroy all stereoselectivity whilst nitrogen substitution is the only type which imparts a strong *cis* preference.

## 1.4 Objectives of the Present Study

As we have seen in the previous section, despite extensive research into fluorination chemistry in recent years, the methods available can be unreliable and it is difficult to predict whether or not a certain approach will prove successful for a given substrate. We intend to investigate the generation and cyclisation reactions of the fluoroalkyl radical, with particular regard to the formation of cyclopentyl fluorides from 5-*exo*-trig ring closure (scheme 30).




**Scheme 30**

It was anticipated that such a ring closure would have interesting electronic and stereochemical features to investigate. We aim to build up a picture of the ability and preference of the fluoroalkyl radical to cyclise onto a variety of different radical acceptor groups C=X. The product of the cyclisation could be either of two diastereomers, or a mixture of both. There has been much discussion and rationalisation of the stereochemistry of alkyl radical cyclisation since it is dependent on the radical substituent (section 1.3). By careful analysis of our products we hope to add significantly to this area of knowledge.

Ultimately, we hope to use the cyclisation of fluoroalkyl radicals to generate pharmaceutically useful agents. Our method is one in which a pre-formed carbon-fluorine bond is introduced into another molecular fragment, the "fluorinated synthon" approach, and relies on the commercial availability of a variety of halofluorocarbons. Nucleosides are appealing targets for a synthetic procedure which generates a five membered ring. Fluoroalkyl radical cyclisation

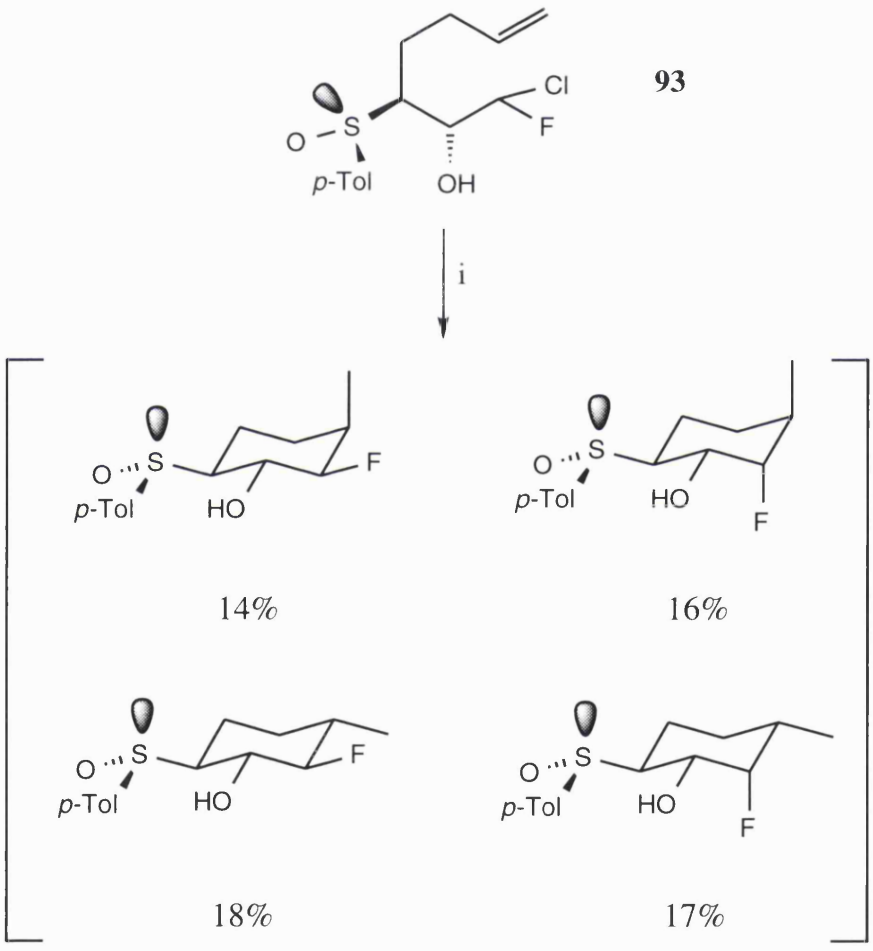
will hopefully prove to be an effective method of ring formation in future synthesis of nucleoside analogues which have a CHF or $CF_2$ group within a carbocyclic, or a modified ribosyl, ring.

# Chapter 2

# Results and Discussion

## 2.1 Introduction: Previous Studies on Fluoroalkyl Radicals

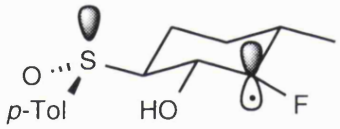
At the beginning of this project there had been no studies carried out on the fluoroalkyl radical (RCHF•). Since then, present study aside, there have been two important contributions to this field. The first was the 6-*exo*-trig radical cyclisation of chiral sulphoxides (scheme 31)[98].



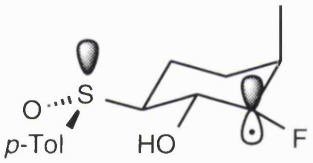

i) 1.5eq.*n*-$Bu_3SnH$, PhH, hv, 35°C

**Scheme 31**

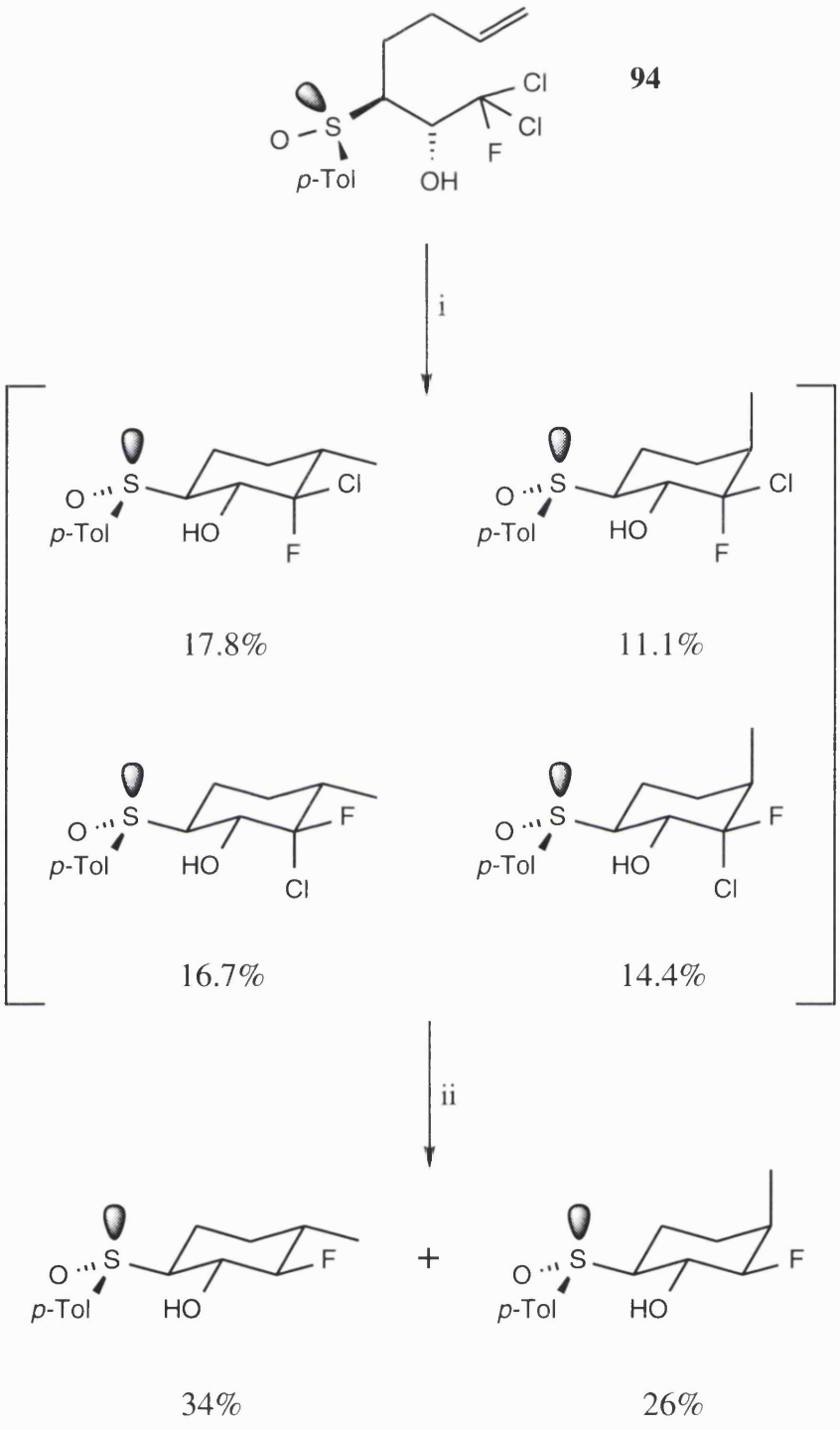
When (93) was treated with tri(*n*-butyl)tin hydride, good overall cyclisation yields were observed, but complicated mixtures of products resulted, even under the mild reaction conditions used for the photolysis. The selectivity problem was circumvented to a certain extent in a second publication. Improved selectivity for the desired product was obtained by cyclising the dichlorofluorosulphoxide (94) (scheme 32)[99]. In that case a chlorofluoroalkyl radical was actually cyclised, and the first formed product was a mixture of four diastereomeric chlorofluorocyclohexanes. Although isolable, under appropriate conditions the mixture could also be reduced *in situ via* a mixture of the two fluorocyclohexyl radicals (95) and (96). Stereospecific delivery of a hydrogen atom to the fluorocyclohexyl radicals completed the convergence of four intermediate products to just two. The problem of generating four diastereomeric products from the fluoroalkyl radical cyclisation was thus avoided. However, the diastereoselectivity of the radical step is not appreciably better than for the fluoroalkyl radical.




**95**




**96**




i) 0.1eqAIBN, 3.6eq.*n*-$Bu_3SnH$, PhH, 74°C, slow addition;
ii) 2eq.*n*-$Bu_3SnH$, PhH, 74°C, slow addition

**Scheme 32**

The second study was a measurement of the rate of addition of the 1-fluoropentyl radical to different alkenes[74]. The results are compared with those of related radicals (table 4). These results are important in understanding the behaviour of the fluoroalkyl radical and are directly relevant to the results of our own cyclisations (sections 2.4.3 and 2.4.4.)

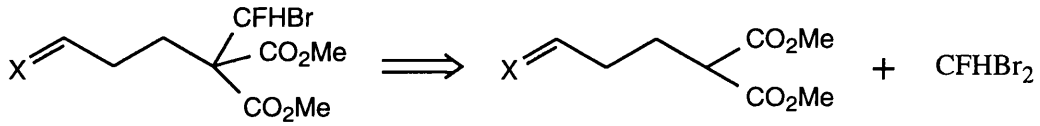
| Radical | $k_{add}/10^6$ $M^{-1}s^{-1}$ $C_6H_5CH=CH_2$ | $k_{add}/10^6$ $M^{-1}s^{-1}$ $C_6F_5CH=CH_2$ |
|---|---|---|
| $CH_3CH_2CH_2CH_2CH_2\cdot$ | 0.12 | 0.31 |
| $CH_3CH_2CH_2CH_2CHF\cdot$ | 0.46 | 0.70 |
| $CH_3CH_2CH_2CH_2CF_2\cdot$ | 2.7 | 3.1 |

**Table 4**

## 2.2 Model Cyclisation Precursors

### 2.2.1 Design of Cyclisation Precursors

The models chosen for the cyclisation study have three important features. There had to be a substituent on the fluorinated carbon which could be removed in a homolytic fashion to generate the fluoroalkyl radical. There had to be a radical acceptor: a multiple bond onto which the radical cyclisation could occur. Finally we needed a model system which would allow us to vary the multiple bond easily in order to investigate different acceptors. We chose the structure (97).



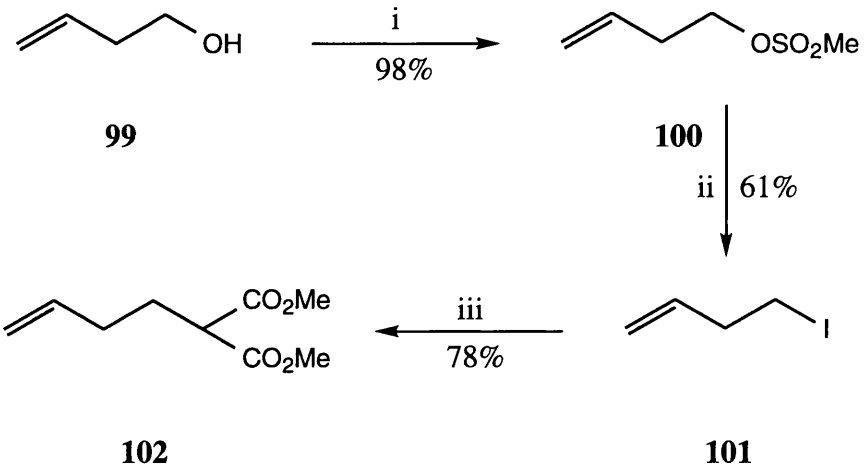

**97** **98**

**Scheme 33**

The carbon-bromine bond can be homolysed to form the radical, the C=X bond onto which cyclisation can occur is away from the other functionality and hence should be independently modifiable, and the dimethyl malonate unit provides a conceptually straightforward method for joining the two aforementioned fragments together. The disconnection initially chosen was such that the bromofluoromethylation reaction would be performed last (scheme 33). The entity (98) is therefore one of a series of molecules which we will refer to as bromofluoromethylation precursors. In the event, although several of these compounds had been prepared[100] for a study of difluoroalkyl radical cyclisation reactions, further work allowed yield optimisation and practical improvements as detailed below.

## 2.2.2 Synthesis of Bromofluoromethylation Precursors

Initially, the alkene (102) was prepared as shown in scheme 34.



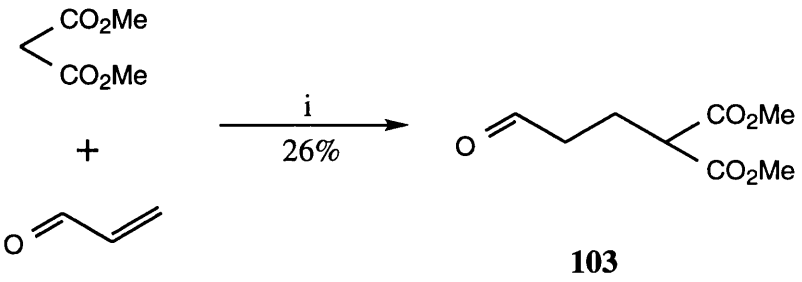

i) $Et_3N$, MsCl, DCM, -5°C-RT, 48h; ii) NaI, acetone, RT, 48h; iii) $NaCH(CO_2Me)_2$, DMF, RT, 40h

**Scheme 34**

This scheme is modified in three ways from that of Buttle[100]. The volatility of the iodide (101) caused the low yield from the second step. More thorough washing with water during work-up was necessary in order to remove acetone (which could not be done by evaporation). Loss of the iodide during evaporation of ether could be minimised by leaving some ether in the product. Use of the iodide contaminated with ether was found not to have a significant effect on the yield of the next step, so we adopted the procedure of evaporation to a saturated solution of ether in iodide (about a 10-15% ether by mass) and used $^1H$ NMR to determine the actual amount of iodide present. In this way, more alkylating agent was made available from the methanesulfonate. DMF was used as the solvent for the alkylation step instead of THF as it appeared to improve the reproducibility of the yield.

The remaining bromofluoromethylation precursors were to be made from the aldehyde (103) by a variety of Wittig-type reactions and a condensation.

The method of Warner and Moe can be used: acrolein adds in Michael fashion to dimethyl sodiomalonate to give the desired product (scheme 35)[101].

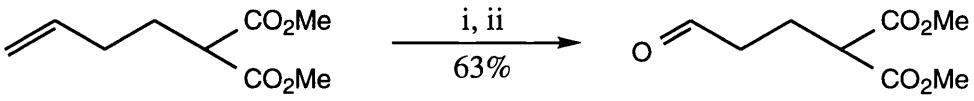



**103**

i) NaOMe, MeOH, 0°C-RT, 18h

**Scheme 35**

This aldehyde is purified by flash distillation, under reduced pressure, at about 200°C. Dimethyl malonate is particularly difficult to remove from the product and much is lost to this contaminant. Variable yields (from the distillation, and possibly because acrolein is supplied as only 90% pure) caused us to use ozonolysis of the alkene (102) instead (scheme 36). Although a longer procedure, this method proved more reliable and gave a product on which purification was not necessary: it was pure enough to use after a standard work-up procedure.

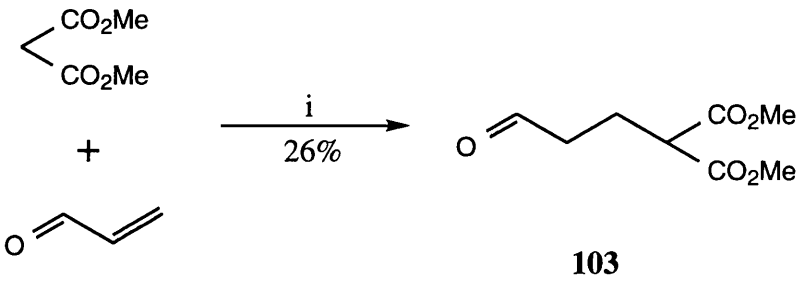



**102** **103**

i) $O_3$, MeOH, -78°C; ii) $Me_2S$, RT, 15h

**Scheme 36**

The method of Warner and Moe can be used: acrolein adds in Michael fashion to dimethyl sodiomalonate to give the desired product (scheme 35)[101].

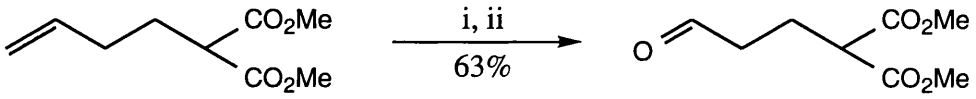



**103**

i) NaOMe, MeOH, 0°C-RT, 18h

**Scheme 35**

This aldehyde is purified by flash distillation, under reduced pressure, at about 200°C. Dimethyl malonate is particularly difficult to remove from the product and much is lost to this contaminant. Variable yields (from the distillation, and possibly because acrolein is supplied as only 90% pure) caused us to use ozonolysis of the alkene (102) instead (scheme 36). Although a longer procedure, this method proved more reliable and gave a product on which purification was not necessary: it was pure enough to use after a standard work-up procedure.




**102** **103**

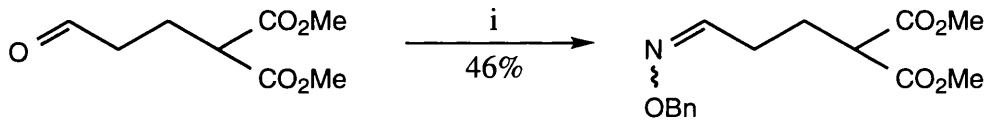
i) $O_3$, MeOH, -78°C; ii) $Me_2S$, RT, 15h

**Scheme 36**

with the additions separated by sufficient intervals for *in situ* generation of more ylid to occur. Whether this was due to an ylid solubility problem, or the protonation of the ylid by the acidic malonate proton of the aldehyde was not ascertained.

The *E*-alkene (105) was prepared using the stabilised Horner-Emmons reagent shown under Masamune-Roush conditions[104]. The *Z* isomer (106) was prepared using the method of Still and Gennari[105]; in this case the adduct formed between the phosphonoester and the aldehyde eliminates faster than it equilibrates to an adduct which would result in the more stable *E* isomer. The enol ether (107) was prepared as mainly the *E* isomer by a Wittig reaction.

The benzyl oxime ether (108) was prepared as previously except that powdered molecular sieves were included in the reaction mixture which alleviated the need to dry the ethanol beforehand (scheme 38). Although the yield was slightly lower than before, this method was also demonstrated to be very effective for generating a methyl oxime ether (scheme 47, section 2.3.6).

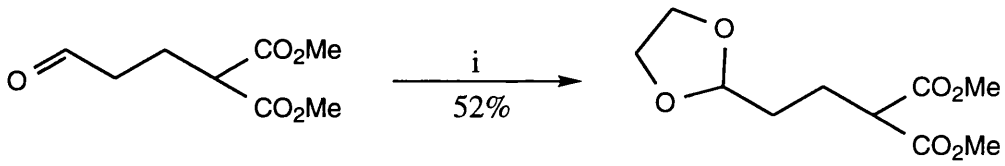



**103** **108**

i) $BnONH_2.HCl$, EtOH, py, sieves, reflux, 5h

**Scheme 38**

Bromofluoromethylation of certain malonate anions was not possible (table 5, section 2.3.1), and thus the protected aldehyde (109) (scheme 39) was also synthesised. We hoped that bromofluoromethylation of (109) followed by deprotection and further elaboration would allow us to access the models that direct bromofluoromethylation did not.




**103** **109**

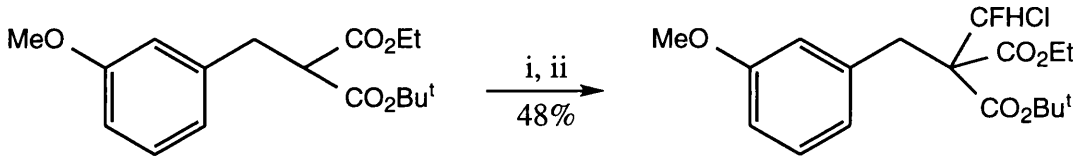
i) $HOCH_2CH_2OH$, *p*-TsOH, PhH, Dean-Stark, 6h

**Scheme 39**

## 2.3 Bromofluoromethylation Studies

### 2.3.1 Bromofluoromethylation *v* Bromodifluoromethylation

Other than in the preparatory work for this study, dibromofluoromethane has not been used as an alkylating agent. However, Schirlin has reacted malonate anions with dichlorofluoromethane[106].

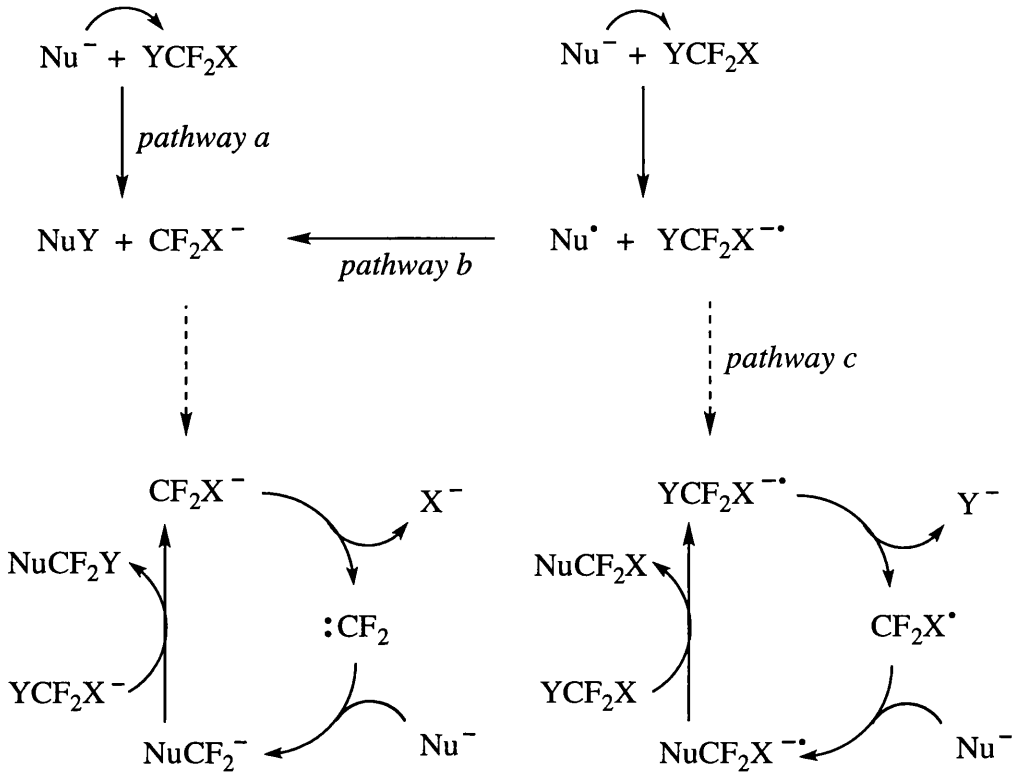



**110** **111**

i) NaH, THF, 50°C; ii) $CFHCl_2$, -20°C

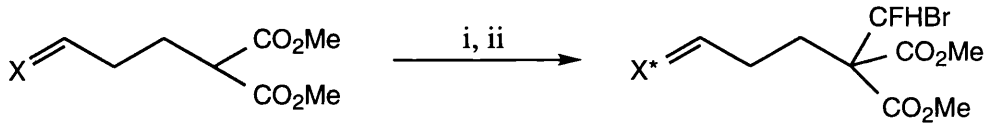
**Scheme 40**

As the brominated material was specifically required our efforts were concentrated on developing the bromine analogue of the reaction. Although at first sight, the overall sequence corresponds to a simple nucleophilic substitution reaction involving a malonate anion nucleophile and a halide anion leaving group, the pathway followed may be much more complex. Thus, Wakselman has made an extensive study[107-112] of the reaction of anionic nucleophiles ($Nu^-$) with perhalomethanes, with three possible reaction mechanisms as a result (scheme 41). The relevance of any of those mechanisms to the current bromofluoromethylation sequence is questionable: in the case of pathways a and b, the rate of decomposition of the anion $CFHBr^-$ to the carbene :CHF would be slower than for $CF_2X^-$[113]. The electron transfer chain pathway c is dependent on the redox properties of the fluorinated system, and a large change (such as F for H in our case) might also affect the ability of the substituted fluoromethane to accommodate an extra electron.




**Scheme 41**

No mechanistic information is available about the reaction of trihalomethanes, so we used Wakselman's work as a starting point. Our initial results are given (scheme 42, table 5). In all cases the malonate was added dropwise, in solution, to the base; this mixture was stirred at 0°C for 40 minutes before the dibromofluoromethane was added, after which stirring was continued at room temperature.




**102, 105-109** **112, 115-119**

i) NaH; ii) $CFHBr_2$

**Scheme 42**

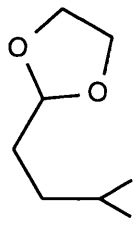
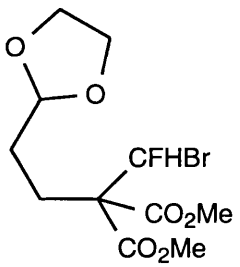
| S.M. | X | Solvent | Product | Product X* | Yield |
|---|---|---|---|---|---|
| **102** | $CH_2$ | THF | **112** | $CH_2$ | 28% |
| **105** | *trans*-$MeO_2CCH$ | THF | **115** | *trans*-$MeO_2CCH$ | 33% |
| **106** | *cis*-$MeO_2CCH$ | THF | **116** | *cis*-$MeO_2CCH$ | 14% |
| **107** | *cis/trans*-MeOCH | THF | **117** | *cis/trans*-MeOCH | 3% |
| **108** | *cis/trans*-BnON | ether | **118** | *cis*-BnON | 10% |
| **109** |  | ether | **119** |  | 2% |



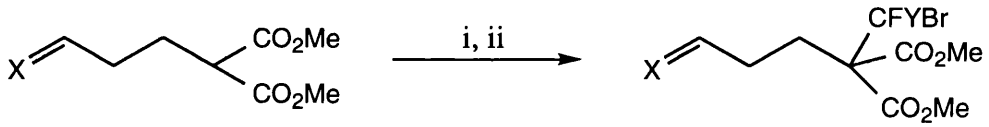


**Table 5**

The first and most significant observation which can be made is that this "simple" alkylation is, from a synthetic standpoint, a disastrous one in terms of yields of isolated products. Curiously, the *cis / trans* oxime ether mixture gave only a *cis* product. Clearly those malonates with oxime and the enol ether side chains were particularly bad substrates for the reaction. The protected aldehyde (109), which we

synthesised in the hope that it would allow us to get around the oxime and enol ether results, also gave an appalling yield of bromofluoromethylated material.

Comparison of the results with the corresponding bromodifluoromethylation reactions which had been carried out in an earlier study in the group[100] (scheme 43, table 6) reveal two features of interest which are worthy of comment. Firstly, the alkylation yields are uniformly lower for $CFHBr_2$ than for $CF_2Br_2$. Secondly, the yields are critically dependent on the nature of the apparently remote functionality present in the alkyl chain in the same way for the bromodifluoromethylation reaction as they are for bromofluoromethylation (*i.e.* poor for the oxime ether and enol ether). Although these reactions gave enough bromofluoromethylated material to cyclise for substrates (112), (115) and (116), we needed to improve the yields for the oxime ether and the enol ether.




i) NaH; ii) $CFYBr_2$

**Scheme 43**

| X | Yield; Y=H | Yield; Y=F |
|---|---|---|
| $CH_2$ | **112** : 28% | **119** : 90% |
| *trans*-$MeO_2CCH$ | **115** : 33% | **120** : 81% |
| *cis*-$MeO_2CCH$ | **116** : 14% | - |
| MeOCH | **117** : 3% | **121** : 56% |
| BnON | **118** : 10% | **122** : 50% |

**Table 6**

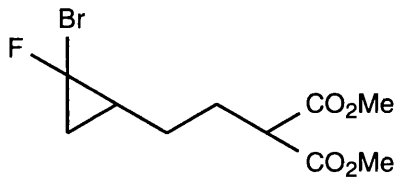
The results thus far suggested to us that there could be some mechanistic overlap of the two reactions, or at least that the generation and reactivity of each of the malonate anions determined the success of the reaction. With this in mind we attempted a series of experiments designed to alter the solvation of the malonate anion and / or the aggregation of those ions.

### 2.3.2 Solvation Effects in Bromofluoromethylation

As the mixture formed when the malonate ions were generated in THF was a milky white suspension, we tried to improve the solvation in a number of ways. Use of DMF, a dipolar aprotic solvent traditionally used for the second alkylation of a malonate, gave a translucent solution of the malonate anion but the yield of the reactions in that solvent were only 0% and 5% for (102) and (105) respectively. Another classical system for malonate alkylation is *tert*-butanol and potassium *tert*-butoxide. Using this system for (102) gave no product in our reaction, although the starting material could not be found after work-up. Use of benzene / toluene, potassium *bis*(trimethylsilyl)amide and 18-crown-6 to generate the "naked" malonate anion of (102) did give a respectable amount of product (112) (20%) and some starting material, although this may just have been as a result of the solvent and not necessarily the complexing crown ether.

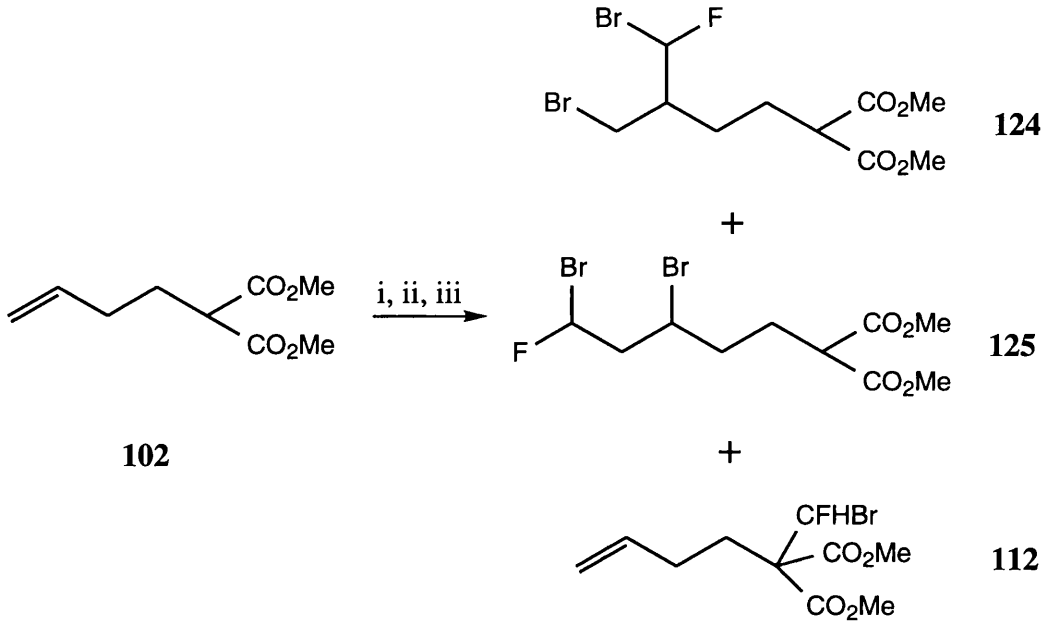
### 2.3.3 Radical *v* Carbene *v* Ionic Chain Mechanisms

Buttle suggested that cyclopropane (123) could be the identity of a major by-product from bromofluoromethylation, although no evidence for any cyclopropanated material was found in our investigation.




**123**

If this had been present, it would be evidence for bromofluorocarbene as an intermediate in the reaction. We made one attempt to create conditions more suitable for formation of carbene intermediates; copper powder was included in the reaction of (105) which was otherwise conducted in the same fashion as the others. This gave a trace of product, but most of the material was destroyed. The use of ether as solvent in subsequent cases has demonstrated that ether is slightly better than THF for bromofluoromethylation reactions. As mentioned earlier (section 2.3.1) the bromofluoromethylation reaction may take an entirely different course to halodifluoromethylations. We thus attempted one radical reaction as an alternative to the ionic chain / carbene mechanisms proposed (scheme 41). Triethylborane was added to the malonate anion, and a trace of air allowed into the mixture before dibromofluoromethane was added. The result was mainly the products expected from the straightforward radical addition to the alkene (124) and (125) in 34% yield, with a trace of the desired product (2%) and starting material (scheme 44). Although triethylborane cannot influence the electron transfer steps required in the chain mechanism operating in pathway c it is clear that either the capture of the bromofluoromethyl radical by malonate anion or the subsequent electron transfer to dibromofluoromethane is very inefficient. The absence of addition products analogous to (124) and (125) from other bromofluoromethylation reactions indicates that the mechanism of those is probably not similar to pathway c of scheme 41.




i) NaH; ii) $Et_3B$, DME; iii) $CFHBr_2$

**Scheme 44**

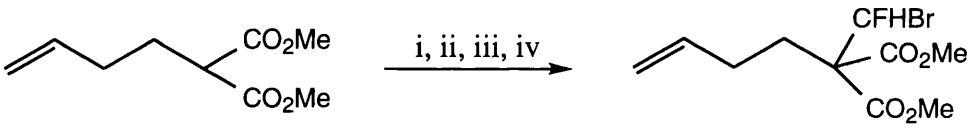
## 2.3.4 Reaction Time and Bromofluoromethylation Yield

The bromofluoromethylation reaction is difficult to monitor by tlc because the product and starting material cannot be distinguished easily. A standard reaction was set up and by taking aliquots at intervals of 26 hours, 38 hours and 64 hours, and working them up individually, we found that the *total* amount of material declined steadily through the reaction, and that the ratio of starting material to product peaked at 38 hours and then dropped away again. The only possible explanation for these observations is that the product is unstable to the reaction conditions. We investigated the use of elevated temperature to speed up the reaction. The dimethyl malonate ion must be generated with room temperature as an upper limit, so we continued to use our standard procedure until the dibromofluoromethane had been added, then allowed a short time at low

temperature before refluxing the material. The results were a slight improvement: mass balance was much higher, and the amount of product also increased. These results formed the basis of our final conditions for the reaction.

### 2.3.5 Final Conditions for Bromofluoromethylation

Our final conditions are complicated. After generating the malonate anion in ether (we found that this was not possible in benzene), the solvent is removed at 0°C and dibromofluoromethane and another solvent added to the gum obtained. The expense of dibromofluoromethane means that use of a large excess is undesirable. Benzene or heptanes were therefore added to the reaction mixture to increase its bulk, with no deleterious effect on the yield. The mixture is stirred for a while at low temperature, then refluxed (table 7, scheme 45).



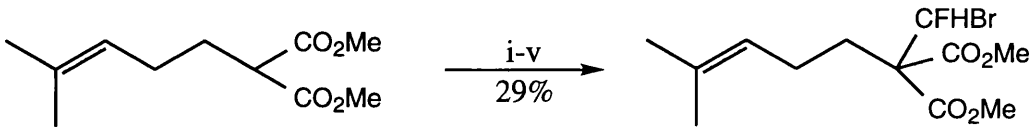

i) NaH, $Et_2O$, 0°C; ii) evaporate, 0°C; iii) $CFHBr_2$, solvent; iv) reflux

**Scheme 45**

| Solvent | Conditions | S.M. | Product |
|---|---|---|---|
| $CHFBr_2$ | 0°C, 30min; RT, 30min; reflux, 30min. | 20% | 43% |
| benzene | 0°C, 1h; RT, 1h; reflux, 11h. | 17% | 46% |
| heptanes | -78°C, 3h; reflux, 12h. | 23% | 49% |
| heptanes | -78°C, 3h; RT, 2days. | 14% | 34% |

**Table 7**

The similarity in yield and in amount of starting material is quite striking for the reactions where reflux was used. The similarity was taken as the final stage in our optimisation, and so we attempted to use the new conditions to bromofluoromethylate the dimethyl alkene (104) and the benzyloxime ether (108). The alkene gave respectable results (scheme 46), but the oxime gave no more success than we had had with the original conditions.




**104** **114**

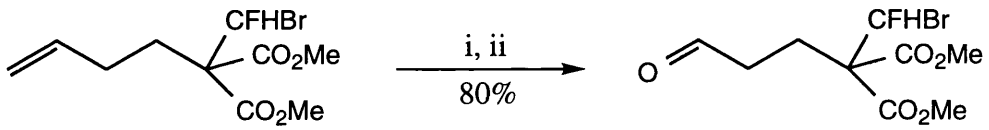
i) NaH, $Et_2O$, 0°C, 2h; ii) evaporate, 0°C;
iii) $CFHBr_2$, 0°C, 1h; iv) RT, 3h; v) PhH, reflux, 6h

**Scheme 46**

Although our optimised conditions failed to produce the required product (118) in good yield, we had generated a stock of the alkene (112), and were able to use this as a route to more fluorinated cyclisation precursors.

## 2.3.6 Dimethyl 1-Bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113)

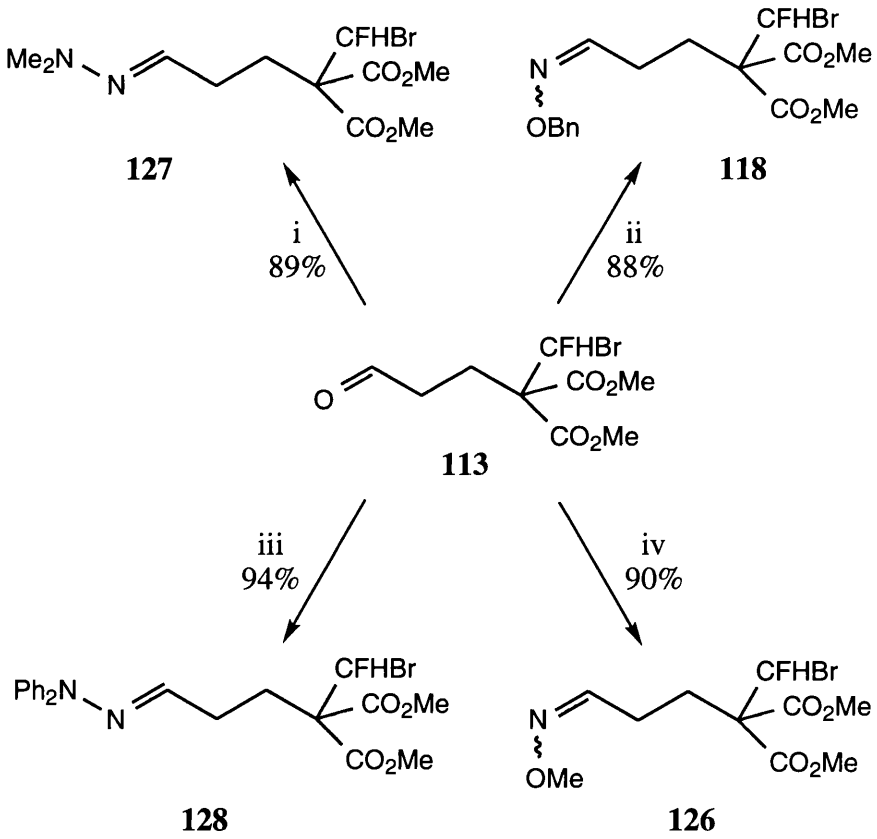
Our synthesis of the aldehyde (113) (scheme 47) allowed a series of condensations to produce cyclisation precursors which had C=N-X as the radical acceptor (scheme 48). The effect of adding the CFHBr group to the aldehyde is pronounced. Aldehyde (113) is stable to silica chromatography (*c.f.* (103)) and the yields of the oxime ethers are *ca.* 90%, whereas only 46% had been obtained for the aldehyde (103) without the CFHBr group.




**112** **113**

i) $O_3$, MeOH, -78°C; ii) $Me_2S$, RT, 18h

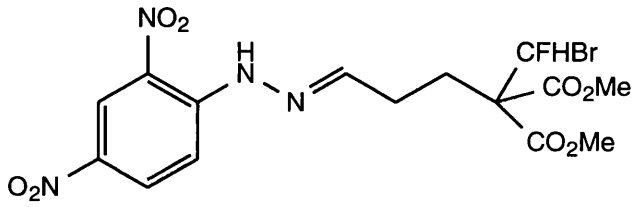
**Scheme 47**



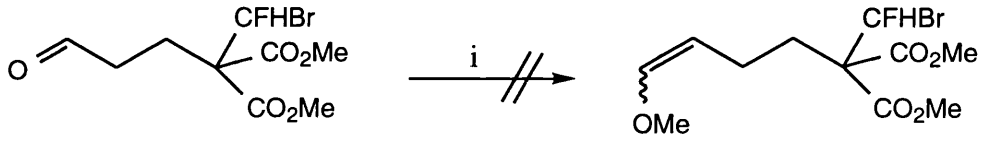

i) $Me_2NNH_2$, $Et_2O$, 0°C-RT, 3h; ii) $BnONH_2$.HCl, py, sieves, MeOH, reflux, 5h; iii) $Ph_2NNH_2$, MeOH, RT, 48h; iv) $MeONH_2$.HCl, py, sieves, MeOH, reflux, 5h

**Scheme 48**

The dimethylhydrazone (127) was prepared by a modification of Normant's method[114], and the diphenylhydrazone (128) by using conditions of Fallis[115]. The 2,4-dinitrophenylhydrazone (129) of (113) was also prepared: all the other models were oils, and having a crystalline derivative would allow bond angles and lengths to be determined from the crystal structure. Availability of these molecular parameters would open up the possibility of molecular mechanics calculations on our cyclisation. Finally, the Wittig reaction shown (scheme 49) was attempted, without success.




**129**




**113** **117**

i) $[MeOCH_2PPh_3]^+ Cl^-$, LDA, THF, -78°C-reflux, 6h

**Scheme 49**

Notwithstanding this failure, we had invested a lot of effort in developing the bromofluoromethylation reaction. The preparation of a total of eight model compounds was some compensation, and we turned our attention to carrying out the cyclisation studies.

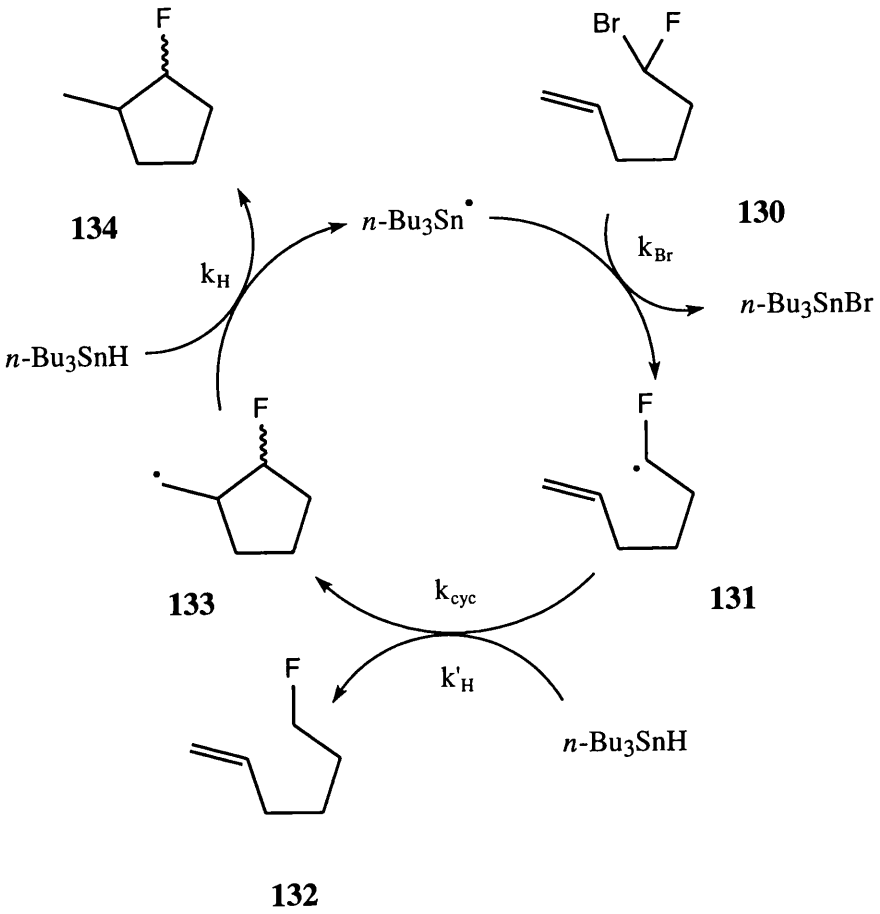
## 2.4 Fluoroalkyl Radical Cyclisation Reactions

### 2.4.1 Introduction

There have been many methods and reagents used for the generation of carbon centred radicals[116], and many of these can be used to carry out radical cyclisations. In our study we attempted to look at three of these techniques, chosen to represent a cross section of all available methods. The major portion of our work was carried out using the classical thermally initiated (by AIBN) tri(*n*-butyl)tin hydride system, with secondary studies on the electron-transfer induced cyclisation by samarium diiodide and a transition metal complex (cobaloxime) mediated cyclisation.

### 2.4.2 Cyclisations Mediated by Tri(*n*-butyl)tin Hydride

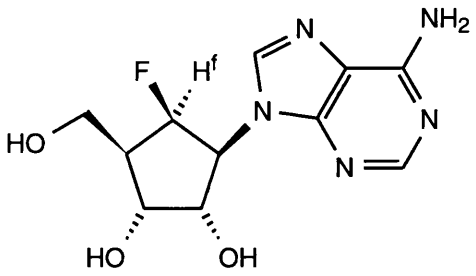
The mechanism of the cyclisation is shown (scheme 50). The rates of the various reactions are crucial. As $k_{cyc}$ falls for a given radical, the reduction of the radical directly by the stannane before cyclisation can begin to compete. For this reason the tri(*n*-butyl)tin hydride is added to the reaction mixture over a long period of time in order to minimise its concentration and hence prevent direct reduction products such as (132) forming. In order to minimise the amount of material lost by radical recombination, the initiator is also added steadily through the course of the reactions. These conditions would allow direct comparison with a previous study on analogous difluoroalkyl radicals[72].


F
Br
F
134
130
n-Bu3Sn•
kH
kBr
n-Bu3SnH
n-Bu3SnBr
F
F
133
131
kcyc
k'H
F
n-Bu3SnH
132

**Scheme 50**

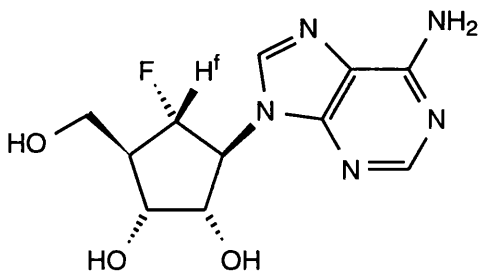
## 2.4.3 Results

*Cis-trans* assignments of the product diastereomers were made by comparison of $^3J_{H\text{-}H}$ coupling constants of the proton on the fluorinated carbon with those from diastereomeric fluorocyclopentanes (48) and (49), on which crystal structures had been obtained[117].




**48**

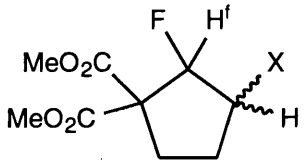
$^3J_{H\text{-}Hf}$ = 3Hz, 3Hz




**49**

$^3J_{H\text{-}Hf}$ = 5Hz, 7Hz

For our systems, only one coupling constant was available because of the two ester functions on $C^1$. The coupling constant measurement can in theory be taken from either of the proton signals concerned, but we chose to use the value measured from the hydrogen atom on the fluorinated carbon. The $C^3$ proton is coupled to at least two, and upto six other protons, and turns out to be a broad multiplet from which couplings cannot be measured by 400MHz NMR. When the protons have a *trans* relationship the coupling constant is greater (predicted by the Karplus equation). This means that in our case the *trans* diastereomer will have a larger coupling constant than the *cis*. Included in the table below is data for the molecules (139-142), the synthesis of which is described in sections 2.6.3 and 2.6.4.




**135-142**

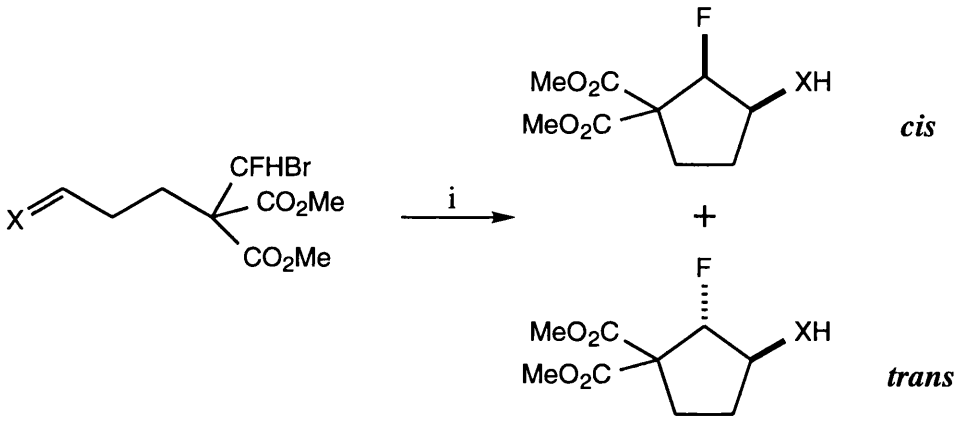
| | X | $^3J_{H\text{-}Hf}$ / Hz, *Cis* diastereomer | $^3J_{H\text{-}Hf}$ / Hz, *Trans* diastereomer |
|---|---|---|---|
| **135** | $CH_3$ | 3.0 | 5.5 |
| **136** | $CHMe_2$ | 2.5 | 5.0 |
| **137** | $CH_2CO_2Me$ | 3.0 | 4.0 |
| **138** | NH-$NPh_2$ | 2.0 | 3.0 |
| **139** | $CH_2Co(dmgH)_2py$ | - | 3.5 |
| **140** | $CH_2Br$ | 3.5 | 4.0 |
| **141** | $CH_2SPh$ | 3.0 | 4.0 |
| **142** | $CH_2SePh$ | 3.0 | 4.0 |

**Table 8**

## 2.4.4 Yields of Fluoroalkyl Radical Cyclisations

In the first instance, our initial concern was to measure the efficiency of the cyclisation process in terms of the isolated yields of the products as a function of the nature of the unsaturated acceptor. In the preparatory work for this study[100] three alkenes (112, 115, 116) were synthesised and cyclised using AIBN / tri(*n*-butyl)tin hydride (scheme 51, table 9). The reactions were however performed on a small scale because of the limited quantities of starting material available at a late stage of the thesis and the low isolated yields of cyclised products were therefore considered to be a potential source of error in terms of *cis* : *trans*

ratios. Gratifyingly, re-examination of these substrates on a larger scale led to improved yields and *cis* : *trans* ratios which mirrored the same trend as previously and probably give a more quantitative measure of the cyclisation process (table 10).




i) 1.1eq.*n*-$Bu_3SnH$, 0.1eq.AIBN, PhH, reflux, slow addition

**Scheme 51**

| S.M. | X | Product | Yield | *cis* : *trans* ratio |
|---|---|---|---|---|
| **112** | $H_2C$ | **135** | 23% | 1 : 3 |
| **115** | *trans*-$MeO_2CCH$ | **137** | 46% | 1 : 2 |
| **116** | *cis*-$MeO_2CCH$ | **137** | 52% | 1 : 2 |

**Table 9**

| S.M. | X | Product | Yield | *cis* : *trans* ratio |
|---|---|---|---|---|
| **112** | $H_2C$ | **135** | 48% | 1 : 3 |
| **114** | $Me_2C$ | **136** | 80% | 2 : 3 |
| **115** | *trans*-$MeO_2CCH$ | **137** | 65% | 1 : 2 |
| **116** | *cis*-$MeO_2CCH$ | **137** | 56% | 1 : 2 |
| **118** | BnON | - | 0% | - |
| **126** | MeON | - | 0% | - |
| **127** | $Me_2NN$ | - | - | - |
| **128** | $Ph_2NN$ | **138** | 71% | 7 : 3 |

**Table 10**

The results in terms of yields and ratios for the entire series are set out in table 10 and, for those substrates in which a radical chain ensued (*vide infra*) cyclisation products were isolated in generally good yield irrespective of the selection of a simple alkene, an unsaturated ester, or a carbon-nitrogen double bond. Furthermore, the products of direct reduction of the bromide without cyclisation were not detected in these reactions. We now examine the various radicophiles in detail.

The diphenylhydrazone (128) is our only isolated example of cyclisation onto a C=N bond. The dimethylhydrazone (127) gave products which decomposed during purification, although cyclisation may have occurred in this case because $^1H$ NMR of the crude reaction material showed distinctive signals attributable to the CHF proton; similar to those seen for the cyclised product of the diphenylhydrazone.

The $\pi$(C=N) bond is approximately 45kJmol$^{-1}$ stronger than the $\pi$(C=C) and the cyclised hydrazyl radical is relatively stable (fig. 7).

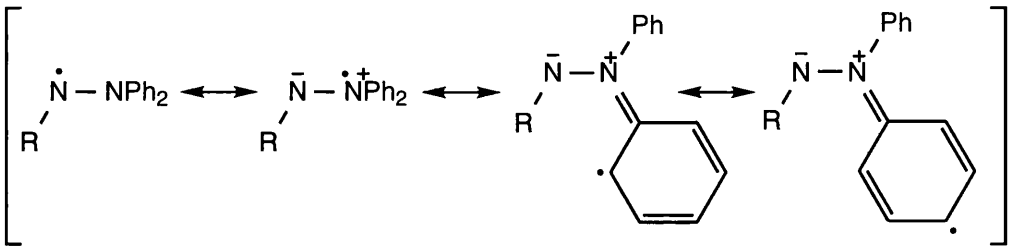
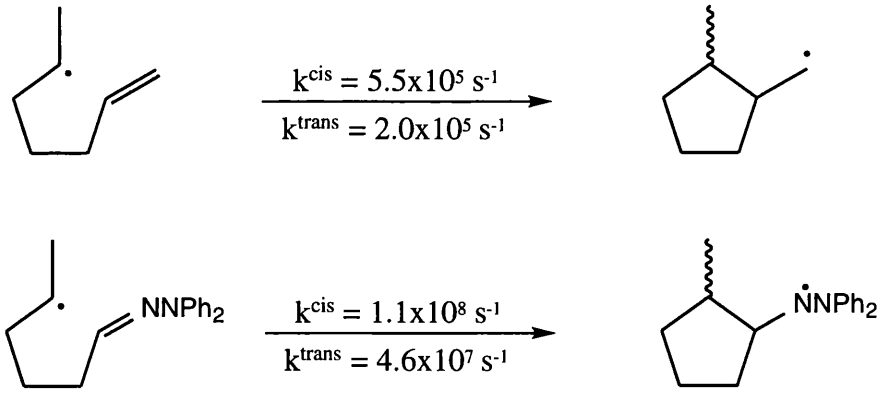


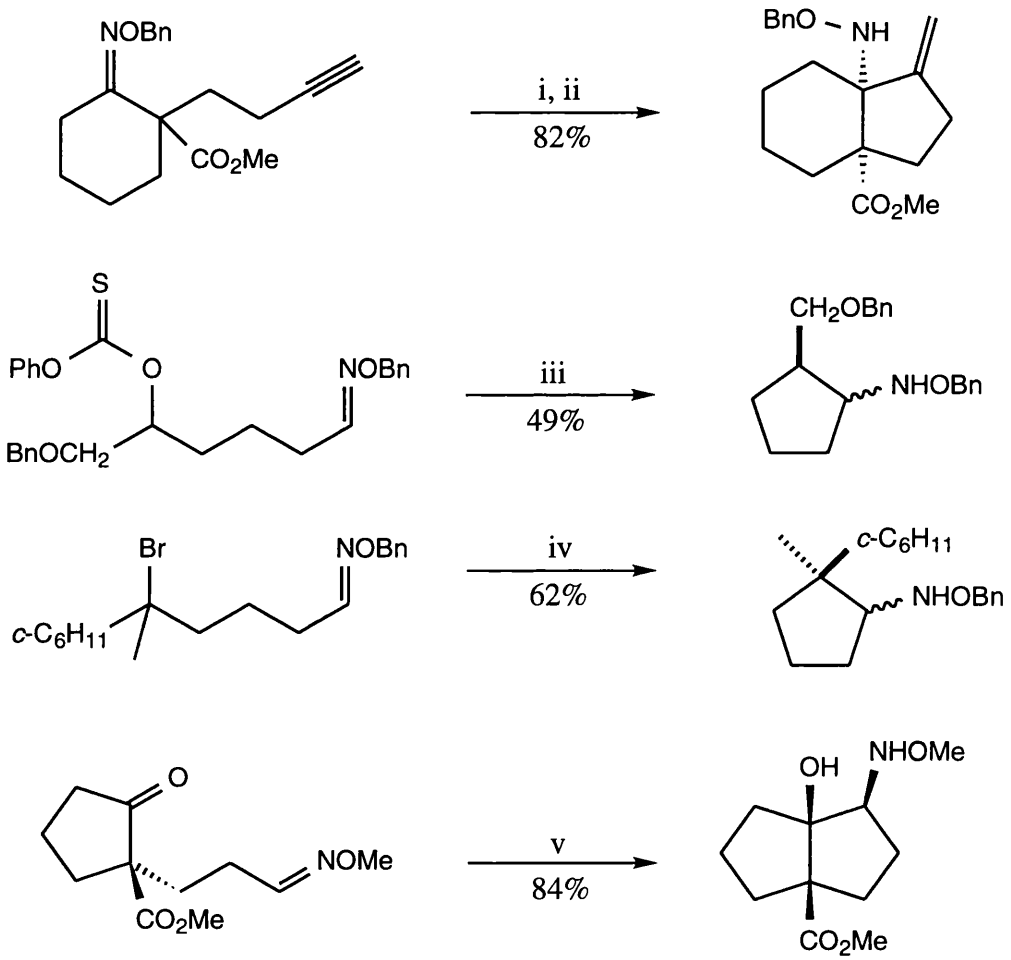
**Figure 7**

Fallis has determined rate constants for cyclisation onto a diphenylhydrazone (scheme 52)[118]. The overall rate of cyclisation onto the hydrazone is approximately 200 times greater than onto the alkene. This is what we would expect from a lower activation energy, to which the radical product stability contributes. The increase also takes the rate of cyclisation substantially above the rate at which a secondary alkyl radical is reduced by tri(*n*-butyl)tin hydride ($k=3x10^6\ s^{-1}$)[80]. This means that slow addition conditions may not be necessary for cyclisation onto diphenylhydrazones. The stereochemistry is also interesting, the preference of the dialkyl radical to cyclise onto alkenes in a *cis* fashion being maintained for cyclisation onto hydrazones. This aspect of these cyclisations is discussed further (section 2.4.5).




**Scheme 52**

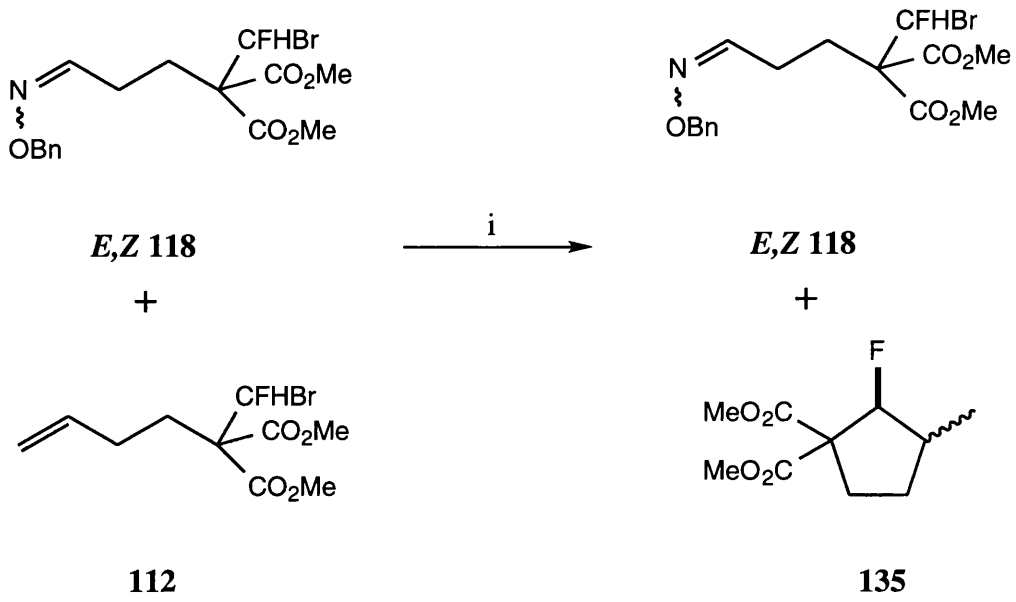
To our great surprise, when we attempted to cyclise the benzyl oxime ether (118) we only managed to isolate starting material. This was a curious result, particularly since cyclisation of radicals onto oxime ethers is well precedented and has been achieved under various conditions. Methods of producing and cyclising radicals onto oxime ether acceptors include hydrostannylation of an alkyne[119], tri(*n*-butyl)tin hydride / AIBN reduction of bromides and thionocarbonates[120] and electron transfer from zinc to an aldehyde / TMSCl mixture[121] (scheme 53).




i) 1.2eq.*n*-$Bu_3SnH$, 0.2eq.AIBN, PhH, reflux; ii) AcOH, MeOH; iii) 3eq.*n*-$Bu_3SnH$, 0.5eq.AIBN, PhMe, reflux; iv) 3eq.*n*-$Bu_3SnH$, 0.5eq.AIBN, PhH, reflux; v) Zn, TMSCl, 2,6-lutidine, THF, reflux

**Scheme 53**

The use of these methods indicates no particular problem associated with generation of a radical in a molecule containing an oxime ether, and that both benzyl and methyl oxime ethers are good acceptors. With no obvious explanation why the oxime should fail to react, we set about an investigation of the techniques used to perform the reaction and purify the starting materials. The tri(*n*-butyl)tin hydride was distilled and redistilled and the IR spectrum ($\nu_{max}$(Sn-H)=1800cm$^{-1}$) used to confirm the presence of hydride and to ensure that tin oxide contamination was not a factor. We checked the entire reaction set up in detail, even down to the height above the reaction mixture from which the AIBN and tri(*n*-butyl)tin hydride was introduced, and the bore of the needle used for its delivery. Extra precautions for exclusion of oxygen were taken but still no reaction was detected. The methyl oxime ether (126) was synthesised solely for the purpose of finding out if the benzyl group had any bearing on the unreactivity of the oxime. Again, though, only starting material could be isolated from the attempted cyclisation. It was conceivable that either some contaminant common to both oxime ethers was preventing the reaction, or that the cyclisation was failing for reasons unconnected with the substrate (which purely by chance happened to manifest themselves only in the oxime cyclisations). Both of these possibilities were ruled out by mixing equimolar quantities of the alkene (112) and the oxime ether (118) and subjecting that mixture to the cyclisation conditions (scheme 54).




**112** **135**

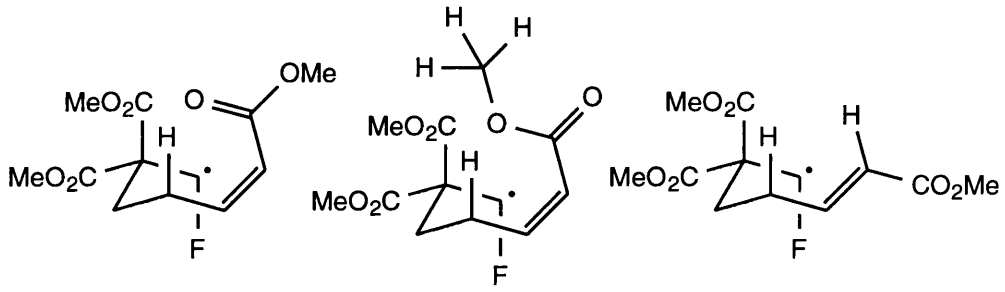
i) 1.1eq.*n*-$Bu_3SnH$, 0.1eq.AIBN, PhH, reflux, slow addition

**Scheme 54**

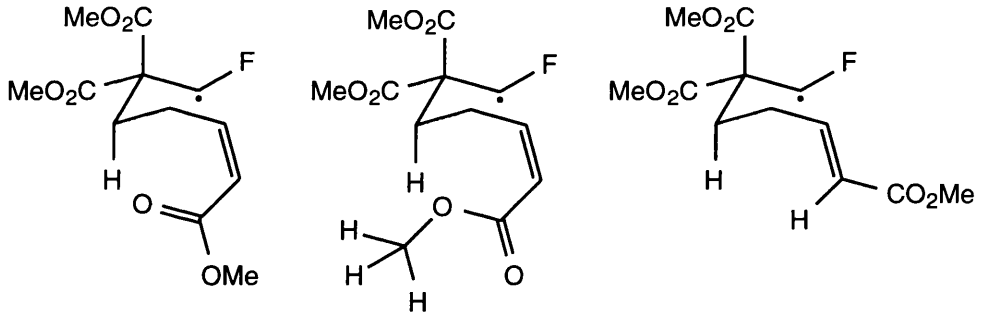
The result was that the alkene cyclised in exactly the same yield as it did on its own, while we recovered unreacted oxime ether starting material. There was sufficient tri(*n*-butyl)tin hydride to allow both entities to react, and the result indicated that inhibition of radical chains is also not occurring otherwise the alkene cyclisation yield would be lower than expected. We still have no explanation whatsoever for these observations, beyond the conclusion, implicit in the isolation of starting material rather than the reduced (*i.e.* debrominated) material, that in the case of the oxime ether there is a more favourable reaction pathway for the tri(*n*-butyl)stannyl radical than abstraction of the bromine atom. Even the possibility that reversible addition of stannyl radicals to the oxime double bond predominates and leads only to distannane is unconvincing.

Turning now to the two $\alpha,\beta$-unsaturated esters, it was of interest to note that the isolated yields were significantly different. This may be due to the crowding of the transition state: the electronic difference between *E* and *Z*

diastereomers is unlikely to be great, and probably not sufficient to cause a 9% yield difference. Figure 8 shows the transition state geometries which lead to the *trans* diastereomer of the cyclised product, but the same arguments apply to those which lead to the *cis* diastereomer.



**139a** **139b** **140a**



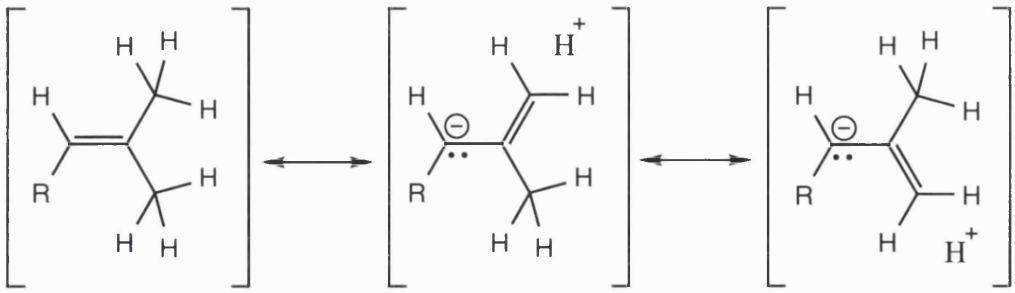
**139c** **139d** **140b**

**Figure 8**

From figure 8 we can see that when the alkene is lying in a pseudo-equatorial position of the chair-like transition state (139a, 139b), 1,3-diaxial-type interactions are possible between the *Z* ester and one of the malonate ester functions. Both *cisoid* (139a) and *transoid* (139b) conformations have this interaction, though it looks worse for the *transoid* form. When the alkene is positioned in a pseudo-axial fashion on a boat-like transition state (139c, 139d) there is a 'flagpole' interaction between the ester and the $\delta$-hydrogen. Once again, this interaction cannot be

avoided by *cisoid-transoid* interconversion. The *E* $\alpha,\beta$-unsaturated ester transition states are also shown (140a, 140b) for comparison.

Both $\alpha,\beta$-unsaturated esters gave cyclisation yields in excess of that obtained from the unsubstituted alkene (112). At first sight this behaviour hints at, and is consistent with, the idea that the fluoroalkyl radical reacts better with electron deficient alkenes. The high yield obtained from the diphenylhydrazone cyclisation may at first sight be taken as evidence to support this: however, care must be taken in this judgement. With a $\pi$-electron density (to a first approximation) essentially the same as that of the unsubstituted alkene (112), the dimethyl analogue (114) gives a reactivity greater than that of the $\alpha,\beta$-unsaturated esters. On the basis of these results it would appear that the fluoroalkyl radical reacts more readily with electron rich species (which, relative to the esters, the dimethyl alkene is); an apparent paradox. The improved yield of the dimethyl alkene cyclisation may be due to three factors. Primarily, stabilisation of the cyclised radical (1° for the unsubstituted alkene and 3° for the dimethyl alkene) makes the cyclisation more exothermic, and as a result probably lowers the energy of the (albeit reactant-like) transition state for the dimethyl alkene. This effect is best described by considering the VB transition state (*vide infra*). Secondly, in ethene there is a $\sigma$ node in the $\pi$ plane and therefore no interaction between the $\sigma$ and $\pi$ frameworks. A methyl substituent makes it possible for electronic interaction between the $\sigma$ and $\pi$ framework of the alkene, resulting in an increased electron density of the alkene, and a corresponding decreased electron density on the methyl substituents. This effect can be thought of as a mixing of the hydrogen 1s atomic orbitals (which are not in the nodal $\pi$ plane) with the $p_z$ orbitals of the alkene carbon atoms: this is equivalent to saying that the $(CH_3)\pi$ orbitals interact with the alkene $\pi$ orbitals. Classically, the non-bonded resonance structures of the valence bond approach are used to demonstrate the effect, and give rise to its name "hyperconjugation" (fig. 9).



Valence Bond Treatment of Hyperconjugation

$(CH_3)\pi$-(C-C)$\pi$ interaction $(CH_3)\pi$-(C-C)$\pi$* interaction

MO treatment of Hyperconjugation

**Figure 9**

It is important to note that while both approaches show a net strengthening of the bonds to the alkene substituents and weakening of the alkene $\pi$ bond itself, only from the MO picture do we see that the energy of the alkene HOMO and the LUMO both increase (fig. 10). The importance of this consideration becomes evident when we look at the MO diagrams used to explain why radicals react preferentially with either electron rich or electron deficient alkenes (figs. 2a, 2b, section 1.2.1).

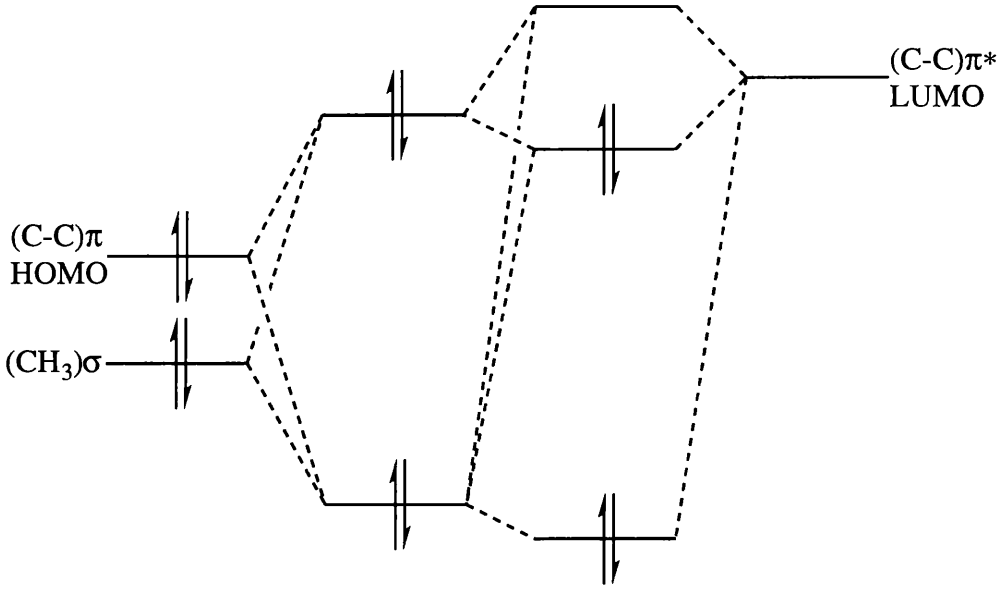



**Figure 10**

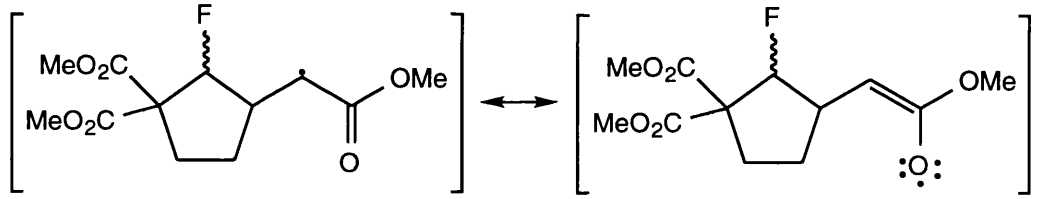
From the results of the alkene (112) and its dimethyl analogue (114) our radical might initially appear to be one of a low SOMO energy. A strong piece of evidence to support this is a theoretical study of SOMO energies for various substituted methyl radicals[84] (table 11). The fluoromethyl radical has indeed a very much lower SOMO than most other similar radicals.

| Radical | $\cdot CH_3$ | $\cdot CH_2NH_2$ | $\cdot CH_2OH$ | $\cdot CH_2F$ |
|---|---|---|---|---|
| $E_{SOMO}$ / eV | -10.273 | -8.154 | -9.839 | -11.306 |

**Table 11**

The problem with using the yields of our cyclisations to make this judgement about SOMO energy cannot be escaped. The yield is essentially a function of how well the propagation steps of scheme 50 fit together to produce long chains. Thus an increase in the rate of cyclisation would not necessarily lead to an increase in yield. For example, if the rate of abstraction of a hydrogen atom from the tin hydride by

the cyclised radical is reduced, chain propagation will not be as effective and the yield may be lower even though the radical is reacting much more effectively with the acceptor. Making the assumption that the rate of reduction of the cyclised radical is not important in determining the yield of cyclised product has allowed us scope for interesting discussion. In the case of the dimethyl alkene (114), the yield is high therefore we know that not only do we have very good chain propagation, but we can also say that the cyclisation of the fluoroalkyl radical onto an alkene with increased LUMO and HOMO energies is very effective (hence the radical should be described as having a low SOMO). Assessment of the effect of the methoxycarbonyl group on the HOMO and LUMO energies has been avoided, but consideration of those cyclisations is instructive. The reason the $\alpha,\beta$-unsaturated esters give an impression that the radical reacts better with electron deficient alkenes may be due to the resonance in the radical produced (fig. 11).




**141a** **141b**

**Figure 11**

This type of resonance stabilises the radical (*e.g.* BDE of H-$CH_2CO_2H$ is 416kJmol$^{-1}$, 441kJmol$^{-1}$ for H-$CH_3$) and lowers the transition state energy for the cyclisation. Thus, using $2k_a/k_e$ values for addition of radicals to substituted alkenes (table 12) we see that both high SOMO and low SOMO radicals react many times faster with butadiene than with ethene. Resonance has been used to account for this reactivity[122]. Addition to acrylonitrile, in which the resonance is not as important

as for butadiene (fig. 12), follows a classic reactivity pattern with rates of addition governed by polar effects.

| | $CH_2=CH_2$ | $CH_2=CH-CH=CH_2$ | $CH_2=CH-CN$ |
|---|---|---|---|
| $2k_a/k_e$ ($CH_3\cdot$) | 1 | 8.1[64] | - |
| $2k_a/k_e$ ($CH_3CH_2\cdot$) | 1 | - | 34[123] |
| $2k_a/k_e$ ($CF_3\cdot$) | 1 | 20[122] | 0.72[67] |

**Table 12**

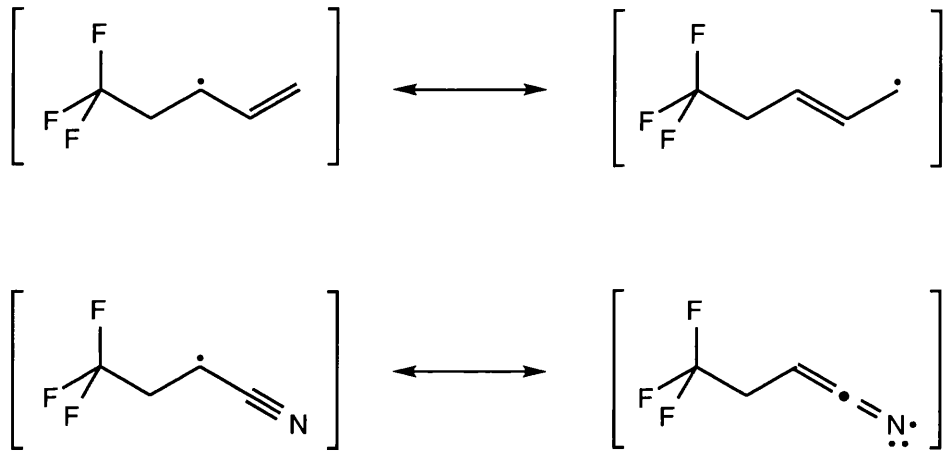
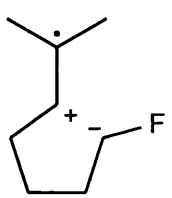
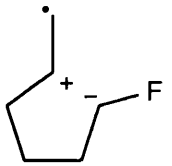


**Figure 12**

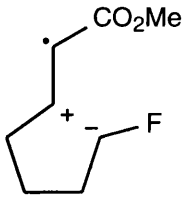
If we examine the valence bond transition states for the reaction (fig. 13), we can see the possible reason why our radical can react well with both the dimethyl alkene and the unsaturated esters.



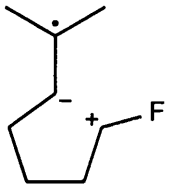
**142a**



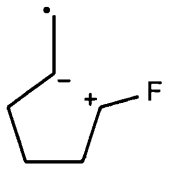
**143a**



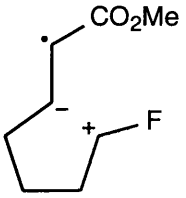
**144a**



**142b**



**143b**



**144b**

**Figure 13**

The radical centre has become a carbanion in the upper series, and a carbocation the lower series. For many radicals, one of those possibilities will be unfavourable leading to a low reaction rate with unsuitable alkenes. The possibility that fluorine can to a certain extent stabilise positive or negative charge on an adjacent carbon atom allows a low energy transition state to form in whichever way the alkene favours. Taking *iso*-butene (145), ethene (146) and methyl acrylate (147) as representative of our electron acceptors, we can see why the dimethyl analogue gives the best yield. Both the low I.P. and high E.A. (table 13)[124] are features which can contribute to a lowering of the transition state energy because the fluoroalkyl radical can accomodate them. If we imagine a nucleophilic radical reacting with such an acceptor, the low I.P. would not be a factor. Similarly, a strongly electrophilic radical would render the high E.A. of the alkene irrelevant to the transition state energy. The unsubstituted alkene has a higher I.P. and a less favourable E.A. hence the rate of cyclisation is reduced (we might expect a nucleophilic radical to maintain a good yield for this acceptor given that the E.A. of

the alkene is still quite high). Comparing this to the unsaturated ester however we see that a lowering of I.P. together with a reduction of E.A. does not adversely affect the yield of the reaction (which would be the case if the fluoroalkyl radical was electrophilic).


**145** **146** **147**

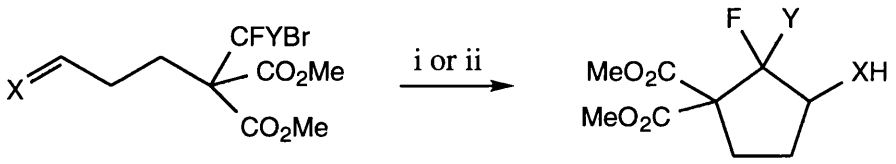
| alkene | I.P. / eV | E.A. / eV | cyclisation yield of analogous acceptor |
|---|---|---|---|
| **145** | 9.6 | -2.19 | 80% |
| **146** | 10.5 | -1.78 | 50% |
| **147** | 9.9 | -0.49 | 56%, 65% |

**Table 13**

This idea is consistent with the behaviour of other radicals. For electrophilic radicals a plot of log k *v* ($I.P._{alkene}$) is roughly linear, and nucleophilic radicals have a correlation of log k with ($E.A._{alkene}$). The ambiphilic radicals $(MeO_2C)_2CH\cdot$ and *t*-$BuCOCH_2\cdot$ give U-shaped plots of log k against either I.P. or E.A. Our data is insufficient to give useful plots.

As mentioned previously, the fluoroalkyl radical had appeared to have nucleophilic character (rate of addition of (*n*-BuCHF·) to $C_6F_5CH{=}CH_2$ is 1.5 times faster than to $C_6H_5CH{=}CH_2$). Perhaps it is worth considering the fluoroalkyl radical to be somewhat ambiphilic in that it is capable of reacting well with both electron rich and electron poor alkenes. Although we have not measured

the rate of addition of the fluoroalkyl radical to any alkenes, we think this conclusion is sound enough to take into account as further studies of the fluoroalkyl radical are being planned. The behaviour of the difluoroalkyl radical is also ambiphilic, and is strikingly similar to that of the fluoroalkyl radical in these cyclisations (scheme 55, table 14).




i) 1.1eq.*n*-$Bu_3SnH$, 0.1eq.AIBN, PhH, reflux, slow addition; ii) $SmI_2$, THF, DMPU, 25°C

**Scheme 55**

| X | % Yield Y=F | % Yield Y=H |
|---|---|---|
| $CH_2$ | 51[i] ; 53[ii] | 48[i] |
| *trans*-$MeO_2CCH$ | 65[ii] | 65[i] |
| BnON | 71[ii] | - |
| $Ph_2NN$ | - | 72[i] |

**Table 14**

## 2.4.5 Diastereoselectivity of 5-*Exo*-trig Fluoroalkyl Radical Cyclisation Reactions

Without giving the matter much thought, one would suppose that the closest mimic of the fluoroalkyl radical would be either the chloroalkyl or the alkoxyalkyl radical. From section 1.3.2 we can see that the oxygenated series seems to give the same diastereoselectivity, favouring *trans* products. Nobody has rationalised the absence of diastereoselectivity in the case of the chloroalkyl radical, but since the *cis* preference of the amidoalkyl and aminoalkyl radicals is predicted by the same rules as explain the *cis* preference of alkyl radicals[75,79] we will try to reason why those rules do not predict the correct diastereoselectivity for the cyclisation of the fluoroalkyl radical onto alkenes.

In our case, the *trans* product predominates, so the transition state is one in which the carbon-fluorine bond lies away from the alkene bond (fig. 14)[100].


**Figure 14**

The observation that the *cis* : *trans* ratio of product is the same for the models with *E* and *Z* methoxycarbonyl substitution of the double bond indicates that this substitution is too remote from the cyclisation centre to have an effect on the diastereoselectivity. Beckwith's theory about orbital interactions cannot account for the preference of our radical to cyclise to a *trans* product. A covalently bound fluorine atom has three effectively non-bonding pairs of electrons. These electrons would be in orbitals pointing out from the fluorine nucleus in the same way as the σ(C-H) bonds of a methyl group; C-F can be considered as isoelectronic and

isostructural with C-$CH_3$, so they share the same orbital symmetries. Thus on orbital symmetry grounds there is no reason why our radical should behave differently to an unsubstituted alkyl radical. The transition state geometry should be similar although the fluoroalkyl radical might be expected to have a pyramidalisation angle greater than that of a dialkyl radical, so there is no steric argument why the carbon-fluorine bond shouldn't lie parallel to the alkene bond. We have two possibilities: there may be a positive electronic or steric effect opposing the orbital interaction, or there might be a total loss or reduction of the effect Beckwith has proposed so that is not powerful enough to direct the products in the case of the fluoroalkyl radical.

The "positive interaction" approach was used by Buttle, who suggested that in the most favoured transition state the C-F bond may lie away from the alkene (fig. 14) because the high electron density on the fluorine atom could be subject to repulsive forces from the $\pi$ electron density of the alkene. This is a subtle effect for which the precise pyramidalisation angle of the radical is important. It is directly comparable with the explanation proposed for *trans* diastereoselectivity of $\alpha$-(trimethylsilyloxy)alkyl radical cyclisation[97] (section 1.3.2.7).

The "loss of Beckwith stabilisation" approach is easier to give a convincing analysis of. There are three reasons why the interaction may not be present for the fluoroalkyl radical. First, the carbon-fluorine bond is much shorter than the corresponding C-$CH_3$ bond of a dialkyl radical (for example, ($CH_3CHF\cdot$) has r(C-F)=1.144Å. and ($CH_3CH_2\cdot$) has r(C-C)=1.487Å). Given the line of approach of the radical to the alkene (fig. 3, section 1.3.1), this bond is probably short enough to ensure that the fluorine orbitals do not reach the "other end" of the alkene to interact with the $\pi^*$. Secondly, the increased angle of pyramidalisation may move the fluorine orbitals too far away from the $\pi$-bond for the secondary interaction to occur. This does explain why *cis* is not preferred over *trans* but cannot account for why *trans* is favoured over *cis*. Finally, the energies of the

orbitals of the F lone pairs and the C-H $\sigma$ bonds might be rather different; a close match between the alkene $\pi^*$ and the $\sigma$ orbitals is needed for efficient mixing to occur (for good mixing of orbitals, it is necessary to have the correct symmetry and a good energy match since mixing is a function of how closely matched the energies of the orbitals are). If the fluorine lone pairs were a lot lower in energy than the C-H bonding electrons then there would be a limited secondary orbital interaction in the case of the fluoroalkyl radical. It is possible that the resulting loss of stabilisation of the *cis* transition state could then mean the sterically less hindered *trans* transition state was lower in energy, and thus the favoured products would become *trans*. It is interesting to note that in the case of the amidoalkyl and aminoalkyl radicals, the orbital energies are still apparently matched well enough to allow the interaction.

Three of the four preceding ideas could account for the *trans* diastereoselectivity of both fluoro- and alkoxy- radicals. As stated earlier (section 2.4.4) cyclisation of dialkyl radicals onto hydrazones is also *cis* diastereoselective. We need to account for the fact that stereochemistry is reversed (*i.e.* favouring *cis*) when the fluoroalkyl radical is cyclised onto a hydrazone, but not when an alkyl radical is cyclised onto a hydrazone. Unsurprisingly, good diastereoselectivity is not obtained for cyclisation onto a hydrazone. With an apparently lower activation energy of cyclisation than the alkene (as judged from reaction rate), we might expect the hydrazone cyclisation to give less diastereoselectivity than an alkene. That it does not suggests that the difference in energy between the *cis* and *trans* transition states is greater for the hydrazone than for the alkene. If we compare the transition states for the hydrazone cyclisation, we see that the carbon-fluorine bond must lie parallel to the C=N bond. This immediately appears to rule out the previous argument based on repulsion of fluorine lone pairs by the $\pi$-electrons: the C=N would have almost the same repulsion as the alkene, the main difference being that an imino lone pair is now in the place of a C-H bond. The C=N bond is

slightly shorter than an alkene bond, which is certainly consistent with the arguments based on the fluorine lone pairs not being able to reach the remote end of the alkene to allow a secondary orbital interaction. Whether the small difference in length can account for such a large stereochemical swing is another consideration however. The (C=N)π* (*i.e.* LUMO) should be lower in energy than the (C=C)π*. If the fluorine "lone pairs" were of slightly lower energy than the $CH_3$ orbitals which Beckwith proposed were involved in the secondary orbital interaction, and the $CH_3$ orbitals between the alkene and hydrazone LUMO energies, then it could be possible that the mixing of the fluorine orbitals was efficient with the hydrazone but inefficient with the alkene (fig. 15). Hence the *cis* stereochemistry predicted by Beckwith's model is retained in the hydrazone case but is not in the case of the alkenes.

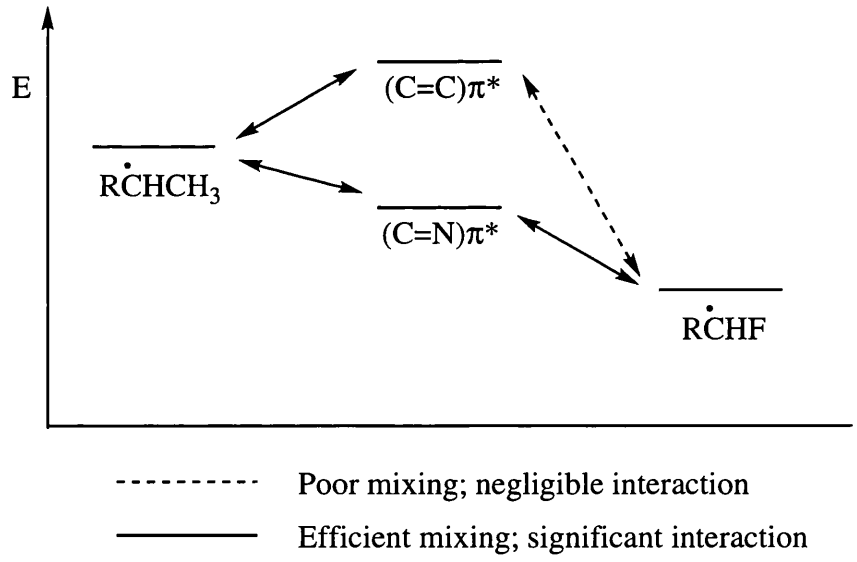
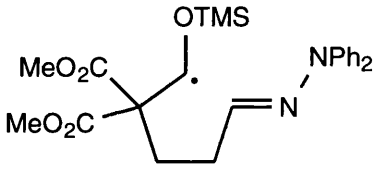



**Figure 15**

Unfortunately, this is a rather fanciful explanation which lacks any theoretical backing. Factors such as the change in geometry of the radical and steric effects will also be important, and perhaps explanation of this system is best left to high level MO calculations. Indeed, prediction of the correct result from this system may

prove to be an excellent test for high level computer simulations / models of radical cyclisation reactions. Given the similarity of diastereoselectivity of fluoroalkyl and alkoxyalkyl radicals it would be interesting to predict the outcome of the cyclisation of, for example, (148). Based on the results reviewed earlier (1.3.2.7) the *trans* appears probable, although from our study the *cis* product would seem just as likely to prevail.

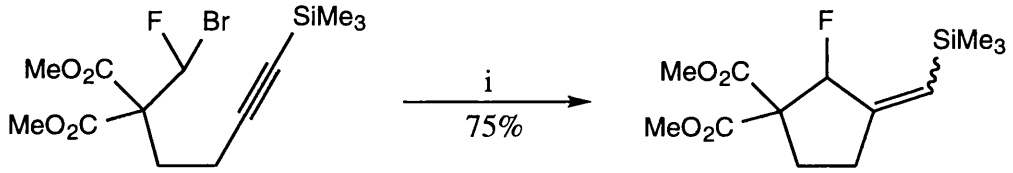



**148**

## 2.5 Cyclisations Initiated by Samarium Diiodide

### 2.5.1 Introduction

Samarium diiodide has been used to generate carbon centred radicals from aldehydes and halides. As a preparatory investigation for the present study, Buttle and Motherwell attempted the cyclisation of (149) using samarium diiodide (scheme 56)[100]. A mixture of diastereomeric cyclised alkenes together with unreacted starting material (in the ratio of 2:1:1) was obtained.

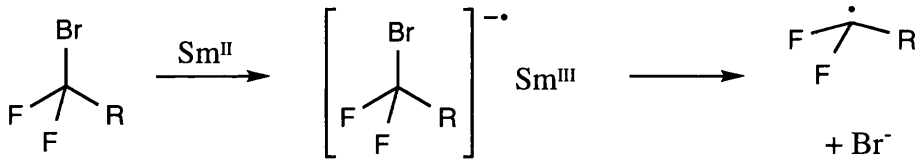



**149** **150**

i) $SmI_2$, THF, DMPU, RT

**Scheme 56**

Electron transfer from samarium diiodide to a halide produces a radical anion which then loses the halide ion to leave a neutral radical (scheme 57).



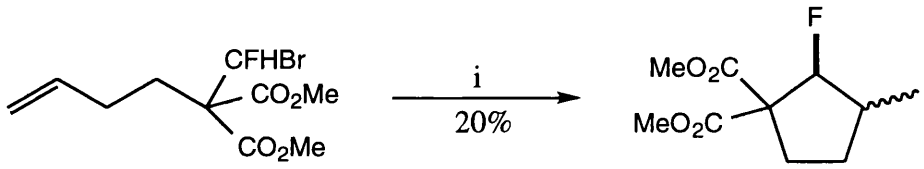

**Scheme 57**

It is important to appreciate here that not only is the stability of the radical to be considered, but the ability of the halide to accommodate negative charge is crucial to determining whether this method of radical generation is successful in any given

case. In a mixture of DMPU and THF, samarium diiodide can reduce a bromodifluoroalkane to a difluoroalkyl radical. The above attempt to generate a fluoroalkyl radical from this method gave significant amounts (~25%) of starting material as well as radical cyclisation product (150) despite use of a twofold excess of the samarium reagent. It seems logical that with one less halogen the halide would be rather more difficult to add an electron to. The choice of solvent system for the reaction is important. A good ion-coordinating solvent is required to solvate the samarium trication, and a chelating solvent such as DMPU serves this purpose well. The effect of good solvation on the electrode potential for the $Sm^{II}$ / $Sm^{III}$ / THF / HMPA system has been investigated since we finished our studies on samarium diiodide cyclisations[125]. The potential reaches its limiting value when four equivalents of HMPA are present. Using THF / DMPU is convenient because there is a clear end point: solutions of $Sm^{III}$ in THF / DMPU are brown in colour, while those of $Sm^{II}$ are purple. Hence when green samarium diiodide in THF is added dropwise to a solution of the material to be cyclised in THF / DMPU, first the brown colour develops then, when no more samarium is being oxidised, the purple colour persists.

### 2.5.2 Results

Addition of just 0.1 equivalents of samarium diiodide to alkene (112) caused the purple colour to persist, indicating that production of the radical was not occurring. Addition was nevertheless continued until two equivalents of samarium diiodide had been added. This procedure gave a low yield of cyclised material (*ca.* 20%) and some starting material (scheme 58).

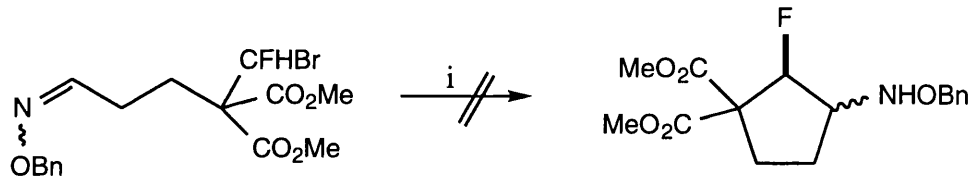



**112** **135**

i) $SmI_2$, THF, DMPU, RT

**Scheme 58**

When only 0.16 equivalents of samarium diiodide were added before work-up, we succeeded in isolating 70% of the starting material and a trace (~1%) of the cyclised product. These results indicate that although a small amount of samarium diiodide is involved in producing a radical, the majority is involved in another, destructive reaction. Once again however, the outcome of the reaction appeared to be critically dependent on the nature of the unsaturated acceptor. Thus, no cyclisation was found to occur for the benzyl oxime ether (118), and again most of the material was not recovered (scheme 59).




**118**

i) $SmI_2$, THF, DMPU, RT

**Scheme 59**

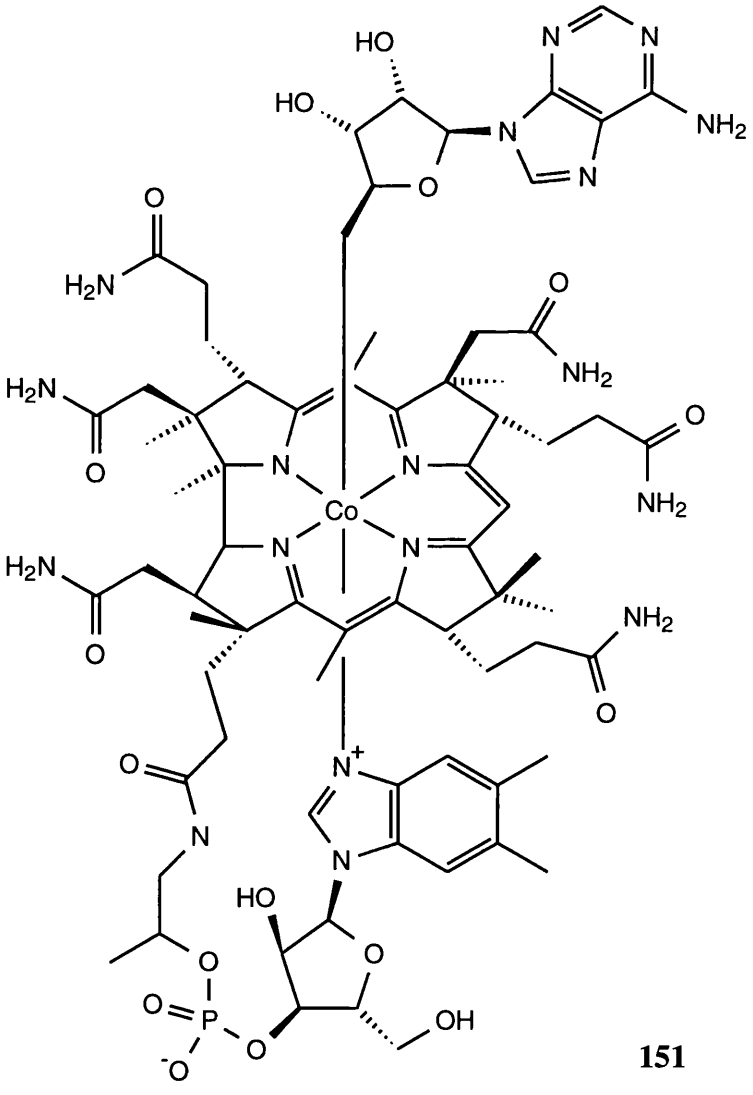
It is encouraging that some cyclisation product was formed from the alkene, and given the dependence of electrode potential on coordination, a study of different solvents to optimise the reaction conditions might lead to increased yield. At

temperatures below those of the previous AIBN / tri(*n*-butyl)tin hydride cyclisations the diastereoselectivity should be greater, although results of Fallis[118] suggest that this might only be a modest improvement until the temperature was substantially below 0°C. Given that our halide appears relatively unreactive towards samarium diiodide, it may not be possible to achieve a reaction at temperatures low enough to significantly improve the diastereoselectivity. At this point we found more encouragement from the cobaloxime approach to radical cyclisation, and so turned our attentions to that as a possible source of increased diastereoselectivity rather than developing the conditions for the samarium diiodide reaction.

## 2.6 Cyclisations Mediated by Cobalt

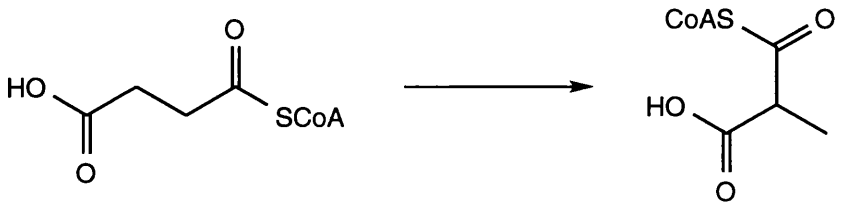
### 2.6.1 Introduction

The chemistry of cobalt centres around the +2 oxidation state, which is by far the most stable under normal conditions. However, when surrounded by ligands coordinated through nitrogen the +3 oxidation state is easily accessible. Vitamin $B_{12}$ (cyanocob(III)alamin) and coenzyme $B_{12}$ (5'-adenosylcob(III)alamin, 151) are cobalt complexes in which the cobalt is surrounded by four in-plane nitrogen ligands, with a neutral axial base and an anionic axial ligand.




**151**

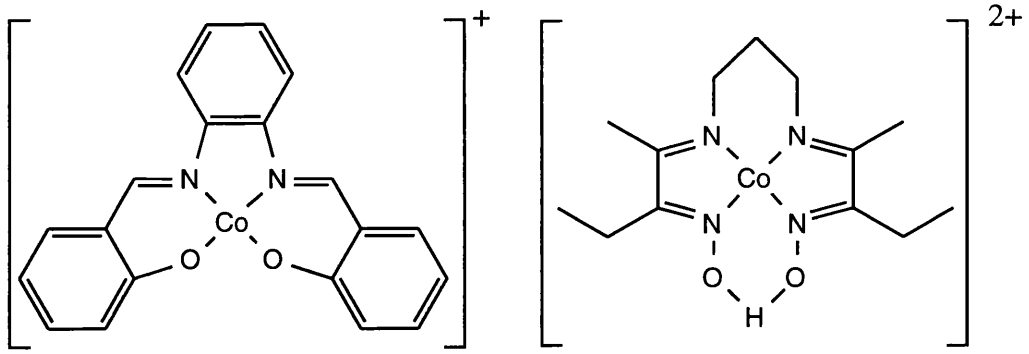
In mammalian systems, coenzyme $B_{12}$ is responsible for the methylmalonyl-coenzyme A mutase rearrangement (scheme 60)[126]. In other biological systems, related molecules (*e.g.* methylcob(III)alamin) carry out methyl transfer reactions.



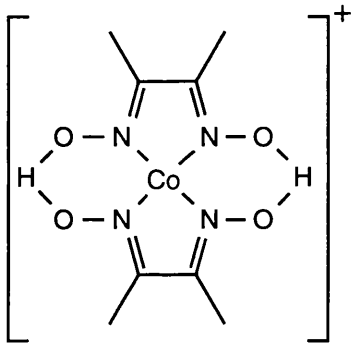

**Scheme 60**

Coenzyme $B_{12}$ is the only known example of a naturally occurring organometallic compound. Investigations into the mode of action of $B_{12}$ have involved the synthesis of various other complexes. All of these have a square planar cobalt environment with a neutral axial ligand and an anionic axial ligand. Some of the various types of complexes are shown below, without their axial ligands (fig. 16).

The Co(III)-C bond of the axial ligand of these complexes is quite weak, only about 70-140kJmol$^{-1}$[127], and can therefore undergo homolysis to generate a radical under thermolytic or photolytic conditions. Light from a tungsten filament (*i.e.* visible frequencies) is sufficient for photolysis of the bond. In 1980, this feature was used to perform a radical cyclisation (scheme 61)[128].

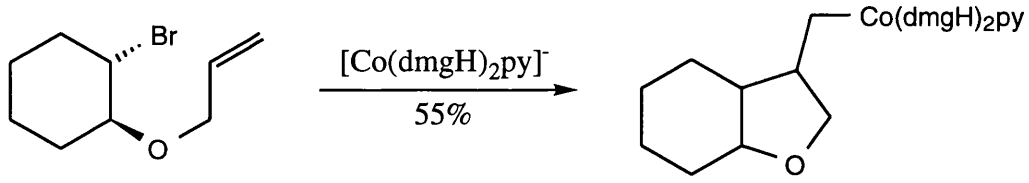


[Co(saloph)]$^+$ [Co{(DO)(DOH)pn}]$^{2+}$



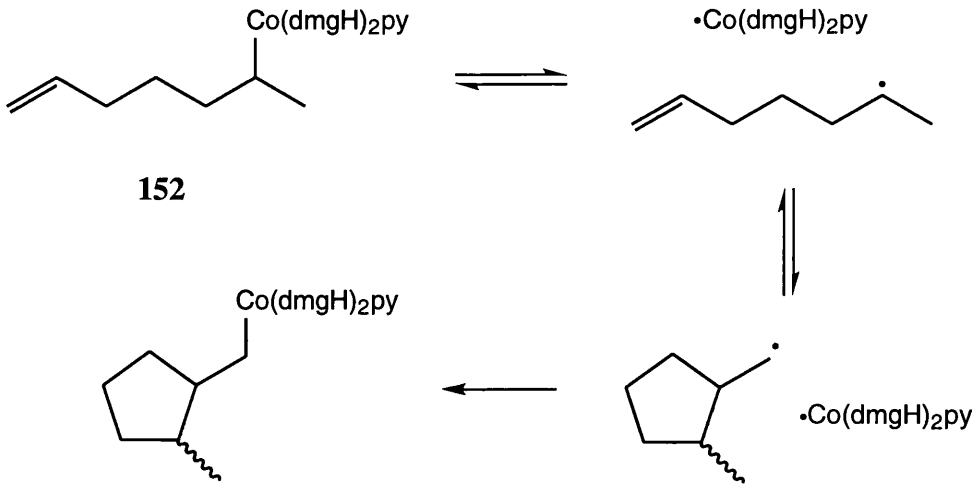
$[Co(dmgH)_2]^+$

**Figure 16**




**Scheme 61**

The mechanism of these reactions involves formation of the cobaloxime (152), which then undergoes C-Co homolysis, followed by radical rearrangement and recombination of the rearranged radical with the cobalt species to generate the final product (153) (scheme 62)[127].

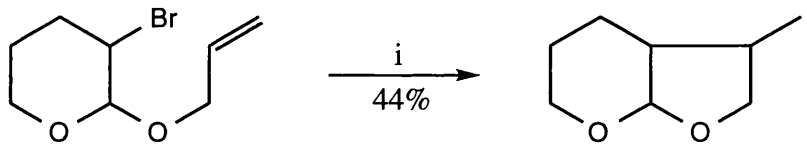



**152**

**153**

**Scheme 62**

More recently, such cyclisations have been carried out without the isolation of the alkyl cobaloxime. Using less than a stoicheiometric amount of chlorocobaloxime, and the starting bromide (154), electrolysis allows generation of the alkyl radical which then rearranges and abstracts a hydrogen atom from the solvent (scheme 63, fig. 17)[129].




**154** **155**

i) 50mol% $CoCl(dmgH)_2py$, $Et_4NOTs$, NaOH, MeOH, $e^-$

**Scheme 63**

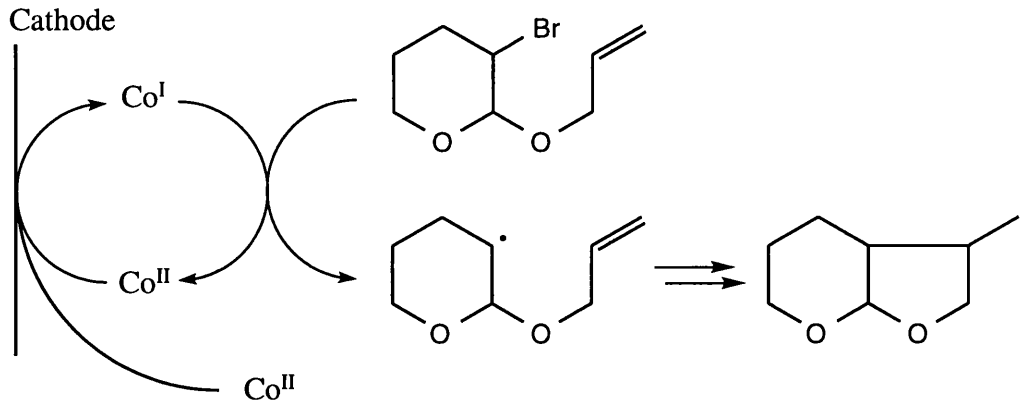
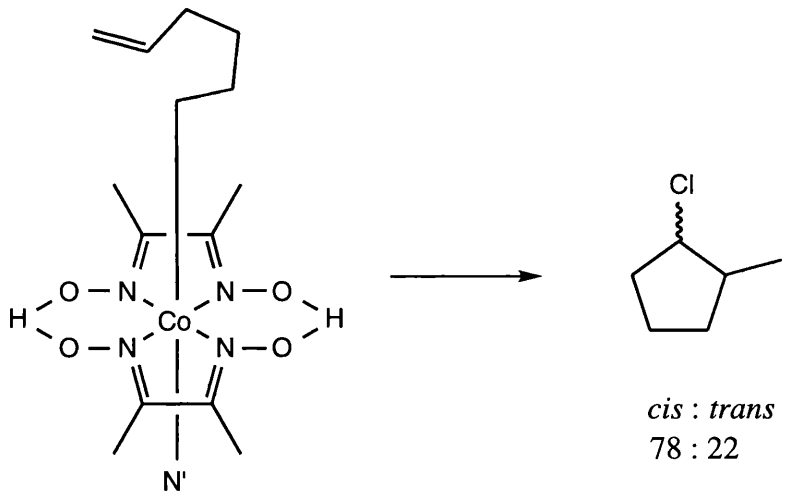



**Figure 17**

We thought that performing cyclisations using photolysis of this type of complex would give us a higher diastereoselectivity than was observed at 80°C (used for the AIBN / tri(*n*-butyl)tin hydride cyclisations). *Cis* / *trans* diastereoisomerism has been observed in the cobaloxime mediated cyclisation of the 5-hexenyl radical (scheme 64)[130].




*cis* : *trans*
78 : 22

**156** **157**

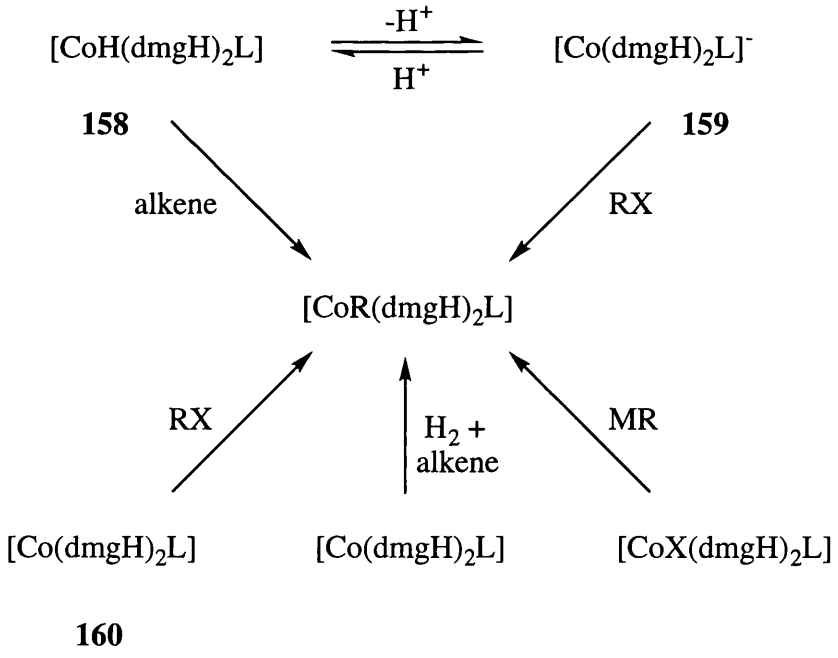
N' = 4-*t*-butylpyridine: i) hν, 26°C, $CCl_4$

**Scheme 64**

In a series of experiments, radicals generated from primary alkyl cobaloximes were found to exhibit the same behaviour in terms of product ratios, rates of cyclisation and intermolecular trapping as the corresponding free radicals generated by other means. Results obtained by Buttle[100] indicated that a compound similar to ours could be cyclised *via* its dimethylglyoxime complex (cobaloxime), so we settled on using that particular type of cobalt complex to perform the fluoroalkyl radical cyclisation.

## 2.6.2 Generation of Cobaloximes

Cobaloximes are usually generated by some type of substitution of the anionic axial ligand of a pre-formed complex (scheme 65)[126].




**Scheme 65**

As we had a bromide from which to synthesise the cobalt complex, we needed to use one of the intermediates (159) or (160). These two intermediates are closely

related, since in the presence of sodium hydroxide, (160) disproportionates giving (159) as one of the products. (159) generally reacts with a halide by $S_N2$.The large steric bulk of the complex (159) does not usually prevent nucleophilic attack even on sterically congested halides, hence the term "supernucleophile" for this entity. (160) reacts with halides in a radical fashion (scheme 66). Two equivalents of the cobalt complex are required for one of the halide in this case.

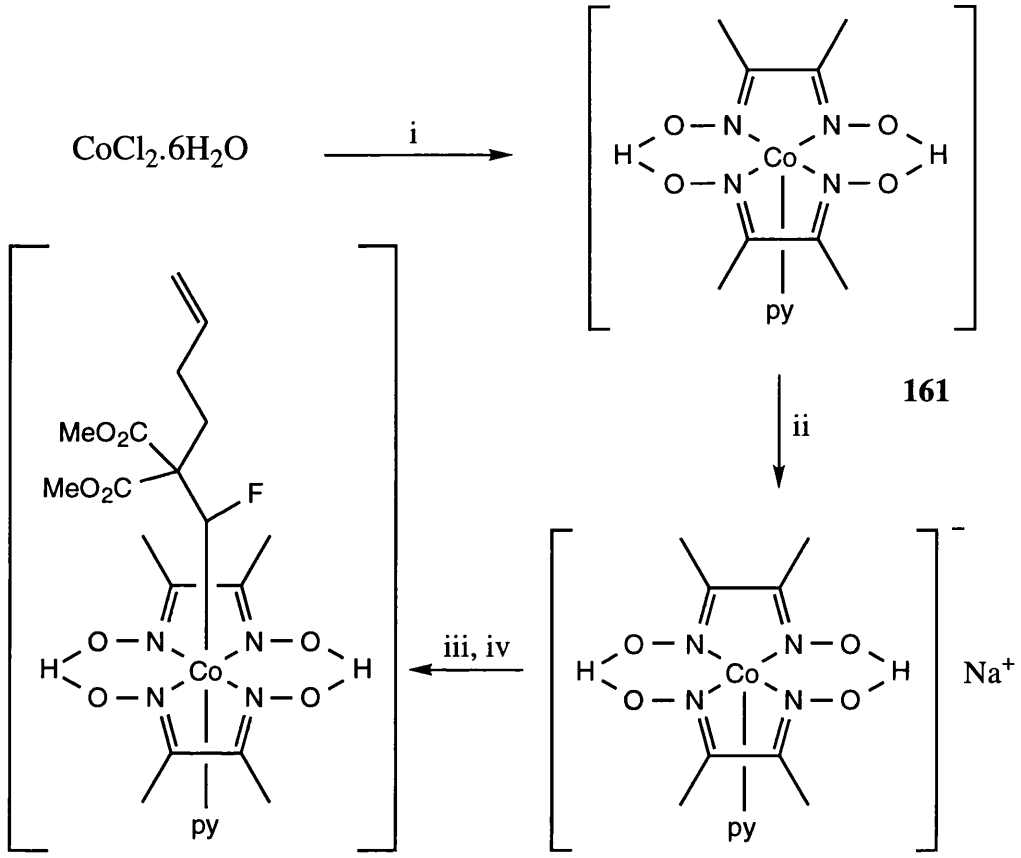
$$[Co(dmgH)_2L] + RX \longrightarrow [CoX(dmgH)_2L] + R\cdot$$

$$[Co(dmgH)_2L] + R\cdot \longrightarrow [CoR(dmgH)_2L]$$

**Scheme 66**

### 2.6.3 Cobaloximes from Fluoroalkyl Radical Precursors

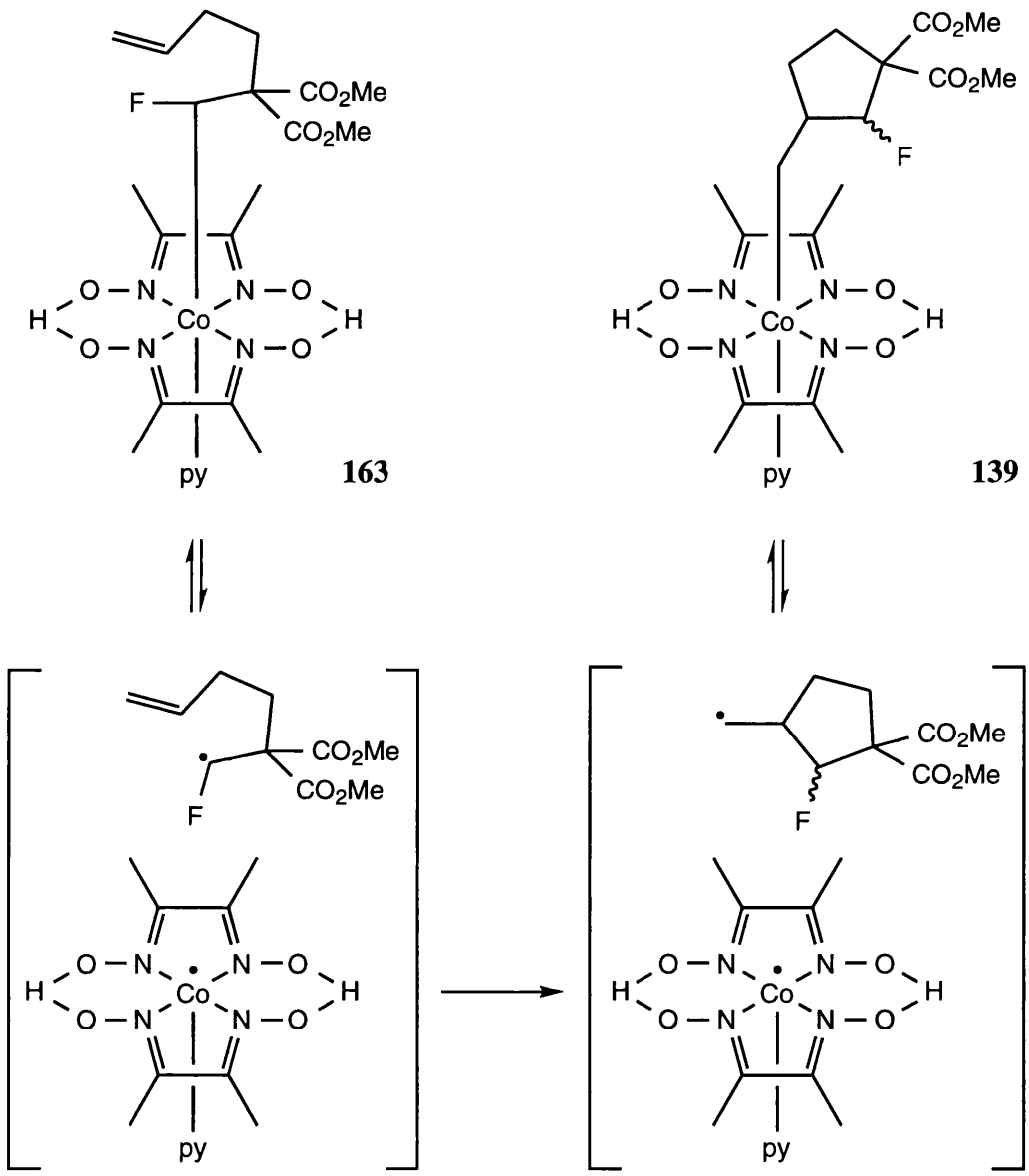
We used one of the simplest methods available[131] for generating sodium *bis*(dimethylglyoximato)pyridine cobaltate (I) ("supernucleophile", 162) and carrying out the halide substitution *in situ* (scheme 67).




i) dimethylglyoxime, NaOH, py, MeOH, 10min;
ii) $NaBH_4$, 10min; iii) (112), 2h; iv) $NaBH_4$, 18h

**Scheme 67**

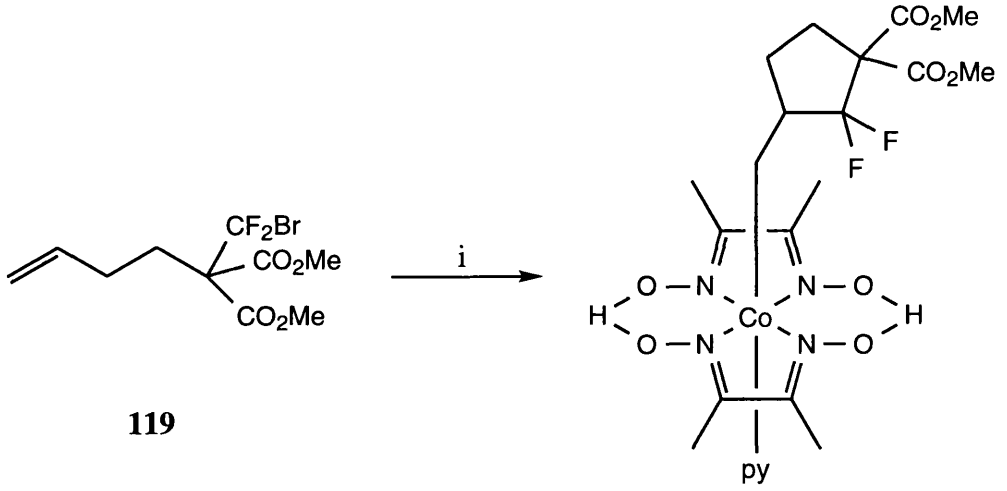
After work-up, a yellow-orange solid was isolated, but it did not correspond to the complex (163) expected from the reaction. Instead, we found that the product was one in which the cyclisation had already taken place (139) (scheme 68).



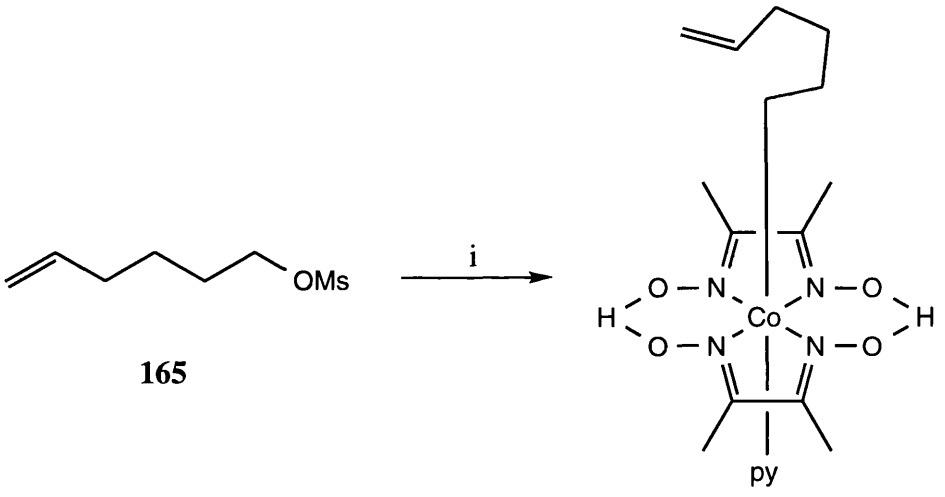

**Scheme 68**

Apparently, the homolysis of (163) had taken place *in situ*. The yield was respectable (59%), and the diastereomeric ratio of the product was 1 : 7. After recrystallisation this could be further increased to 1 : 8, in favour of the *trans* isomer. Buttle found a similar result for the analogous difluoroalkyl radical, where no aliphatic product (167) was found, although Branchaud had demonstrated[131]

that treatment of hex-5-ene methanesulphonate (165) with the supernucleophile gave uncyclised, aliphatic cobaloxime (166) rather than the cyclised product (168) (scheme 69).



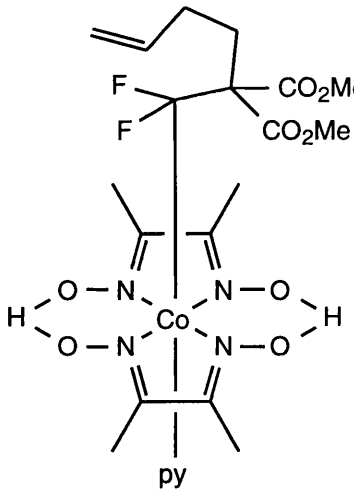

**119** **164**



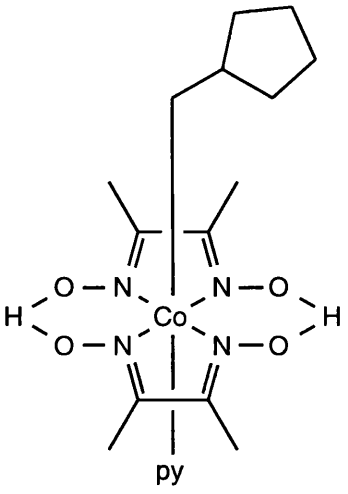

**165** **166**

i) $Na^+ [Co(dmgH)_2py]^-$

**Scheme 69**




**167**




**168**

Buttle suggested that the most likely explanation for the difference in products isolated was that the fluorine atoms were sterically demanding, so that the complex with the cobalt bound to the difluorinated carbon (167) had a weaker bond than would normally be expected, and hence was converted immediately into the cyclised form (164) where the cobalt is bound to a relatively unhindered primary carbon atom. This is a view supported by the fact that secondary alkyl cobaloximes are less stable to oxygen in solution than primary ones, and escaped isolation for a longer time relative to their primary analogues. In slightly acid solution a value of 112±7kJmol$^{-1}$ has been obtained for cyclopentylmethylcob(III)alamin[132]. When a large alkyl group is present, the corrin ring distorts downwards toward the base ligand. The distortion can be enough to sever the coordinate bond to that ligand, giving a "base-off" complex. Likewise, the displaced Lewis base has an affinity for the now positively charged cobalt atom, and can reattach, causing an upward displacement of the corrin system, which repels the alkyl group (*i.e.* the axial anionic base). At this pH, the base exists in partially protonated form, and has a reduced affinity for the cobalt atom. The study was comparing *neo*pentyl and cyclopentylmethyl groups; only in the cyclopentylmethyl case was stabilisation found to be necessary to ensure that Co-C homolysis occurred "at a conveniently

measurable rate". The instability of the cyclopentylmethylcob(III)alamin relative to *neo*pentylcob(III)alamin does not rule out the steric argument, but is not in its favour. The stability of the aliphatic complex first formed in the reaction must be considered as well as the product. The Co-C bond energies for some $B_{12}$ analogues have been determined (table 15)[133], and demonstrate that the logic of Buttle's argument is sound.

| Entry | Cob(III)alamin R group | C-Co Bond energy ($kJmol^{-1}$) |
|---|---|---|
| 1 | $Me_3CCH_2$ | 98 |
| 2 | $Me_2CHCH_2$ | 112 |
| 3 | $PhCH_2$ | 103 |
| 4 | $Me_2CH$ | 87 |

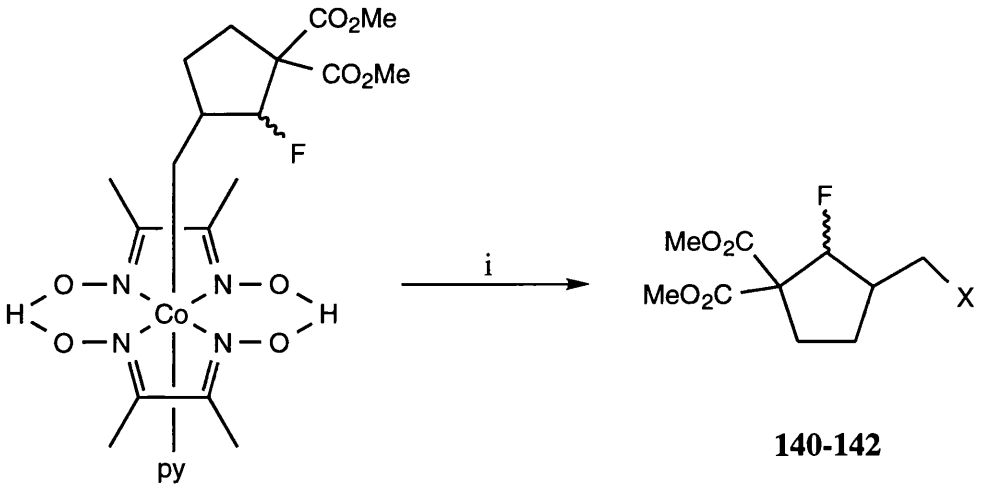
**Table 15**

Entry 4 in the table shows how important the proximity of alkyl substitution to the cobalt is in determining the cobalt-carbon bond strength. The *iso*propyl complex has a much weaker cobalt-carbon bond than any of the primary alkyl groups. The measurements seem to be consistent with the steric hindrance argument since in the difluoroalkyl cobaloxime case, we have effectively three substituents on the $\alpha$-carbon. In addition, entries 1 and 2 indicate that increasing substitution at the $\beta$-carbon is also responsible for weakening the cobalt-carbon bond, and so strain from the presence of the malonate ester groups would also contribute to inducing homolysis of the cobalt-carbon bond in the aliphatic form; the strain is reduced by the cyclisation, since the malonate esters 'move' one carbon further away from the cobalt. In the monofluoroalkylcobaloxime case, we have two $\alpha$ substituents and three $\beta$, which become one $\alpha$ and two $\beta$ after cyclisation. It is not unreasonable, we think, to suggest that similar steric factors are responsible for the immediate

cyclisation of the fluoroalkyl cobaloxime. Of course, it should be noted that whether this reactivity is solely to do with the fluorine or not is not known: to the best of our knowledge the effect of $\beta$-methoxycarbonyl groups has not been considered explicitly. However, if the trend of thermal behaviour of cobaloximes holds true for fluorine substituted alkyl groups the $\beta$-malonate must play a decisive part. The least stable cobaloximes dissociate at or below ambient temperature and 2° alkyl complexes show some evidence of homolysis above 80°C, whereas 1° alkylcobaloximes show little decomposition below 100°C[127].

### 2.6.4 Photolysis of Cobaloximes

Since the cyclisation of our radical has already occurred, photolysis now serves the purpose not of generating a radical to cyclise, but of removing the cobalt and introducing some useful functional group into the product. Photolyses were carried out using a 500W tungsten light bulb to irradiate a solution of the cobaloxime in the presence of a radical trapping agent[134,135] in benzene (scheme 70). The products were conveniently isolated by evaporation of the solution onto silica followed by column chromatography. The results are contained in table 16.




**139**

**140-142**

i) hν, radical trap, PhH

**Scheme 70**

| S.M. *cis* : *trans* | Trapping agent | Product : X | Product *cis* : *trans* | Yield |
|---|---|---|---|---|
| 1 : 8 | $BrCCl_3$ | **140** : Br | 1 : 8 | 72% |
| 1 : 8 | PhSSPh | **141** : SPh | 1 : 8 | 66% |
| 1 : 7 | PhSeSePh | **142** : SePh | 1 : 7 | 84% |

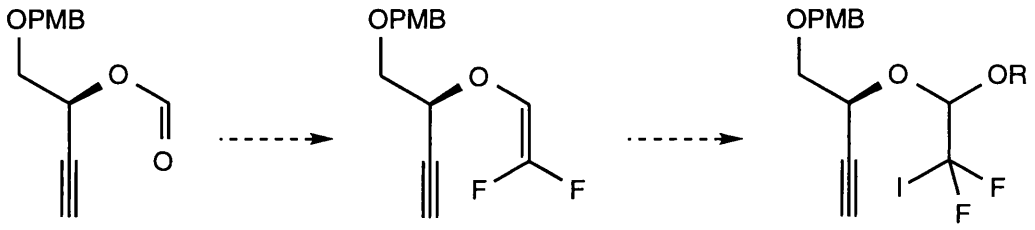
**Table 16**

The diastereomeric product ratios are, as expected, maintained during the photolysis. The yields are good, although when combined with the formation of the cobaloxime the overall result is a lower yield of the cyclised material. However, the variation of functionality possible in the photolysis is a significant advantage, as is the increased diastereoselectivity.

## 2.7 Initial Studies Toward Fluorinated Synthetic Nucleoside Analogues

### 2.7.1 Introduction

While the previously described fundamental study was in progress we had also decided to use fluoroalkyl and difluoroalkyl radical cyclisations to make potentially useful carbocycles and nucleoside analogues. We envisaged synthesis of the formate ester (178) of a known alcohol as a basis for further elaboration. Scheme 71 shows that difluoromethylenation followed by "iodoalkoxylation", could generate cyclisation precursors (170).



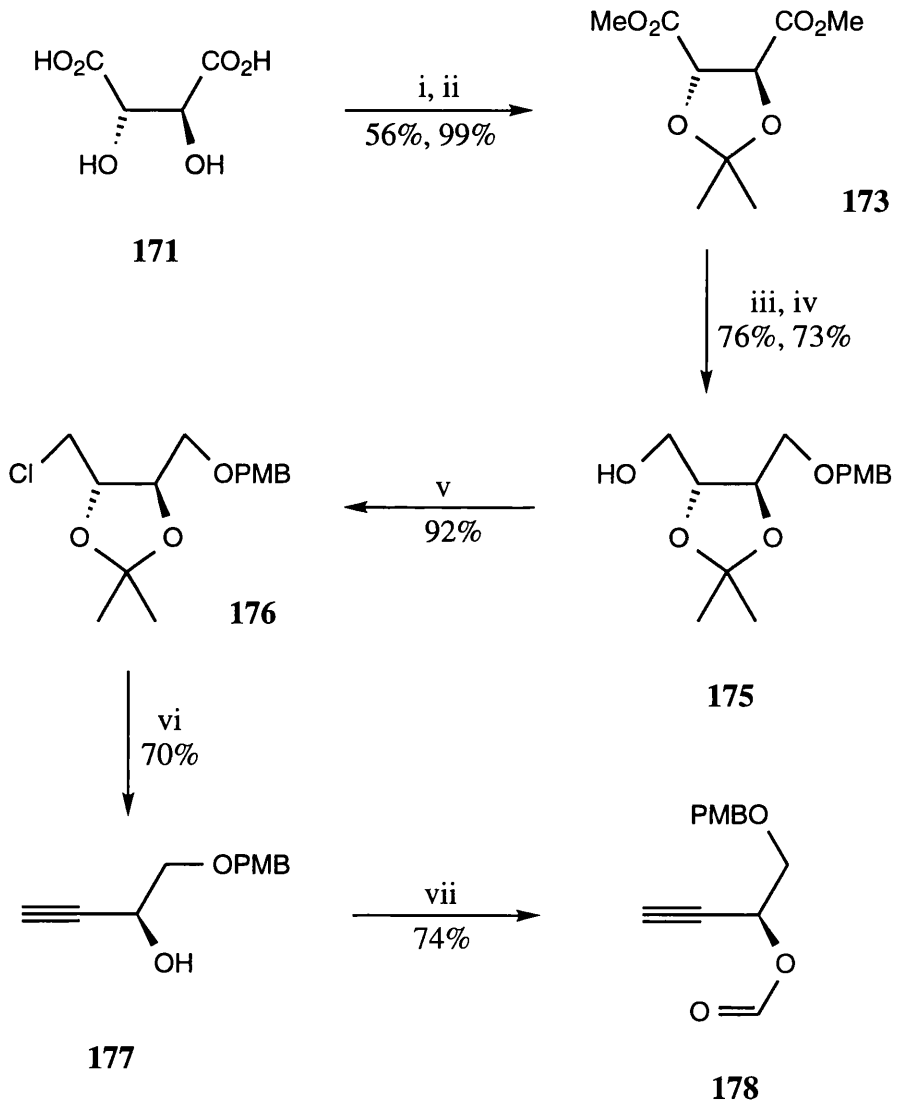

**178** **169** **170**

**Scheme 71**

### 2.7.2 (S) (*p*-methoxybenzyl)oxy-3-butyne-2-ol (178)

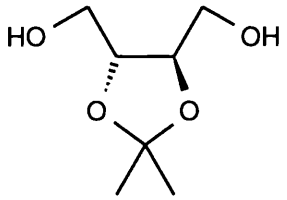
The synthesis shown in scheme 72 was carried out. To ensure correct chirality in the product, (*i.e.* to give analogues with C-4' stereochemistry akin to that of naturally occurring nucleosides) we used unnatural tartaric acid. The first step, methyl ester formation, was performed using a catalytic quantity of acid and molecular sieves and was stopped before complete conversion to preserve the chiral purity of the product. The acetonide formation and reduction were carried out, in excellent yield, according to Fletcher and Murphy[136]. Interestingly sodium borohydride is the best reducing agent for this particular diester. The

desymmetrisation of protected threitol (174) was found to require addition of sodium hydride to the threitol rather than the other way around, to avoid large amounts of diprotection. There are practical difficulties involved in generating and then adding oil-free sodium hydride to a reaction mixture, so we carried out



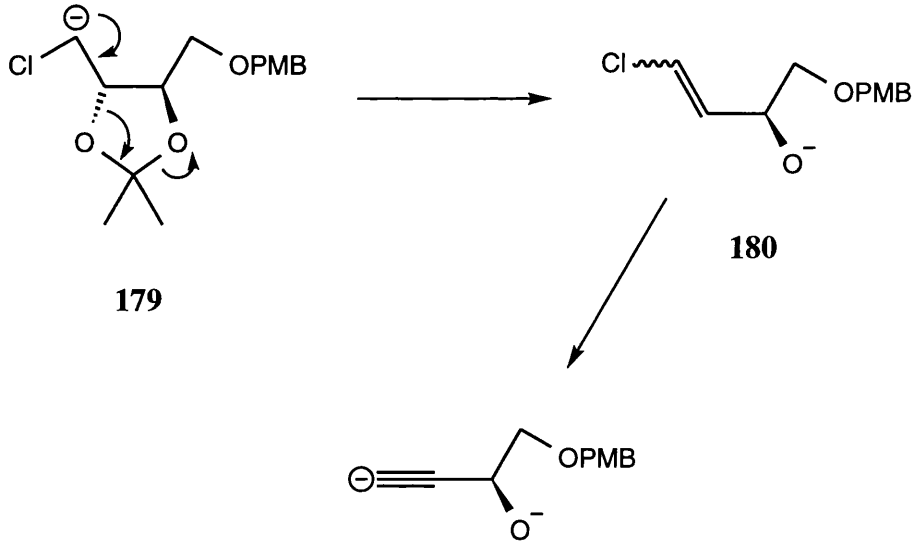

i) $H_2SO_4$, MeOH, sieves, reflux; ii) $(MeO)_2CMe_2$, *p*-TsOH, PhH, sieves, reflux; iii) $NaBH_4$, MeOH; iv) NaH, PMBCl, DMF, hexane, -15°C-reflux; v) $Ph_3P$, $CCl_4$, reflux; vi) *n*-BuLi, THF, -15°C-RT; vii) HCOOAc

**Scheme 72**




**174**

the reaction in a vigorously stirred (immiscible) mixture of DMF and hexane at reduced temperature. The reaction takes place in the DMF, with the hexane serving to wash the oil from the sodium hydride *in situ*. Following generation of the anion, addition of the halide and gradual raising of the temperature to reflux gave the desired product (175) in good yield. Our optimisation gave conditions similar to those published during the course of our studies[137].




**179** **180** **181**

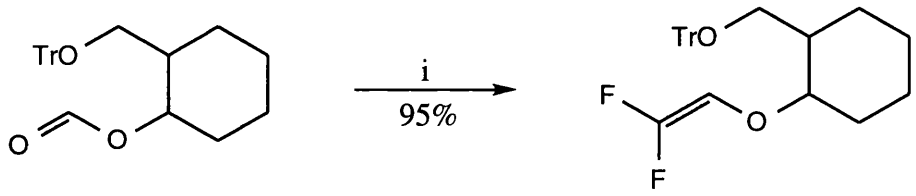
**Scheme 73**

The chloride (176) was formed using the method of Yadav[138]. The formal elimination of HCl and acetone from this chloride was achieved using lithium amide, generated by dissolving lithium in liquid ammonia. The proposed

mechanism (scheme 73) starts with deprotonation $\alpha$- to the chlorine atom to give the carbanion (179). Elimination of acetone to give the alkoxide (180) is then followed by another elimination to the dianion (181) which is then quenched. Following his original work, Yadav found that LDA could also bring about the elimination[139]. We found that addition of *n*-butyllithium in hexanes to a solution of the chloride in THF at -78°C could bring about the elimination in 70% yield.

## 2.7.3 Difluoromethylenation

The formate (178) of the alcohol (177) was obtained in a straightforward fashion using the mixed anhydride acetic formic anhydride. The next step, using *tris*(dimethylamino)phosphine and dibromofluoromethane had previously been used[140] to achieve the difluoromethylenation of the formate ester (182) (scheme 74).

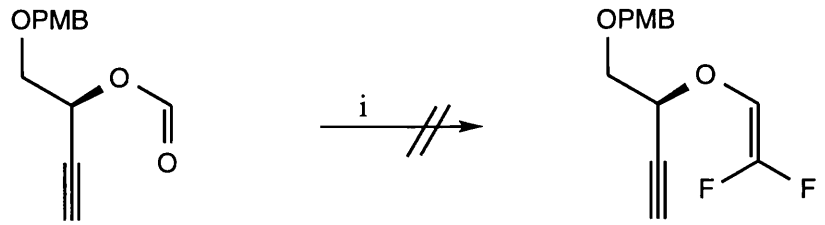



**182**

i) $(Me_2N)_3P$, $CF_2Br_2$, triglyme, 85°C

**Scheme 74**

In our hands however despite repeated attempts we found that we could not generate the desired product (170) (scheme 75), only the formate ester starting material (178) being isolated. We therefore decided to use the alcohol (177) in a related approach.



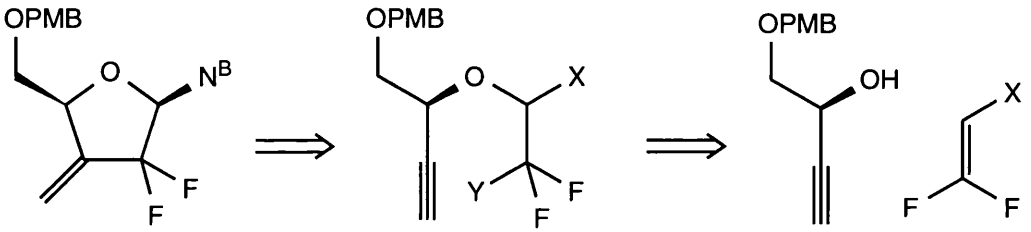

**178** **170**

i) $(Me_2N)_3P$, $CF_2Br_2$, triglyme, 85°C

**Scheme 75**

## 2.7.4 Alkoxyhalogenation and Alkoxyphenylselenation

The structure (183) was of interest to us because it can be disconnected to the alcohol (177) and to available difluoroethenol derivatives (186) and (188)[141,142] (scheme 76, X=OMEM (186); X=ODEC (188); Y=Br, I, PhSe, AcOHg).

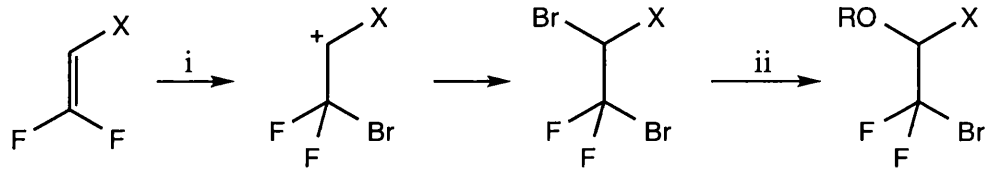



**183** **184** **177** **186, 188**

**Scheme 76**

The ribosyl $C^{2'}$-$C^{3'}$ bond was a convenient bond to form during the cyclisation step, as this allowed us to put the fluorine substituents next to the hemi-acetal portion of the molecule (the importance of which has been discussed in section

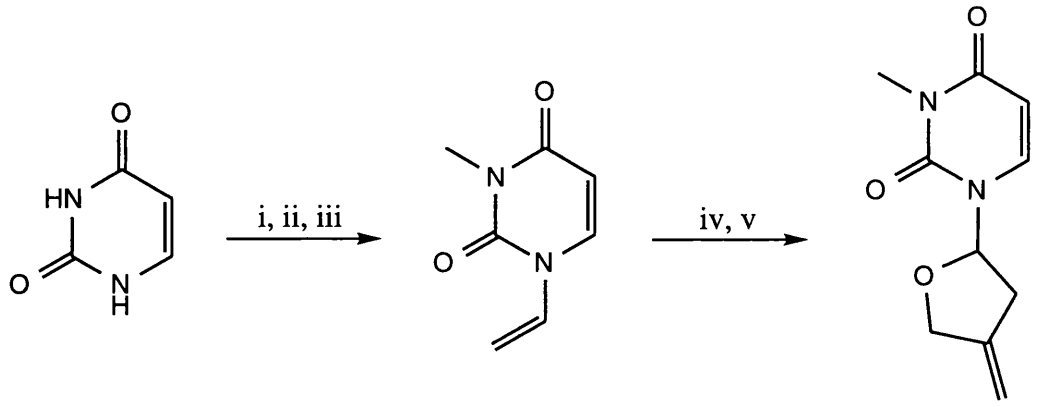
1.1.8). The product (183) has a useful exocyclic double bond for further modification, and the synthesis allows for alkyl substitution of that double bond[138], making available a whole homologous series of compounds. The key step is the addition of an electrophile (which could conceivably be $Br^+$, $I^+$, $PhSe^+$ or $CF_3CO_2Hg^+$) to the difluoroethenol derivative, which would be followed by nucleophilic addition of the alcohol to give (184). Scheme 77 shows the intermediates where bromine is the electrophile.




i) $Br_2$; ii) ROH

**Scheme 77**

A nucleoside analogue synthesis with a final disconnection similar to this was published[143] as we began work (scheme 78 shows the case for propargyl alcohol, although other substituted propargyl alcohols were also used). The key difference was that our synthesis has a fluorinated enol ether or carbamate rather than an enamide of a nucleoside base to which the propargyl alcohol is added; we planned to add the base at the end of the synthesis, which allows for ease of formation of many different compounds, using a variety of bases.



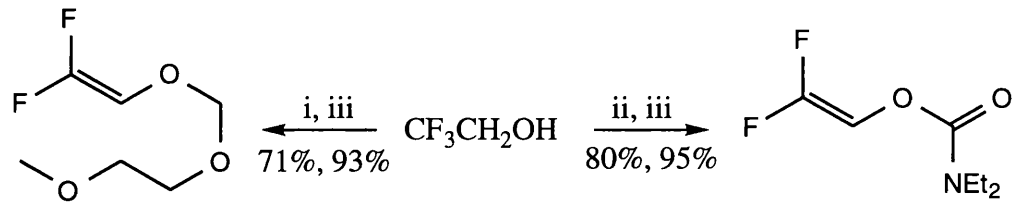

**2a** **189** **190**

i) $(Me_3Si)_2NH$, reflux; ii) $BrCH_2CH_2Br$, DMF, 80°C; iii) MeI, KOH, DMSO, 90°C; iv) NBS, propargyl alcohol, -40°C; v) *n*-$Bu_3SnH$, AIBN, PhH, reflux

**Scheme 78**

## 2.7.5 Synthesis of 2,2-Difluoroethenol Derivatives

The enol ether (186) and enol carbamate (188) were synthesised using literature methods (scheme 79)[141,142].

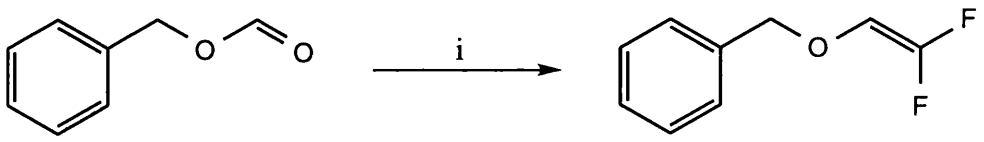



**186** **188**

i) NaH, $ClCH_2OCH_2CH_2OCH_3$, THF, 0°C-RT;
ii) NaH, $Et_2NCOCl$, THF, 0°C-RT; iii) LDA, THF, -78°C

**Scheme 79**

In each case trifluoroethanol is protected with the relevant group and then HF eliminated in the second step. We added a copper sulphate wash during the work up to ensure that no amines contaminated either product. The heteroatoms in the protecting groups are needed to direct and to stabilise the formation of the difluorovinyl anions produced in the second step. Without stabilisation these products are either not formed, or eliminate again to give a terminal fluoroalkyne. We also attempted the preparation of the benzyl ether (192) by difluoromethylenation of benzyl formate (191) (scheme 80) but the product, which had a $^1H$ NMR corresponding to that expected for (192), was volatile and no further investigations along this avenue were pursued.




**191** **192**

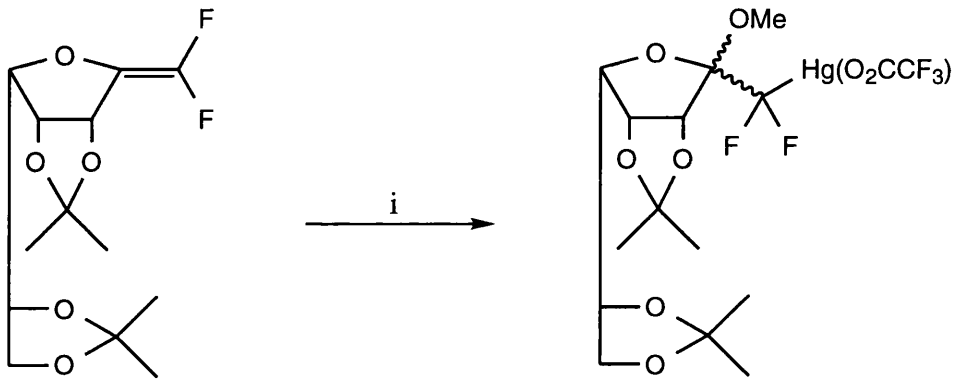
i) $(Me_2N)_3P$, $CF_2Br_2$, triglyme, 0°C-85°C

**Scheme 80**

With the two available difluoroenol ether derivatives in hand, we then decided to use commercially available propargyl alcohols to develop conditions for effective haloetherification reactions. The combination of propargyl alcohol, phenylselenyl bromide and DIPA[144] with (186) gave only starting materials. NIS gave small amounts of products, but nothing identifiable and none of the products had the MEM group. More interesting results were obtained from the attempted addition of bromine. The $^1H$ NMR of both starting difluoroenol ethers have a very distinctive double doublet for their alkene proton. When either (186) or (188) were treated with bromine and then octyn-3-ol the main product had a double doublet shifted ~0.4ppm to lower field. This is an odd result, since the existence of the double

doublet suggests that there is still a difluoroalkene proton present. Addition of bromine to the alkyne and immediate $^1H$ NMR also showed a double doublet but shifted by 0.2ppm (in a different solvent) to lower field. Unfortunately, these products appeared prone to decomposition and could not be identified.

Although time did not permit, it is however suggested that solvomercuration may be more effective. Thus, within the carbohydrate series, mercuric trifluoroacetate has been shown to be an effective electrophile for gem difluoroenol ethers (scheme 81)[145].




**193** **194**

i) $Hg(O_2CCF_3)_2$, MeOH

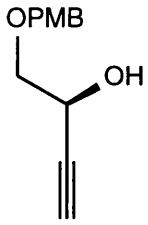
**Scheme 81**

It is therefore possible that stoichiometric mercuration followed by exchange of trifluoroacetate with a propargylic alcohol could yield useful precursors for radical cyclisation.

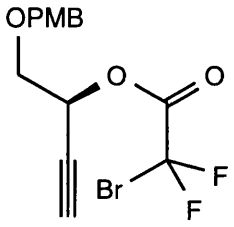
## 2.8 Fluorinated "2-C" Fragments

### 2.8.1 Ruthenium and Tin Mediated Cyclisation Reactions of Chiral Halofluoroacetate Esters

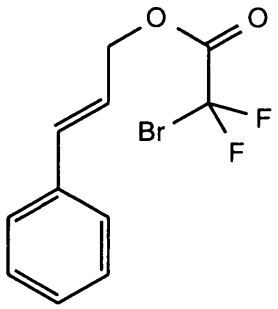
An alternative strategy for incorporation of the requisite fluorinated two carbon synthon lay in conversion of the chiral alcohol (177) into the derived halodifluoroacetate with the aim of investigating the possibility of a cyclisation onto the alkyne bond. The chlorodifluoroacetate ester was available from chlorodifluoroacetic anhydride, but we preferred to have a brominated derivative (*e.g.* 195) for ease of homolysis. For this we would require transesterification from, for example, ethyl bromodifluoroacetate. Cinnamyl alcohol was selected as a model alcohol for development purposes, so in the first instance we were actually attempting to synthesise (196).




**177**




**195**

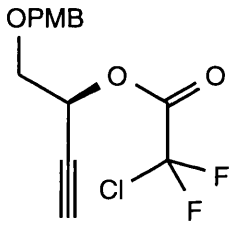



**196**

Our first attempt at forming cinnamyl bromodifluoroacetate (196) directly relied on the distillation of ethanol out of a mixture of ethyl bromodifluoroacetate, tosic acid and 1.2 equivalents of cinnamyl alcohol, a classic method for driving the reaction to completion[146]. Although milky drops of benzene similar to those seen in a steam distillation were condensed out of the reaction, and the starting material was consumed based on tlc, work-up and column chromatography furnished only cinnamyl alcohol. The reaction product was unstable on both silica and alumina.

Similar experiments with an excess of the ester and only a small quantity of cinnamyl alcohol showed that again the alcohol was entirely used up, but these also gave the alcohol as the product. Since titanate mediated transesterification is also known to fail for allylic alcohols[147], and other methods[148-151] were not considered to increase the likelihood of success, this approach was not continued.

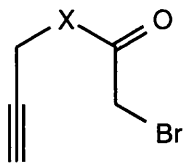
Concomitant attempts to hydrolyse ethyl bromodifluoroacetate to its potassium salt, with the idea of a subsequent alkylation reaction with cinnamyl bromide were also examined. Unfortunately, the methods used to accomplish the hydrolysis all required aqueous conditions for removal of reaction solvents and unwanted salts and the apparent hydrolytic instability of the desired product might explain why this was also unsuccessful. Given the expertise apparently required for the synthesis and handling of bromofluoroacetate esters, we therefore returned to the chlorinated analogues. The ester (197) was accordingly prepared and subjected to two different cyclisation methods.

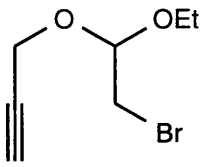



**197**

### 2.8.1.1 Tin Mediated Cyclisation Reactions

5-*Exo*-dig cyclisation of haloesters and amides of the form (198) is usually slow enough that direct reduction of the radical prior to cyclisation can compete effectively. The process of reduction to an acetal (*e.g.* (199)[152]), cyclisation, then oxidation back to the ester is more effective than is direct cyclisation of the initial ester.

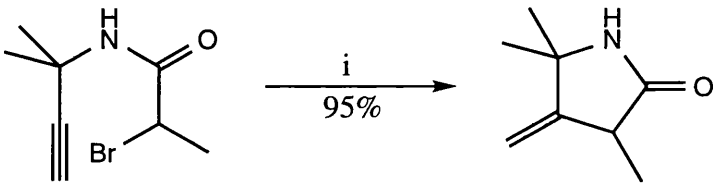



**198** : X=O, NH, NR

**199**

It is generally accepted that when the $sp^2$ and sp centres are in the cyclisation precursor, the radical is too far from the alkyne bond to react. However, such a reaction is possible as depicted in scheme 82[153].




**200** **201**

i) *n*-$Bu_3SnH$, AIBN, PhMe, reflux, slow addition

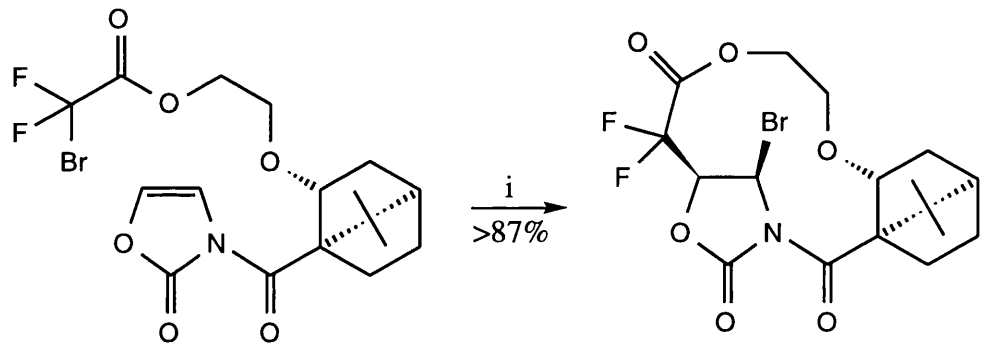
**Scheme 82**

Treatment of the ester (197) with tri(*n*-butyl)tin hydride and AIBN in refluxing benzene gave the alcohol (177) as the major isolated product. Cyclisation clearly did not occur on this material, though without isolation of the acid-derived fragment it is not possible to determine why. The radical could have been generated, then reduced prior to cyclisation, or alternatively it may be that reduction of the halide to a radical did not occur at all. The ester starting material is known to decompose (giving the alcohol (177)) under the chromatographic conditions used for product purification. The second product formed was curious inasmuch as the $^1H$ NMR spectrum indicated that it contained the *p*-methoxybenzyl group but not the

diastereotopic protons of the alcohol. There was no alkene proton, and nothing close to the alkyne proton of the starting material. The low yield of this material however precluded a positive identification.

### 2.8.1.2 Ruthenium Mediated Cyclisation Reaction

*Tris*(triphenylphosphine)ruthenium (II) chloride has been used as an efficient catalyst for the macrocyclisation shown in scheme 83[154].

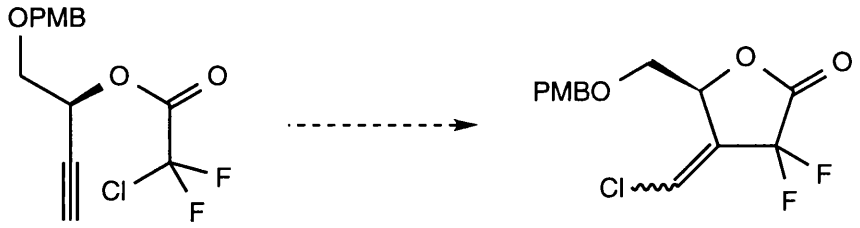



**202** **203**

i) 7.5mol% $[Ru(PPh_3)_3Cl_2]$, PhH, reflux, 72h

**Scheme 83**

This catalyst was of interest to us as it appears to succeed in bringing together reactive elements which are quite far apart. We therefore attempted the perform an atom transfer cyclisation indicated in scheme 84. Whilst tlc showed that no, or very little, starting material remained, the alcohol (177) and a product running faster than the starting ester were observed. After column chromatography the main identifiable material was found to be *p*-methoxybenzyl alcohol (10%). Nothing corresponding to an alkene proton could be found in $^1H$ NMR of any of the products.

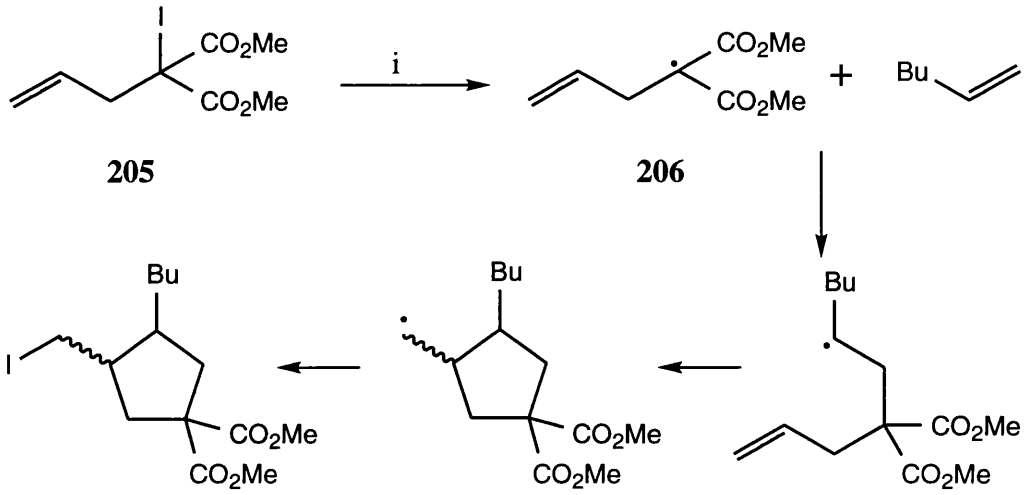



**197** **204**

**Scheme 84**

## 2.8.2 Iodine Atom Transfer Cyclisation Reactions

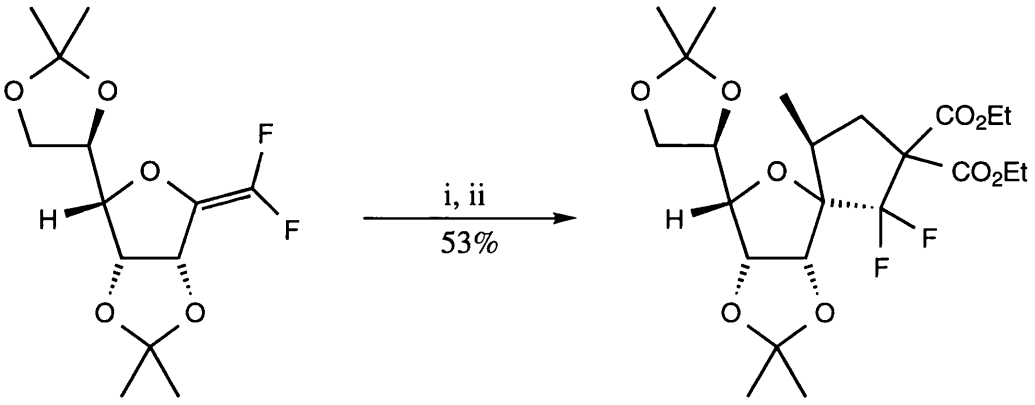
The availability of Percy's difluoroenol ether (186)[141] and carbamate (188)[142] which had failed to participate in haloetherification reactions (section 2.7.5) prompted us to examine the use of these intermediates in atom transfer chemistry to generate usefully functionalised fluorinated cyclopentane building blocks. Dimethyl alkyliodomalonates are a source of alkylmalonyl radicals[85] *via* homolysis of the weak carbon-iodine bond. The resulting radicals will undergo intramolecular cyclisation if the alkyl chain has a suitable acceptor. Dimethyl allyliodomalonate (205) can be used to generate dimethyl allylmalonyl radical (206) and this added to an alkene. The resulting 5-hexenyl type radical cyclises (*i.e.* onto what was originally the allyl fragment), and finally the iodine atom quenches the radical[155-157] (scheme 85).

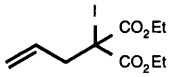



i) ($n$-$Bu_3Sn)_2$, hν, PhH; 58%

**Scheme 85**

As this method had been successfully applied to difluoroenol ethers[158] (scheme 86) we considered it a reasonable proposition to substitute Percy's enol ethers and expect cyclisation with diethyl allyliodomalonate (207).

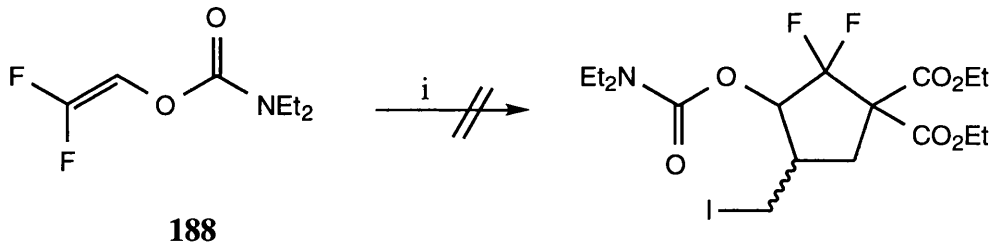



i) 

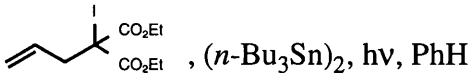
, ($n$-$Bu_3Sn)_2$, hν, PhH; ii) $n$-$Bu_3SnH$

**Scheme 86**

Since the difluoroenol ether (186) was unstable to silica, we anticipated possible problems in isolating and identifying the products from the reaction of this. Our studies therefore concentrated on the enol carbamate (188).




**188**




**Scheme 87**

Unfortunately however, most of the attempts to bring about the desired reaction indicated in scheme 87 failed; mass balance was very low and although small quantities of material with identifiable fragments (usually the diethyl carbamate group) were sometimes obtained from the complicated mixtures of products, no definitive structural assignments could be made.

## 2.9 Conclusions and Perspectives

In this thesis is described the first study of 5-*exo*-trig cyclisation reactions of fluoroalkyl radicals. Having demonstrated that such reactions were possible, we have further investigated their features and methods by which they can be brought about. The classical tri(*n*-butyl)tin hydride / AIBN method for generating and cyclising radicals proved effective, as did the use of a cobalt complex. In the latter case, diastereoselectivity was improved and fluorocyclopentane derivatives with different substituents synthesised. The use of samarium diiodide for carrying out SET-induced cyclisation was found to be ineffective for the type of substrates on which we were working.

From the yield of cyclisation reactions we have shown that the fluoroalkyl radical cyclises effectively onto a variety of radical acceptors, apparently showing some ambiphilic character. This is in keeping with the trend seen for increasing fluorination of an alkyl radical which leads to electrophilic character.

We have also found that fluoroalkyl radical cyclisation reactions generally show *trans* diastereoselectivity, which is comparable with the selectivity of alkoxyalkyl radical cyclisation reactions. However, we have one example where the diastereoselectivity is reversed (a rather surprising result).

The novel use of dibromofluoromethane as a malonate alkylating agent has been investigated. This reagent is a liquid and had the potential to be used instead of dichlorofluoromethane (a gas, b.p. 9°C, which can be particularly difficult to handle) where the choice of halogen was available. The alternative was shown not to be an effective method because of the dependence of yield on apparently irrelevant remote functionality and low yield.

Progress has been made towards using the fluoroalkyl radical cyclisation reaction in a useful synthesis, and there remain important questions which our research has uncovered. The reversal of diastereoselectivity for the diphenylhydrazone (128) cyclisation reaction was completely unexpected, as was

the apparent failure of the oxime ethers (118) and (126) to provide fluoroalkyl radicals. Thus there is great scope for investigation into these peculiarities of the fluoroalkyl radical and for the extension of this study along theoretical and / or synthetic lines.

# Chapter 3

# Experimental

Melting points were determined using a Reichert stage melting point apparatus and are uncorrected. $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were recorded on a Varian XL400 spectrometer by Mrs. G. Maxwell. $^{1}H$ and $^{13}C$ spectra were referenced internally to the residual protic solvent. $^{19}F$ spectra were referenced internally to $CFCl_3$. Unless otherwise stated, spectra were run in $CDCl_3$; $^{1}H$ at 400MHz, $^{13}C$ at 100.6MHz and $^{19}F$ at 376.3MHz. Solvent peaks are not quoted. $^{13}C$ assignments are based on prediction of chemical shift[159] and expected intensity, aided by analogy with similar compounds, proton coupled spectra, and APT spectra[160,161]. Low resolution mass spectra were recorded on a V.G. ZAB-SE, V.G. 7070 H/F or V.G. 305 by Dr. M. Mruzek or Dr. J. Hill at UCL, by GlaxoWellcome (Medicines Research Centre, Stevenage), or by the University of London mass spectrometry service. High resolution work was carried out by the University of London mass spectrometry service or by GlaxoWellcome (Medicines Research Centre, Stevenage). Infra red spectra were recorded on a Perkin Elmer 1605 FT-IR spectrometer. Unless otherwise stated, all were determined as liquid films. With the exception of chlorodifluoroethanal, only peaks which were assigned are quoted. Many final products were isolated as inseparable diastereomeric mixtures. In these cases mass spectrometric and infra red data are given for the mixture, followed by NMR data which could not be assigned to a specific diastereomer (for example, two diastereomers with two methyl ester functions each may have up to four carbon signals for the C=O, four carbon signals for the methyls, and four methyl proton signals, listed before the rest of the data). This is followed by NMR data for the major component of the mixture. The NMR data of the minor component follows and includes only that which could clearly be assigned to that structure and was deemed to demonstrate clear evidence for that structure and its presence. $^{3}J_{C\text{-}F}$ for the $CO_2Me$ groups of the cyclopentyl fluorides was ignored in making the C=O assignments and arbitrarily these carbons were designated as singlets. In the case of the ABX system, chemical shift was

calculated[159], but the frequencies expressed are line separations and do not correspond to coupling constants.

THF and ether, when used as reaction solvents, were distilled from sodium-benzophenone ketyl. Benzene and toluene were distilled from sodium, DCM was distilled from phosphorous pentoxide. Methanol, ethanol and *iso*-propanol were distilled from magnesium. Acetonitrile and *tert*-butanol were distilled from calcium hydride. Where dry acetone is specified this was dried over, and distilled from, calcium sulphate. Petrol was distilled. DMF was dried over, and distilled under reduced pressure from, magnesium sulphate. Pyridine, diethylamine, DIPA and DIPEA were distilled from potassium hydroxide. Other reagents were purified using literature procedures[162], or were used as purchased. Flash column chromatography was performed using BDH Flash Silica, mesh size 40-63μm. Where base washed silica is specified, this was prepared as follows;

For pre-adsorbtion: 1% triethylamine in ether (2ml per gram of silica) was evaporated from the silica. For column chromatography: the column was packed wet using 1% triethylamine in the solvent system to be used for running the column.

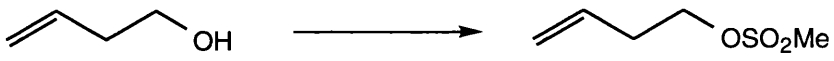
All reactions were performed using oven dried glassware under a positive pressure of nitrogen unless otherwise stated. Cobaloxime photolyses were performed in a vessel, referred to as "the standard photolysis cell", containing an internal water cooling device, and with a porous glass frit, above which the solution was held by a positive pressure of nitrogen. Hence nitrogen was constantly bubbled through the solution, whilst being irradiated by a 500W tungsten bulb placed such that the filament was 18cm from the centre of the cell. Atom transfer cyclisations were attempted using a 125W mercury discharge lamp.

Non-SI units used in this thesis are defined:

760mmHg=101.325kPa; 1Å=0.1nm;

a°C=(a+273.15)K; 1eV=1.602x$10^{-19}$J

**Preparation of Methyl but-3-ene sulphonate (100)[100]**

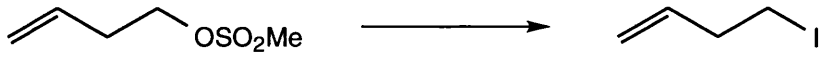



**99** **100**

To a stirred solution of 3-buten-1-ol (99) (17.5g, 0.24mol) in DCM (400ml) at -5°C was added slowly triethylamine (51.6ml, 0.36mol). This solution was maintained between -10°C and -5°C whilst methanesulphonyl chloride (20.9ml, 0.26mol) was added dropwise over 40 minutes, then stirred at room temperature for 48 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (1M, 100ml), and extracted with ether (4x200ml). The combined extracts were washed with brine (100ml), dried ($MgSO_4$) and evaporated under reduced pressure to give methyl but-3-ene sulphonate (100) as a pale yellow liquid which was used without further purification. Yield 35.6g (0.24mol, 98%).

$\delta_H$: 5.75 ddt 17.0Hz, 10.5Hz, 6.5Hz 1H ($C^3H$); 5.2-5.0 m 2H ($C^4H_2$); 4.21 t 6.5Hz 2H ($C^1H_2$); 2.96 s 3H ($CH_3$); 2.46 m 2H ($C^2H_2$).$\delta_C$: 132.5 ($C^3$); 118.4 ($C^4$); 69.0 ($C^1$); 37.4 ($CH_3$); 33.2 ($C^2$).$\nu_{max}$: 1643cm$^{-1}$ (C=C); 1352cm$^{-1}$, 1174cm$^{-1}$ (S=O).**m/z(EI)**: 54 (100%), 150 (2%, $[M]^+$).

**Preparation of 4-Iodobutene (101)[100]**



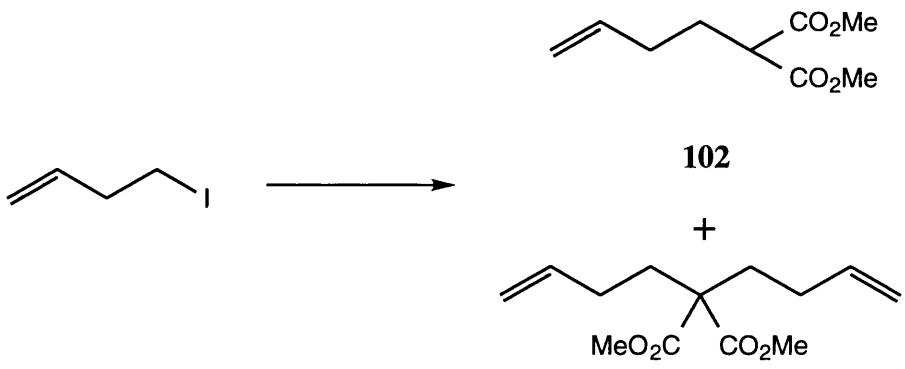

**100** **101**

To a stirred solution of methyl but-3-ene sulphonate (100) (35.6g, 0.24mol) in dry acetone (660ml), in a room temperature water bath, was added sodium iodide (130g, 0.87mol) over 5 minutes, during which the mixture turned bright yellow.

After 18 hours another portion of sodium iodide (20g) was added, then a further 30 hours later the mixture was poured into water (500ml) and extracted with ether (3x600ml). The organic extracts were washed with water (7x300ml), brine (2x200ml), dried ($MgSO_4$) and evaporated under reduced pressure at 0°C to a volume of *ca.* 300ml. This solution was washed with water (3x300ml), brine (2x200ml), dried ($MgSO_4$) and evaporated under reduced pressure at 0°C to give a solution of 4-iodobutene (101) containing 13% by mass of ether (by $^1H$ NMR). This solution was used directly in the next step. Yield of 4-iodobutene 26.6g (0.15mol, 61%).

$\delta_H$: 5.65-5.80 m 1H ($C^2H$); 5.2-5.0 m 2H ($C^1H_2$); 3.16 t 7.0Hz 2H ($C^4H_2$); 2.59 m 2H ($C^3H_2$).$\delta_C$: 136.8 ($C^2$); 117.0 ($C^1$); 30.9 ($C^3$); 4.6 ($C^4$).$\nu_{max}$: 1640$cm^{-1}$ (C=C); 992$cm^{-1}$, 920$cm^{-1}$ (RCH=$CH_2$).**m/z(FAB)**: 32 (100%); 55 (44%, $[C_4H_7]^+$); 128 (1%, $[HI]^+$).

**Preparation of Dimethyl 4-pentene-1,1-dicarboxylate (102)**[100]




**102**

**101** **208**

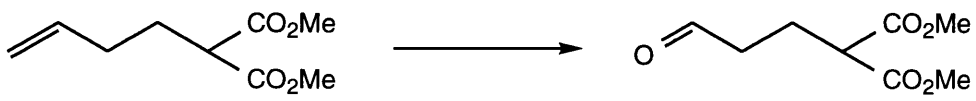
To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 3.86g, 0.16mol) in DMF (80ml), in a room temperature water bath, was added dropwise a solution of dimethyl malonate (21.3g, 0.16mol) in DMF (125ml). After 30 minutes

a thick white suspension had formed to which was added DMF (50ml) followed, over 5 minutes with swirling, by a solution of 4-iodobutene (101) (26.6g, 0.15mol) in DMF (50ml). A translucent solution formed over 10 minutes. After stirring for 40 hours the resulting suspension was poured into water (450ml) and extracted with ether (3x500ml). The organic extracts were washed with water (2x300ml) then brine (200ml), dried ($MgSO_4$) and evaporated under reduced pressure to a pale green oil. Column chromatography (4-10% ether / petrol) gave dimethyl 4-pentene-1,1-dicarboxylate (102) (21.3g, 0.11mol, 78%) and dimethyl 1,8-nonadiene-5,5-dicarboxylate (208) (1.10g, 2.9mmol, 4%) as colourless oils.

Dimethyl 4-pentene-1,1-dicarboxylate:$\delta_H$: 5.73 ddt 17.0Hz, 10.0Hz, 6.5Hz 1H ($C^4H$); 5.1-4.9 m 2H ($C^5H_2$); 3.71 s 6H ($CH_3$); 3.37 t 7.0Hz ($C^1H$); 2.03-2.15 m 2H ($C^3H_2$); 1.99 td 7.5Hz, 1.5Hz 2H ($C^2H_2$).$\delta_C$: 169.8 ($\underline{C}O_2Me$); 136.7 ($C^4$); 116.0 ($C^5$); 52.5 ($CH_3$); 50.8 ($C^1$); 31.3 ($C^3$); 27.9 ($C^2$).$\nu_{max}$: 1736$cm^{-1}$ (C=O); 1642$cm^{-1}$ (C=C).**m/z(FAB)**: 187 (100%, $[M+H]^+$).

Dimethyl 1,8-nonadiene-5,5-dicarboxylate:$\delta_H$: 5.77 ddt 17.0Hz, 10.0Hz, 6.5Hz 2H ($C^2H$ & $C^8H$); 5.07-4.99 m 2H (one of $C^1H_2$ & one of $C^9H_2$); 4.99-4.90 m 2H (one of $C^1H_2$ & one of $C^9H_2$); 3.72 s 6H ($CH_3$); 2.05-1.85 m 8H ($C^3H_2$, $C^4H_2$, $C^6H_2$, $C^7H_2$).$\delta_C$: 171.9 ($\underline{C}O_2Me$); 137.4 ($C^2$ & $C^8$); 115.1 ($C^1$ & $C^9$); 57.0 ($C^5$); 52.4 ($CH_3$); 31.3 ($C^3$ & $C^7$); 27.9 ($C^4$ & $C^6$).$\nu_{max}$: 1736$cm^{-1}$ (C=O); 1642$cm^{-1}$ (C=C).**m/z(TS)**: 241 (100%, $[M+H]^+$).**High Res.(TS)**: Found ($[M+H]^+$) 241.1450; $[C_{13}H_{20}O_4+H]^+$ requires 241.1440.

## Preparation of Dimethyl 4-oxobutane-1,1-dicarboxylate (103)[100]

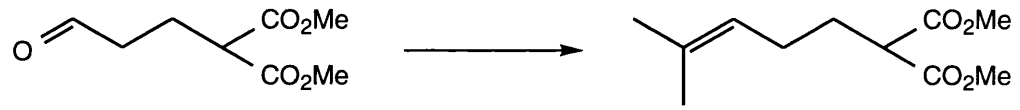



**102** **103**

Into a stirred solution of dimethyl 4-pentene-1,1-dicarboxylate (102) (1.50g, 8.1mmol) in methanol (120ml) at -78°C was bubbled a mixture of ozone and oxygen until the solution appeared blue. The mixture was then stirred under a flow of nitrogen until the blue colour disappeared, warmed to room temperature and dimethyl sulphide (15ml, excess) added. After 15 hours the solution was evaporated under reduced pressure. The residue was dissolved in ether (150ml), washed with water (50ml), brine (50ml), dried ($MgSO_4$), and evaporated under reduced pressure to give dimethyl 4-oxobutane-1,1-dicarboxylate (103) as a colourless oil which was used without further purification Yield 0.96g (5.1mmol, 63%).

$\delta_H$: 9.72 s 1H (CHO); 3.70 s 6H ($CH_3$); 3.42 t 7.5Hz 1H ($C^1H$); 2.54 t 7.0Hz 2H ($C^3H_2$); 2.18 q 7.0Hz 2H ($C^2H_2$).$\delta_C$: 173.1 (CHO); 169.1 ($\underline{C}O_2Me$); 52.4 ($CH_3$); 50.0 ($C^1$); 40.7 ($C^3$); 20.8 ($C^2$).$\nu_{max}$: 1732$cm^{-1}$ (C=O).**m/z(FAB)**: 157 (100%, $[M-OMe]^+$), 189 (84%, $[M+H]^+$).

**Preparation of Dimethyl 5-methyl-4-hexene-1,1-dicarboxylate (104)**



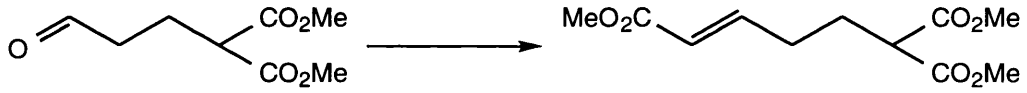

**103** **104**

To a stirred, 1:1 mixture of *iso*propylidene triphenylphosphonium bromide and sodium amide (2.0g, 4.7mmol) in THF (10ml) at room temperature was added, in three portions over 90 minutes, dimethyl 4-oxobutane-1,1-dicarboxylate (103) (500mg, 2.7mmol) in THF (8ml). The resulting orange mixture was refluxed for 3 hours, cooled and poured into aqueous sodium hydrogencarbonate solution (1M, 40ml). The aqueous phase was extracted with ether (2x80ml), then the combined

organic layers were washed with water (30ml), brine (30ml), dried ($MgSO_4$), and preadsorbed onto silica. Column chromatography (0-6% ether / petrol) gave dimethyl 5-methyl-4-hexene-1,1-dicarboxylate (104) as a colourless oil. Yield 0.24g (1.1mmol, 41%).

$\delta_H$: 5.04 m 1H ($C^4H$); 3.71 s 6H ($OCH_3$); 3.35 t 7.5Hz 1H ($C^1H$); 2.10-1.85 m 4H ($C^2$ & $C^3$); 1.66 s 3H ($CH_3$); 1.55 s 3H ($CH_3$).$\delta_C$: 170.0 ($\underline{C}O_2Me$); 133.4 ($C^5$); 122.5 ($C^4$); 52.5 ($OCH_3$); 50.9 ($C^1$); 28.9 ($C^3$); 25.7 (*cis*-$CH_3$); 25.6 ($C^2$); 17.6 (*trans*-$CH_3$).$\nu_{max}$: 1751$cm^{-1}$ (C=O); 1674$cm^{-1}$ (C=C).**m/z(FAB)**: 215 (100%, $[M+H]^+$), 151 (92%), 183 (39%, $[M-OMe]^+$), 237 (31%, $[M+Na]^+$). **High Res.(FAB)**: Found ($[M+H]^+$) 215.1290; $[C_{11}H_{18}O_4+H]^+$ requires 215.1283.

## Preparation of Trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105)[100]



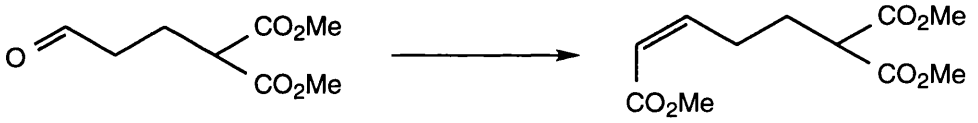

**103** **105**

To a stirred suspension of anhydrous lithium chloride (348mg, 8.2mmol) in acetonitrile (35ml) was added trimethyl phosphonoacetate (1.3ml, 8.0mmol), DIPEA (1.2ml, 6.6mmol) and finally a solution of dimethyl 4-oxobutane-1,1-dicarboxylate (103) (1.22g, 6.5mmol) in acetonitrile (10ml). A white precipitate formed almost immediately. After 6 hours, the mixture was poured into aqueous sodium hydrogencarbonate solution (1M, 100ml) and extracted with ether (3x100ml). The extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Column chromatography (25% ether / petrol) gave three colourless oils; dimethyl 4-oxobutane-1,1-dicarboxylate (103) (200mg,

16%), trimethyl *Z* 4-pentene-1,1,5-tricarboxylate (106) (85mg, 0.35mmol, 5% (6% based on amount of starting material recovered)), and trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105). Yield 867mg (3.6mmol, 55% (65% based on amount of starting material recovered)).

Trimethyl *E* 4-pentene-1,1,5-tricarboxylate:$\delta_H$: 6.82 dt 15.5Hz, 6.5Hz 1H ($C^4H$); 5.81 dt 15.5Hz, 1.5Hz 1H ($C^5H$); 3.66 s 6H ($RCH(CO_2C\underline{H}_3)_2$); 3.64 s 3H ($=CHCO_2C\underline{H}_3$); 3.30 t 7.5Hz 1H ($C^1H$); 2.18 q 7.0Hz, 6.5Hz 2H ($C^3H_2$); 1.95 q 8.0Hz, 7.5Hz 2H ($C^2H_2$).$\delta_C$: 169.3 ($RCH(\underline{C}O_2Me)_2$); 166.7 ($=CH\underline{C}O_2Me$); 146.9 ($C^4$); 122.2 ($C^5$); 52.6 ($RCH(CO_2\underline{C}H_3)_2$); 51.5 ($=CHCO_2\underline{C}H_3$); 50.7 ($C^1$); 29.6, 27.0 ($C^2$ & $C^3$).$\nu_{max}$: 1732cm$^{-1}$ (C=O); 1659cm$^{-1}$ (C=C).**m/z(FAB)**: 213 (100%), 245 (60%, $[M+H]^+$), 267 (29%, $[M+Na]^+$).

**Preparation of Trimethyl *Z* 4-pentene-1,1,5-tricarboxylate (106)**[100]



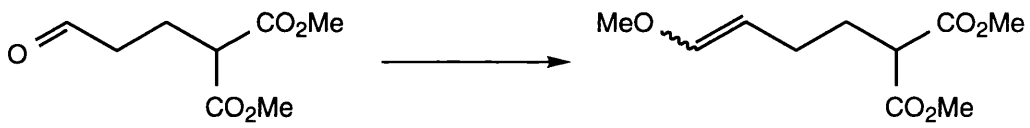

**103** **106**

To a stirred suspension of *bis*(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (0.48g, 1.5mmol) and 18-crown-6 (1.99g, 7.5mmol) in THF (30ml) at -78°C, was added a solution of potassium *bis*(trimethylsilyl)amide in toluene (0.5M, 3ml, 1.5mmol). After 20 minutes a solution of dimethyl 4-oxobutane-1,1-dicarboxylate (103) (282mg, 1.5mmol) in THF (15ml) was added, the mixture stirred for 5 hours, brought to room temperature for a further 36 hours, then poured into aqueous ammonium chloride solution (sat., 50ml). After extraction with ether (4x100ml) the organic phase was washed with water (100ml), brine (100ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow

oil. Column chromatography (40% ether / petrol) gave trimethyl *Z* 4-pentene-1,1,5-tricarboxylate (106) as a colourless oil. Yield 244mg (1.0mmol, 67%).

$\delta_H$: 6.15 dt 11.5Hz, 7.5Hz 1H ($C^4H$); 5.79 dt 11.5Hz, 1.5Hz 1H ($C^5H$); 3.71 s 6H ($RCH(CO_2C\underline{H}_3)_2$); 3.67 s 3H ($=CHCO_2C\underline{H}_3$); 3.37 t 7.5Hz 1H ($C^1H$); 2.69 m 2H ($C^3$); 2.03 m 2H ($C^2$).$\delta_C$: 169.5 ($RCH(\underline{C}O_2Me)_2$); 166.4 ($=CH\underline{C}O_2Me$); 147.9 ($C^4$); 120.6 ($C^5$); 52.5 ($RCH(CO_2\underline{C}H_3)_2$); 51.1 ($=CHCO_2\underline{C}H_3$); 51.0 ($C^1$); 27.9, 26.5 ($C^2$ & $C^3$).$\nu_{max}$: 1732cm$^{-1}$ (C=O); 1650cm$^{-1}$ (C=C).**m/z(FAB)**: 245 (100%, $[M+H]^+$); 213 (70%, $[M-OMe]^+$).

## Preparation of Dimethyl 5-methoxy-4-pentene-1,1-dicarboxylate (107)[100]




**103** **107**

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (2.52g, 7.35mmol) in THF (20ml) at -78°C was added dropwise a freshly prepared solution of LDA (DIPA 1.0ml, 0.79g, 7.8mmol and *n*-butyllithium 1.5M in hexane, 5.1ml, 7.9mmol) in THF (10ml) at -78°C. A red solution was obtained, and after 40 minutes a solution of dimethyl 4-oxobutane-1,1-dicarboxylate (103) (0.69g, 3.7mmol) in THF (20ml) at -78°C was added dropwise, and the mixture allowed to warm to room temperature. After 16 hours the mixture was poured into aqueous sodium hydrogencarbonate solution (1M, 100ml), extracted with ether (3x130ml), and the combined extracts washed with brine (100ml). The solvent was evaporated under reduced pressure, the residue dissolved in THF (30ml), refluxed for 4 hours, cooled, and the THF evaporated under reduced pressure. Column

chromatography (20% ether / petrol) gave dimethyl 5-methoxy-4-pentene-1,1-dicarboxylate (107) (mainly the *E* isomer) as a colourless oil. Yield 310mg (1.4mmol, 38%).

$\delta_H$: 6.26 d 12.5Hz 1H ($C^5H$); 4.62 dt 12.5Hz, 7.0Hz 1H ($C^4H$); 3.71 s 6H ($CO_2CH_3$); 3.47 s 3H (=CHOC<u>H</u>$_3$); 3.37 t 2.5Hz 1H ($C^1H$); 2.00-1.90 m 4H ($C^2H_2$ & $C^3H_2$).$\delta_C$: 169.8 (<u>C</u>$O_2$Me); 148.2 ($C^5$); 100.7 ($C^4$); 55.8 (=CHO<u>C</u>$H_3$); 52.4 ($CO_2$<u>C</u>$H_3$); 50.6 ($C^1$); 29.6, 25.4 ($C^2$ & $C^3$).$\nu_{max}$: 1736cm$^{-1}$ (C=O); 1655cm$^{-1}$ (C=C).**m/z(FAB)**: 153 (100%), 84 (91%), 217 (62%, $[M+H]^+$).

**<u>Preparation of *E* and *Z* Dimethyl 4-(benzyloxyimino)butane-1,1-dicarboxylate (108)</u>**[100]

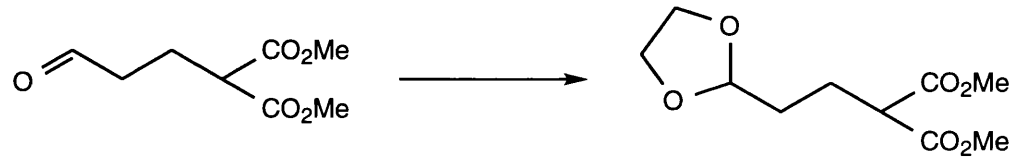

**103** ***E,Z* 108**

A stirred mixture of dimethyl 4-oxobutane-1,1-dicarboxylate (103) (390mg, 2.1mmol), pyridine (0.5ml), molecular sieves (4Å, powdered, 1g) and *O*-benzylhydroxylamine hydrochloride (516mg, 3.2mmol) in ethanol (10ml) was refluxed for 5 hours. After cooling the solvent was evaporated under reduced pressure to give a dry powder, which was stirred in ether (100ml) for 15 minutes. The ether was filtered and evaporated under reduced pressure to a yellow oil. Column chromatography (20% ether / petrol) gave a mixture of *E* and *Z* isomers of dimethyl 4-(benzyloxyimino)butane-1,1-dicarboxylate, in the ratio 10 : 17 (by $^1H$ NMR), as a colourless oil. Yield 283mg (0.96mmol, 46%). Small samples of each isomer for characterisation were also obtained from the column chromatography.

Dimethyl *E* 4-(benzyloxyimino)butane-1,1-dicarboxylate:$\delta_H$: 7.28-7.39 m 5H (ArH); 6.68 t 5.5Hz 1H (CH=N); 5.09 s 2H ($OCH_2$); 3.72 s 6H ($CH_3$); 3.37 t 6.5Hz 1H ($C^1H$); 2.40 td 8.0Hz, 5.5Hz 2H ($C^3H_2$); 2.10 q 7.5Hz 2H ($C^2H_2$).$\delta_C$: 169.3 (C=O); 150.1 (C=N); 137.8 (C-$CH_2O$-); 128.0, 127.9, 127.8 (Aromatic CH); 75.9 ($OCH_2$); 52.6 ($CH_3$); 51.0 ($C^1$); 25.4, 23.7 ($C^2$ & $C^3$).$\nu_{max}$: 1732$cm^{-1}$ (C=O); 1633$cm^{-1}$ (C=N).**m/z(FAB)**: 91 (100%, $[PhCH_2]^+$), 294 (87%, $[M+H]^+$).

Dimethyl *Z* 4-(benzyloxyimino)butane-1,1-dicarboxylate:$\delta_H$: 7.41 t 5.5Hz 1H (CH=N); 7.28-7.39 m 5H (ArH); 5.04 s 2H ($OCH_2$); 3.74 s 6H ($CH_3$); 3.41 t 7.5Hz 1H ($C^1H$); 2.30-2.20 m 2H ($C^3H_2$); 2.10 q 7.5Hz 2H ($C^2H_2$).$\delta_C$: 169.4 (C=O); 149.3 (C=N); 137.5 (C-$CH_2O$-); 128.4, 128.3, 127.8 (Aromatic CH); 75.7 ($OCH_2$); 52.6 ($CH_3$); 50.7 ($C^1$); 27.3, 25.5 ($C^2$ & $C^3$).$\nu_{max}$: 1735$cm^{-1}$ (C=O).**m/z(FAB)**: 91 (100%, $[PhCH_2]^+$), 189 (89%, $[M+H]^+$).

## Preparation of 2-(3',3'-Di(methoxycarbonyl)propyl)-1,3-dioxolane (109)



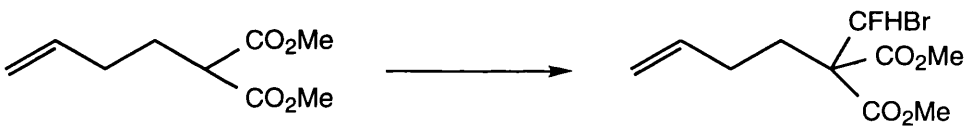

**103** **109**

A mixture of dimethyl 4-oxobutane-1,1-dicarboxylate (103) (1.00g, 5.3mmol), ethylene glycol (0.35g, 5.6mmol), *p*-toluenesulphonic acid (8mg) and benzene (5ml) was refluxed for 6 hours below a Dean-Stark apparatus containing magnesium sulphate, then cooled and poured into aqueous sodium hydrogencarbonate solution (sat., 50ml). This mixture was extracted with ether

(3x80ml) and the combined organic layers dried ($MgSO_4$) and evaporated under reduced pressure to give a pale brown oil. Distillation gave 2-(3',3'-di(methoxycarbonyl)propyl)-1,3-dioxolane (109) as a colourless oil. Yield 642mg (2.8mmol, 52%).

**b.p.**~150°C at 0.35mmHg.$\delta_H$: 4.85 t 4.5Hz 1H ($C^2H$); 4.00-3.75 m 4H ($C^4H_2$ & $C^5H_2$); 3.71 s 6H ($CH_3$); 3.44 t 7.5Hz 1H ($C^{3'}H$); 2.01 dt 8.0Hz, 7.5Hz 2H ($C^{2'}H_2$); 1.75-1.6 m 2H ($C^{1'}H_2$).$\delta_C$: 169.7 ($\underline{C}O_2Me$); 103.7 ($C^2$); 64.9 ($C^4$ & $C^5$); 52.5 ($CO_2\underline{C}H_3$); 51.2 ($C^{3'}$); 31.1 & 23.1 ($C^{1'}H_2$ & $C^{2'}H_2$).$\nu_{max}$: 1752cm$^{-1}$ (C=O); 1735cm$^{-1}$ (C=O).**m/z(FAB)**: 233 (100%, $[M+H]^+$).**High Res.**: Found ($[M+H]^+$) 233.1020; $[C_{10}H_{16}O_6+H]^+$ requires 233.1025.

## Preparation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112)[100]



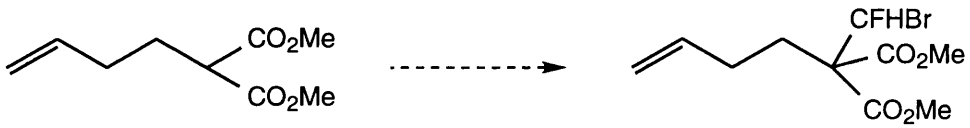

**102** **112**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with pentane, 100mg, 2.5mmol) in ether (4ml) at 0°C, was added over 15 minutes a solution of dimethyl 4-pentene-1,1-dicarboxylate (102) (298mg, 1.6mmol) in ether (5ml). After 35 minutes the mixture was evaporated under reduced pressure at 0°C then heptane (10ml, pre-cooled in an ice bath) was added, and the mixture cooled to -78°C. Dibromofluoromethane (3ml, excess) was added over 40 minutes, the mixture rapidly stirred for 2.5 hours before being warmed to room temperature, when a milky appearance was attained. After 12 hours at reflux, the mixture was cooled, poured into water (50ml) and the aqueous phase extracted with ether

(3x75ml). The combined organic extracts were washed with water (50ml), brine (50ml), dried ($MgSO_4$) and evaporated. The resulting pale yellow oil was preadsorbed and chromatographed (0-4% ether / petrol) to give dimethyl 4-pentene-1,1-dicarboxylate (102) (70mg, 23%) and dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (233mg, 0.78mmol, 49% (64% based on starting material recovered)) as colourless oils.

$\delta_H$: 6.90 d 47.5Hz 1H ($C^1H$); 5.76 ddt 17.0Hz, 10.0Hz, 6.0Hz 1H ($C^5H$); 5.05 ddd 17.0Hz, 3.0Hz, 1.5Hz 1H (one of $C^6H$); 5.01-4.95 m 1H (one of $C^6H$); 3.79 s 3H ($CH_3$); 3.76 s 3H ($CH_3$); 2.30-2.10 m 3H ($C^3H_2$ & one of $C^4H_2$); 2.10-1.90 m 1H (one of $C^4H_2$).$\delta_C$: 167.0, 166.9 ($\underline{C}O_2Me$); 136.9 ($C^5$); 115.5 ($C^6$); 94.0 d 263.5Hz ($C^1$); 63.9 d 18.0Hz ($C^2$); 53.1, 53.0 ($CH_3$); 30.7 ($C^4$); 28.6 d 3.0Hz ($C^3$).$\delta_F$: -146.5 d 48.0Hz.$\nu_{max}$: 1745$cm^{-1}$ (C=O); 1641$cm^{-1}$ (C=C).**m/z(FAB)**: 149 (100%), 297 (80%, $[M\{^{79}Br\}+H]^+$), 299 (71%, $[M\{^{81}Br\}+H]^+$).

## Attempted Preparation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) using Potassium *tert*-butoxide

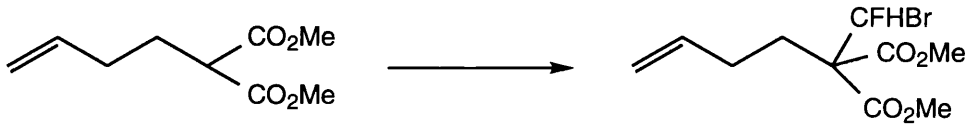



**102** **112**

To a stirred suspension of potassium *tert*-butoxide (200mg, 1.8mmol) in *tert*-butanol (5ml) at 0°C, was added over 10 minutes a solution of dimethyl 4-pentene-1,1-dicarboxylate (102) (306mg, 1.6mmol) in *tert*-butanol (3ml). After 10 minutes the mixture had solidified and was warmed to room temperature where it liquified, and dibromofluoromethane (2ml, excess) was added over 10 minutes. Stirring continued for 24 hours then the mixture poured into water (100ml) and the aqueous

phase extracted with ether (3x100ml). The combined organic extracts were washed with water (50ml), brine (50ml), dried ($MgSO_4$) and evaporated to give an oil (8mg) which contained nothing identifiable.

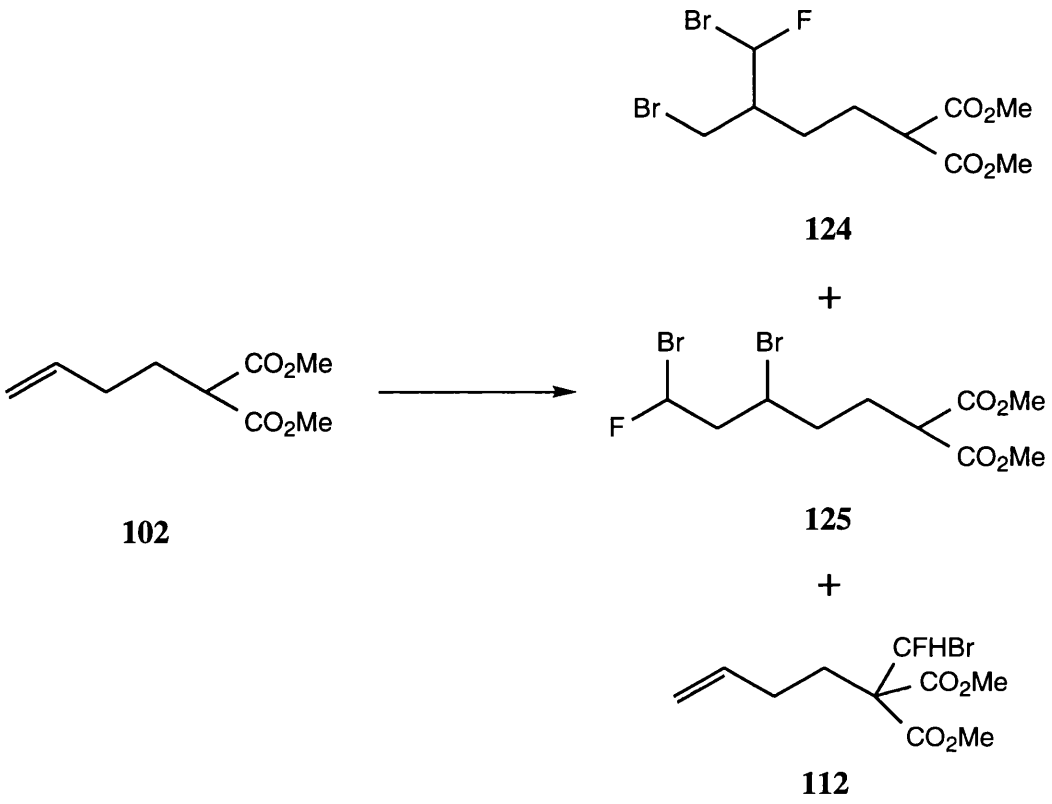
**Attempted Preparation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) using Potassium *bis*(trimethylsilyl)amide**




**102** **112**

To a stirred mixture of 18-crown-6 (400mg, 1.5mmol) and potassium *bis*(trimethylsilyl)amide (0.5M in toluene, 2.4ml, 1.2mmol) at 0°C, was added dropwise a solution of dimethyl 4-pentene-1,1-dicarboxylate (102) (150mg, 0.81mmol) in benzene (2ml). After 20 minutes the mixture had changed through red to black, and dibromofluoromethane (1.5ml, excess) was added in one portion. Stirring continued for 24 hours then the mixture was poured into aqueous sodium hydrogen carbonate solution (sat., 100ml) and the aqueous phase extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil Column chromatography (2-6% ether / petrol) gave two colourless oils; dimethyl 4-pentene-1,1-dicarboxylate (102) (30mg, 20%) and dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112). Yield 49mg (0.16mmol, 20%).

**Reaction of Dimethyl 4-pentene-1,1-dicarboxylate (102) with Dibromofluoromethane in the Presence of Triethylborane**



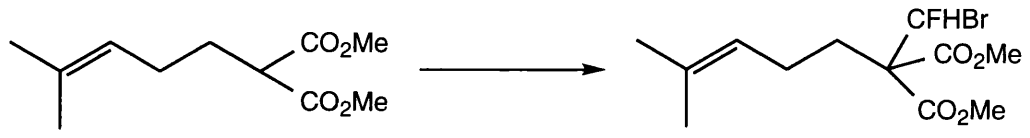

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed in pentane, 100mg, 2.5mmol) in ether (1ml) at 0°C was added dropwise over 10 minutes dimethyl 4-pentene-1,1-dicarboxylate (102) (300mg, 1.6mmol) in ether (4ml). After 30 minutes, the mixture was evaporated under reduced pressure at 0°C, and DME (5ml) added, followed by triethylborane (0.23ml, 1.6mmol). After 10 minutes dibromofluoromethane (2.5ml, excess) was added, the mixture stirred for 1 hour, warmed to room temperature and stirred for another 12 hours. Air was bubbled into the mixture for 10 minutes, then the mixture was poured into water (75ml) and extracted with ether (3x75ml). The combined organic layers were washed with water (50ml) and brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography (2-6% ether / petrol) gave three colourless oils; dimethyl 4-pentene-1,1-dicarboxylate (102) (99mg, 33%), dimethyl

1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (11mg, 37μmol, 2%) and the final fraction which was a mixture of inseparable materials (207mg, 0.55mmol, 34%). The following data from the mixture led us to believe it was a mixture of dimethyl 4,6-dibromo-6-fluorohexane-1,1-dicarboxylate (125) with a small amount of dimethyl 5-bromo-4-bromomethyl-5-fluoropentane-1,1-dicarboxylate (124) with a trace of another fluorinated impurity.

Dimethyl 4,6-dibromo-6-fluorohexane-1,1-dicarboxylate:$\delta_H$: 6.8-6.5 dm 51.0Hz 1H (CFHBr); 4.15-4.0 br s 1H (CHBr); 3.75 s 6H ($CO_2CH_3$); 3.50-3.40 m 1H ($RC\underline{H}(CO_2CH_3)_2$); 2.85-2.65 m 1H (one of $C^5H_2$); 2.65-2.45 m 1H (one of $C^5H_2$); 2.19 s tdd 14.0Hz, 6.5Hz, 1.5Hz 1H (one of $C^3H_2$); 2.03 tdd 14.0Hz, 6.0Hz, 1.0Hz 1H (one of $C^3H_2$); 1.95-1.85 m 2H ($C^2H_2$) $\delta_C$: 169.3 ($CO_2Me$); 94.8 d 251.0Hz (CFHBr); 52.7 ($R\underline{C}H(CO_2Me)_2$); 50.7 ($CO_2\underline{C}H_3$); 49.7 ($C^5$); 48.1 ($C^6$); 36.0 ($C^4$); 26.4 ($C^3$).$\delta_F$: -133.5 dt 49.5Hz, 11.0Hz (CFHBr).$\nu_{max}$:1735cm$^{-1}$ (C=O), 3287 cm$^{-1}$ (NH).**m/z(FAB)**: 176 (100%), 378.938 (94%, [M{$^{79}$Br,$^{81}$Br}]$^+$), 376.940 (51%, [M{$^{79}$Br,$^{79}$Br}]$^+$), 380.936 (50%, [M{$^{81}$Br,$^{81}$Br}]$^+$).The [MH]$^+$ triplet was also observed.**High Res.(FAB)**: Found ([M{$^{79}$Br,$^{79}$Br}]$^+$) 376.9390; $[C_{21}H_{23}FBr_2O_4]^+$ requires 376.9399.

| | | | | |
|---|---|---|---|---|
| **Analysis**: | Observed | C 32.28% | H 4.00% | Br 42.58% |
| | $C_{21}H_{23}FBr_2O_4$ requires | C 31.86% | H 3.74% | Br 42.58% |

**Preparation of Dimethyl 1-bromo-1-fluoro-6-methyl-5-heptene-2,2-dicarboxylate (114)**

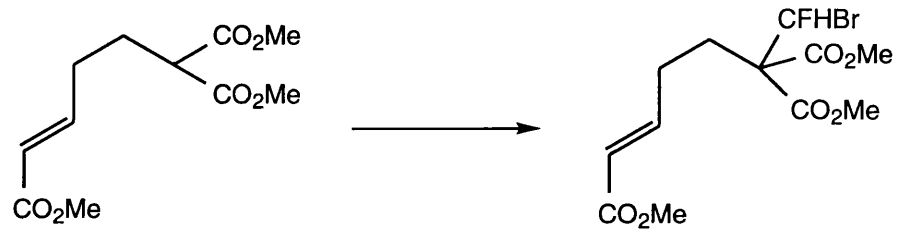



**104** **114**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with pentane, 90mg, 2.2mmol) in ether (4ml) at 0°C, was added over 15 minutes a solution of dimethyl 5-methyl-4-hexene-1,1-dicarboxylate (104) (308mg, 1.4mmol) in ether (5ml). After 2 hours the mixture was evaporated under reduced pressure at 0°C, dibromofluoromethane (2ml, excess) added dropwise, and the mixture stirred for 1 hour before being warmed to room temperature. After 3 hours, benzene (10ml) was added, the mixture refluxed for 6 hours, cooled, poured into water (50ml) and the aqueous phase extracted with ether (3x80ml). The combined organic phases were washed with water (50ml), brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting pale yellow oil was preadsorbed and chromatographed (0-4% ether / petrol) to give dimethyl 1-bromo-1-fluoro-6-methyl-5-heptene-2,2-dicarboxylate (114) as a colourless oil. Yield 128mg (0.39mmol, 28%).

$\delta_H$: 6.90 d 47.5Hz 1H ($C^1H$); 5.15-5.05 m 1H ($C^5H$); 3.81 s 3H ($OCH_3$); 3.78 s 3H ($OCH_3$); 2.25-1.90 m 4H ($C^3H_2$ & $C^4H_2$); 1.69 s 3H ($CH_3$); 1.60 s 3H ($CH_3$).$\delta_C$: 167.2, 167.2 ($\underline{C}O_2Me$); 133.2 ($C^6$); 122.6 ($C^5$); 94.0 d 263.5Hz ($C^1$); 64.1 d 17.5Hz ($C^2$); 53.1, 53.0 ($OCH_3$); 31.8 ($C^4$); 25.6 (*cis*-$CH_3$); 23.1 d 2.5Hz ($C^3$); 17.6 (*trans*-$CH_3$).$\delta_F$: -140.8 d 47.5Hz.$\nu_{max}$: 1750$cm^{-1}$ (C=O); 1736$cm^{-1}$ (C=O).**m/z(FAB)**: 325 (100%, $[M\{^{79}Br\}+H]^+$), 323 (55%), 327 (45%, $[M\{^{81}Br\}+H]^+$).**High Res.(FAB)**: Found ($[M\{^{79}Br\}+H]^+$) 325.0440; $[C_{12}H_{18}{}^{79}BrFO_4+H]^+$ requires 325.0451.

**Preparation of Trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115)[100]**



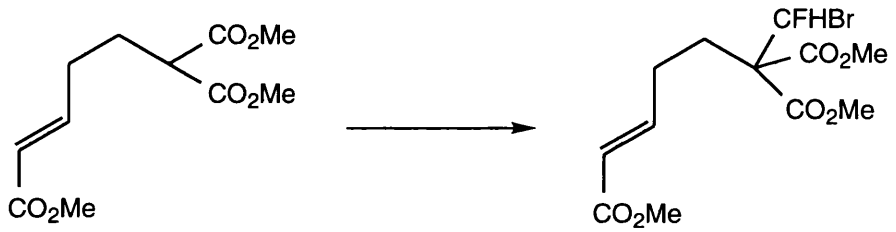

**105** **115**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 80mg, 2.0mmol) in THF (4ml) at 0°C was added over 30 minutes a solution of trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105) (299mg, 1.1mmol) in THF (16ml). After 30 minutes dibromofluoromethane (4ml, excess) was added, the mixture allowed to reach room temperature, and stirring continued for a further 48 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 50ml) and extracted with ether (3x100ml). The organic phase was washed with brine (100ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (30% ether / petrol) gave two colourless oils; trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105) (17mg, 6%) and trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115), which gave colourless crystals on extended storage in the refrigerator. Yield 145mg (0.41mmol, 33% (35% based on amount of starting material recovered)).

**m.p.**50-51°C.$\delta_H$: 6.93 d 47.5Hz 1H ($C^1H$); 6.91 dt 16.0Hz, 6.5Hz 1H ($C^5H$); 5.85 dt 15.5Hz, 1.5Hz 1H ($C^6H$); 3.79 s 3H ($CH_3$); 3.76 s 3H ($CH_3$); 3.71 s 3H ($CH_3$); 2.50-2.20 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 166.8, 166.7, 166.6 ($CO_2Me$); 147.2 ($C^5$); 121.7 ($C^6$); 94.0 d 263.0Hz ($C^1$); 63.7 d 18.5Hz ($C^2$); 53.4, 53.3, 51.5 ($CH_3$); 29.4 ($C^4$); 27.1 d 2.5Hz ($C^3$).$\delta_F$: -146.9 d 47.5Hz.$\nu_{max}$: 1743$cm^{-1}$

(C=O); 1659cm$^{-1}$ (C=C).**m/z(FAB)**: 355 (100%, [M{$^{79}$Br}+H]$^+$), 357 (91%, [M{$^{81}$Br}+H]$^+$).

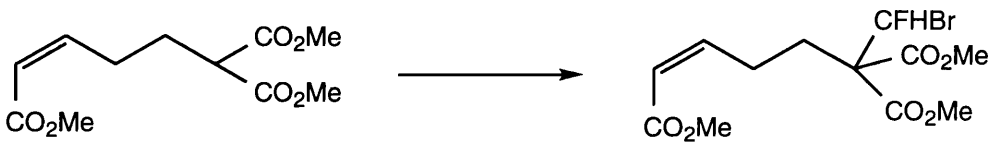
**Attempted Preparation of Trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115) Using Copper Powder**




**105** **115**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 80mg, 2.0mmol) and copper powder (185mg, 1.2mmol) in ether (4ml) at 0°C was added over 10 minutes a solution of trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105) (311mg, 1.2mmol) in ether (16ml). After 40 minutes dibromofluoromethane (2ml, excess) was added, the mixture allowed to reach room temperature, and stirring continued for a further 24 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 50ml) and filtered through Celite, washing through with ether (2x50ml). The layers were separated, and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (20% DCM / petrol) gave a colourless oil, which was a mixture of trimethyl *E* 4-pentene-1,1,5-tricarboxylate (105) (20mg, 6%) and trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115) (5mg, 17μmol, 1%),

**Preparation of Trimethyl *Z* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (116)[100]**

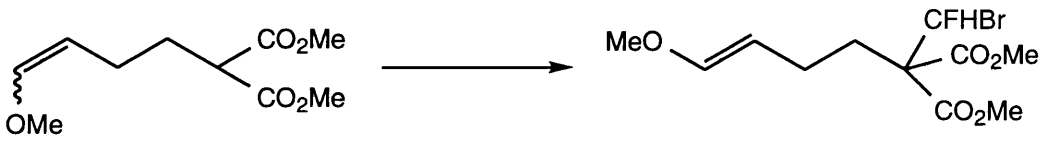



**106** **116**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 76mg, 1.9mmol) in ether (5ml) at 0°C was added dropwise a solution of trimethyl *Z* 4-pentene-1,1,5-tricarboxylate (106) (258mg, 1.1mmol) in ether (10ml). After 40 minutes dibromofluoromethane (2ml, excess) was added, the mixture allowed to reach room temperature, and stirring continued for a further 20 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 50ml) and extracted with ether (3x75ml). The organic phase was washed with brine (50ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (35% ether / petrol) gave two colourless oils; trimethyl *Z* 4-pentene-1,1,5-tricarboxylate (106) (32mg, 12%) and trimethyl *Z* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (116). Yield 146mg (0.41mmol, 39%).

$\delta_H$: 6.90 d 47.5Hz 1H ($C^1H$); 6.16 dt 11.5Hz, 4.0Hz 1H ($C^5H$); 5.78 dt 11.5Hz, 1.5Hz 1H ($C^6H$); 3.79 s 3H ($CH_3$); 3.76 s 3H ($CH_3$); 3.67 s 3H ($CH_3$); 2.5-2.9 m 2H ($C^4H_2$); 2.3-2.1 m 2H ($C^3H_2$).$\delta_C$: 166.9, 166.8, 166.3 ($CO_2Me$); 147.7 ($C^5$); 120.3 ($C^6$); 93.8 d 263.5Hz ($C^1$); 63.9 d 17.5Hz ($C^2$); 53.3, 53.2, 51.1 ($CH_3$); 30.5 ($C^4$); 24.0 d 3.0Hz ($C^3$).$\delta_F$: -147.3 d 47.5Hz.$\nu_{max}$: 1738$cm^{-1}$ (C=O); 1660$cm^{-1}$ (C=C).**m/z(FAB)**: 355 (100%, $[M\{^{79}Br\}+H]^+$), 357 (94%, $[M\{^{81}Br\}+H]^+$).

**Preparation of Dimethyl *E* 1-bromo-1-fluoro-5-methoxy-4-pentene-2,2-dicarboxylate (117)**

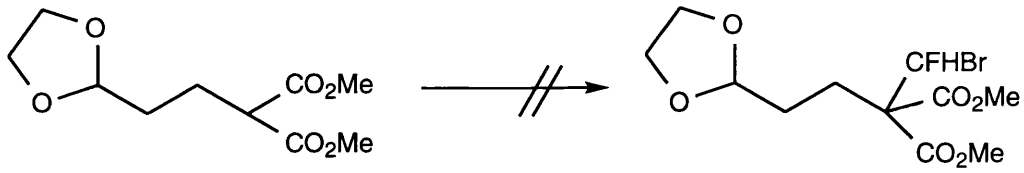



*E,Z* **107** *E* **117**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed (pentane), 102mg, 2.5mmol) in THF (6ml) and ether (6ml) at 0°C was added over 10 minutes a solution of dimethyl 5-methoxy-4-pentene-1,1-dicarboxylate (107) (299mg, 1.1mmol) in THF (4ml) and ether (4ml). After 2 hours dibromofluoromethane (4ml, excess) was added over 4 minutes, the mixture allowed to reach room temperature, and stirring continued for a further 48 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 50ml) and extracted with ether (3x100ml). The organic phase was washed with brine (100ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (20% ether / petrol) gave two colourless oils; dimethyl 5-methoxy-4-pentene-1,1-dicarboxylate (107) (89mg, 29%) and dimethyl *E* 1-bromo-1-fluoro-5-methoxy-4-pentene-2,2-dicarboxylate (117). Yield 17mg (0.05mmol, 2% (5% based on amount of starting material recovered)).

$\delta_H$: 6.89 d 47.5Hz 1H ($C^1H$); 6.31 d 12.5Hz 1H ($C^6H$); 4.66 quin 12.5Hz, 6.5Hz 1H ($C^5H$); 3.79 s 3H ($CO_2CH_3$); 3.76 s 3H ($CO_2CH_3$); 3.48 s 3H (=CHO$\underline{C}H_3$); 2.3-2.0 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 167.1, 166.9 ($CO_2Me$); 148.0 ($C^6$); 101.3 ($C^5$); 94.0 d 261.5Hz ($C^1$); 64.1 d 18.0Hz ($C^2$); 55.9 (=CH(O$\underline{C}H_3$); 53.4, 53.3 ($CO_2\underline{C}H_3$); 32.9, 23.0 ($C^3$ & $C^4$).$\delta_F$: -141.3 d 47.5Hz.$\nu_{max}$: 1735$cm^{-1}$ (C=O); 1662$cm^{-1}$ (C=C).**m/z(FAB)**: 75 (100%), 84 (86%), 434 (65%), 436 (61%), 329 (54%, $[M\{^{81}Br\}+H]^+$), 327 (54%, $[M\{^{79}Br\}+H]^+$).**High Res.(FAB)**: Found ($[M\{^{79}Br\}+H]^+$) 327.0255; $[C_{11}H_{16}{}^{79}BrFO_5+H]^+$ requires 327.0243.

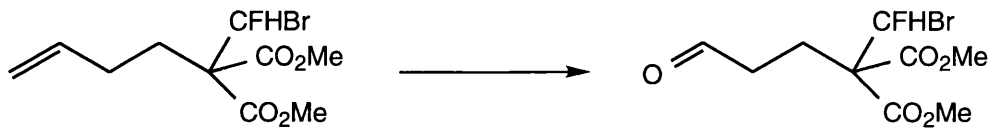
**Attempted Preparation of 2-(4'-Bromo-4'-fluoro-3',3'-di(methoxycarbonyl)butyl)-1,3-dioxolane (119)**




**109** **119**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed (ether), 77mg, 1.9mmol) in THF (2ml) at 0°C was added dropwise a solution of 2-(3',3'-di(methoxycarbonyl)propyl)-1,3-dioxolane (109) (280mg, 1.2mmol) in THF (5ml). After 30 minutes dibromofluoromethane (2.5ml, excess) was added dropwise, the mixture allowed to reach room temperature, and stirring continued for a further 48 hours. The mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 75ml) and extracted with ether (3x100ml). The combined organic phases were washed with aqueous sodium hydrogencarbonate solution (0.5M, 75ml), brine (75ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (30% ether / petrol) gave 2-(3',3'-di(methoxycarbonyl)propyl)-1,3-dioxolane (109) as a colourless oil (176mg, 63%).

**Preparation of Dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113)**

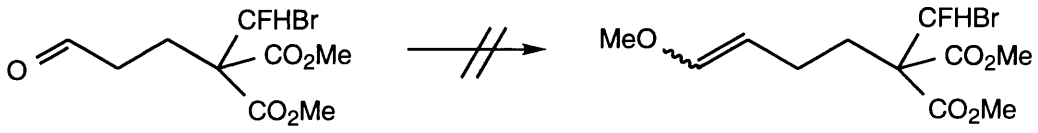



**112** **113**

Into a stirred solution of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (643mg, 2.1mmol) in methanol (50ml) at -78°C was bubbled a mixture of ozone and oxygen until the solution appeared blue. The mixture was stirred under a flow of nitrogen until the blue colour disappeared, warmed to room temperature and dimethyl sulphide (6ml, excess) added. Nitrogen was bubbled through the solution for 18 hours, then evaporation under reduced pressure gave a colourless oil. Column chromatography (30% ether / petrol) gave dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) as a colourless oil. Yield 535mg (1.7mmol, 80%).

$\delta_H$: 9.74 s 1H (CHO); 6.94 d 47.5Hz ($C^1H$); 3.79 s 3H ($CH_3$); 3.76 s 3H ($CH_3$); 2.85-2.70 m 1H (one of $CH_2$); 2.70-2.55 m 1H (one of $CH_2$); 2.55-2.40 m 2H ($CH_2$).$\delta_C$: 200.1 (CHO); 166.5, 166.6 ($CO_2Me$); 94.4 d 262.0Hz ($C^1$); 63.3 d 18.5Hz ($C^2$); 53.4, 53.5 ($CH_3$); 39.2, 22.9 ($C^3$ & $C^4$).$\delta_F$: -141.7 d 47.5Hz.$\nu_{max}$: 1739$cm^{-1}$ (C=O).**m/z(FAB)**: 299 (100%, $[M\{^{79}Br\}+H]^+$), 301 (89%, $[M\{^{81}Br\}+H]^+$).**High Res.**: Found ($[M\{^{79}Br\}+H]^+$) 298.9920; $[C_9H_{12}{}^{79}BrFO_5+H]^+$ requires 298.9930.

## Attempted Preparation of Dimethyl 1-bromo-1-fluoro-6-methoxy-5-hexene-2,2-dicarboxylate (117)




**113** **117**

To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (364mg, 1.1mmol) in THF (3ml) at 0°C was added dropwise a freshly prepared solution of LDA (DIPA 0.144ml, 0.11g, 1.1mmol and *n*-butyllithium 2.5M in

hexane, 0.44ml, 1.1mmol) in THF (2ml) at -78°C. A red solution was obtained, and after 40 minutes the mixture was cooled to -78°C and a solution of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (150mg, 0.5mmol) in THF (10ml) at -78°C added dropwise. The mixture was allowed to warm to room temperature then refluxed. After 16 hours the mixture was poured into aqueous sodium hydrogencarbonate solution (1M, 30ml), extracted with ether (3x30ml), and the combined extracts washed with brine (30ml), dried ($MgSO_4$). The solvent was evaporated under reduced pressure to a thick brown oil which was preadsorbed onto silica. Column chromatography (30% ether-petrol) gave no identifiable products.

**Preparation of *Z* Dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118)**

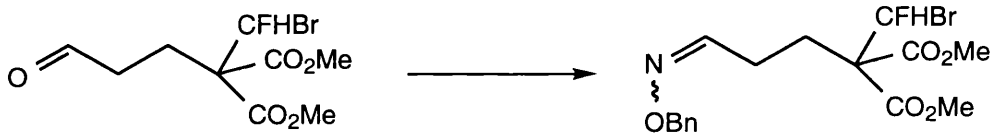

***E,Z* 108** ***Z* 118**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with pentane, 74mg, 1.6mmol) in ether (2ml) at 0°C, was added dropwise a solution of dimethyl 4-(benzyloxyimino)butane-1,1-dicarboxylate (108) (293mg, 1.0mmol) in ether (6ml). After 30 minutes dibromofluoromethane (2ml, excess) was added dropwise. The solution was allowed to room temperature, stirred for a further 24 hours, poured into aqueous sodium hydrogencarbonate solution (sat., 50ml), and extracted with ether (3x75ml). The organic phase was washed with brine (75ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. Column chromatography (25% ether / petrol) gave two colourless oils;

*E,Z* dimethyl 4-(benzyloxyimino)butane-1,1-dicarboxylate (108) (49mg, 17%) and dimethyl *Z* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118). Yield 42mg (0.10mmol, 10% (13% based on starting material recovered)).

$\delta_H$: 7.43 t 5.5Hz 1H (CH=N); 7.5-7.3 m 5H (ArH); 6.92 d 47.5Hz 1H ($C^1H$); 5.04 s 2H ($OCH_2$); 3.78 s 3H ($CH_3$); 3.75 s 3H ($CH_3$); 2.5-2.2 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 166.6, 166.7 ($CO_2Me$); 149.5 (C=N); 137.4 (C-$OCH_2$); 128.2, 128.4, 127.8 (Aromatic CH); 93.9 d 263.0Hz ($C^1$); 75.7 ($OCH_2$); 63.7 d 18.0Hz ($C^2$); 53.4, 53.3 ($CO_2CH_3$); 27.8, 25.0 ($C^3$ & $C^4$).$\delta_F$: -141.5 d 47.0Hz.$\nu_{max}$: 1743cm$^{-1}$ (C=O); 1436cm$^{-1}$ (C=C).**m/z(FAB)**: 91 (100%, $[PhCH_2]^+$), 404 (64%, $[M\{^{79}Br\}+H]^+$), 406 (63%, $[M\{^{81}Br\}+H]^+$).**High Res.(FAB)**: Found ($[M\{^{79}Br\}+H]^+$) 404.0500; $[C_{16}H_{18}{}^{79}BrFNO_5+H]^+$ requires 404.0509.

## Preparation of *E* and *Z* Dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118)



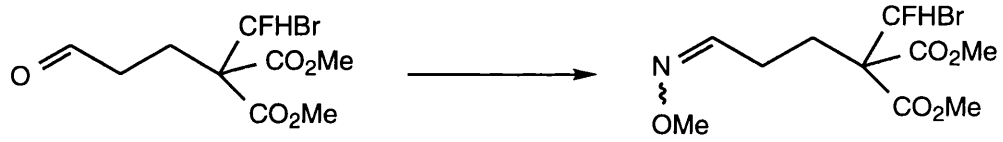

**113** ***E,Z* 118**

A stirred mixture of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (299mg, 1.0mmol), pyridine (0.3ml), molecular sieves (3Å, powdered, 1g) and *O*-benzylhydroxylamine hydrochloride (0.50g, 3.1mmol) in methanol (10ml) was refluxed for 5 hours. After cooling the solvent was evaporated under reduced pressure to give a dry powder, which was stirred in ether (100ml) for 15 minutes. The ether was filtered and evaporated under reduced pressure to give a yellow oil. Column chromatography (5-20% ether / petrol) gave two colourless oils; *E* dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118)

(160mg, 0.40mmol, 40%) and *Z* dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) (194mg, 0.48mmol, 48%), as colourless oils.

Dimethyl *E* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate:$\delta_H$: 7.5-7.25 m 5H (ArH); 6.92 d 47.5Hz ($C^1H$); 6.67 t 5.0Hz (CH=N); 5.09 s 2H ($OCH_2$); 3.75 s 3H ($CH_3$); 3.73 s 3H ($CH_3$); 2.62-2.47 m 1H (one of $CH_2$); 2.47-2.20 m 3H ($CH_2$ & one of $CH_2$).$\delta_C$: 166.7 ($CO_2Me$); 150.2 (C=N); 137.8 (C-$OCH_2$); 128.4, 128.0, 127.8 (Aromatic CH); 93.9 d 263.0Hz ($C^1$); 75.9 ($OCH_2$); 63.8 d 18.0Hz ($C^2$); 53.4, 53.3 ($CO_2CH_3$); 27.7 ($C^4$); 21.3 d 3.5Hz ($C^3$). $\delta_F$: -141.5 d 47.0Hz.$\nu_{max}$: 1744cm$^{-1}$ (C=O); 1631cm$^{-1}$ (C=N); 1436cm$^{-1}$ (C=C).**m/z(FAB)**: 404 (100%, $[M+H]^+$), 406 (93%, $[M\{^{81}Br\}+H]^+$).**High Res.(FAB)**: Found ($[M\{^{79}Br\}+H]^+$) 404.0520; $[C_{16}H_{18}{}^{79}BrFNO_5+H]^+$ requires 404.0509.

## Preparation of *E* and *Z* Dimethyl 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126)




**113** ***E,Z* 126**

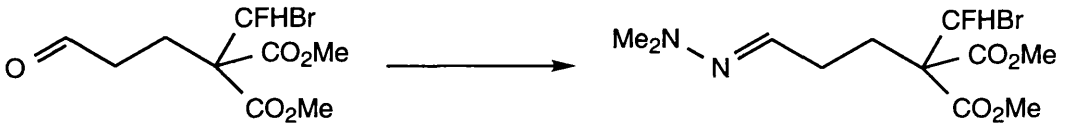
A mixture of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (299mg, 1.0mmol), pyridine (0.3ml), molecular sieves (3Å, powdered, 1g) and *O*-methylhydroxylamine hydrochloride (0.12g, 3.1mmol) in methanol (10ml) was refluxed for 5 hours, cooled, and the solvent evaporated under reduced pressure to give a dry powder, which was stirred in ether (100ml) for 15 minutes. The ether was filtered and evaporated under reduced pressure to a yellow oil. Column

chromatography (5-20% ether / petrol) gave dimethyl *Z* 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126) (188mg, 0.6mmol, 57%) as a pale yellow oil and dimethyl *E* 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126) (109mg, 0.33mmol, 33%) as a pale green oil.

Dimethyl *Z* 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate:$\delta_H$: 7.31 t 5.5Hz 1H (CH=N); 6.89 d 47.5Hz 1H ($C^1H$); 3.77 s 3H ($CH_3ON$); 3.77 s 3H ($CO_2CH_3$); 3.74 s 3H ($CO_2CH_3$); 2.5-2.1 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 166.7 ($CO_2Me$); 148.8 (C=N); 93.9 d 263.0Hz ($C^1$); 63.6 d 18.0Hz ($C^2$); 61.3 ($CH_3ON$); 53.3, 53.3 ($CO_2\underline{C}H_3$); 27.8 ($C^4$); 24.9 d 3Hz ($C^3$). $\delta_F$: -141.5 d 47.0Hz.$\nu_{max}$: 1743cm$^{-1}$ (C=O).**m/z(FAB)**: 328 (100%, [M{$^{79}$Br}+H]$^+$), 330 (98%, [M{$^{81}$Br}+H]$^+$).**High Res.(FAB)**: Found ([M{$^{79}$Br}+H]$^+$) 328.0910; [$C_{10}H_{14}{}^{79}BrFNO_5$+H]$^+$ requires 328.0916.

Dimethyl *E* 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate:$\delta_H$: 6.92 d 47.5Hz 1H ($C^1H$); 6.60 t 5.0Hz 1H (CH=N); 3.83 s 3H ($CH_3ON$); 3.79 s 3H ($CO_2CH_3$); 3.76 s 3H ($CO_2CH_3$); 2.6-2.4 m 1H (one of $CH_2$); 2.4-2.2 m 3H ($CH_2$ & one of $CH_2$).$\delta_C$: 166.7 ($CO_2Me$); 149.5 (C=N); 93.8 d 264.0Hz ($C^1$); 63.7 d 18.0Hz ($C^2$); 61.7 ($CH_3ON$); 53.4, 53.3 ($CO_2\underline{C}H_3$); 27.7 ($C^4$); 21.0 d 3Hz ($C^3$). $\delta_F$: -141.6 d 47.5Hz.$\nu_{max}$: 1747cm$^{-1}$ (C=O); 1632cm$^{-1}$ (C=N).**m/z(FAB)**: 328 (100%, [M{$^{79}$Br}+H]$^+$), 330 (95%, [M{$^{81}$Br}+H]$^+$). **High Res.(FAB)**: Found ([M{$^{79}$Br}+H]$^+$) 328.0910; [$C_{10}H_{14}{}^{79}BrFNO_5$+H]$^+$ requires 328.0916.

**Preparation of (Dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-Dimethylhydrazone (127)**

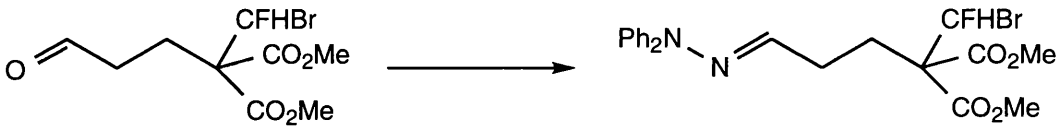



**113** **127**

To a stirred solution of *N,N*-dimethylhydrazine (0.11g, 0.14ml, 1.7mmol) in ether (5ml) at 0°C was added dropwise a solution of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (510mg, 1.7mmol) in ether (5ml). After 5 minutes, the mixture was warmed to room temperature, and 3 hours later anhydrous potassium carbonate (2g) added. The mixture was stirred for another hour, filtered and preadsorbed onto base washed silica. Column chromatography (base washed silica, 40% ether / cyclohexane gave (dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-dimethylhydrazone (127) as a colourless oil. Yield 518mg (1.5mmol, 89%).

$\delta_H$: 6.89 d 47.5Hz 1H ($C^1H$); 6.54 t 5.0Hz 1H (CH=N); 3.79 s 3H ($CO_2CH_3$); 3.76 s 3H ($CO_2CH_3$); 2.71 s 6H ($N(CH_3)_2$); 2.50-2.15 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 167.0, 167.0 ($CO_2Me$); 135.9 (C=N); 93.9 d 263.5Hz ($C^1$); 63.9 d 18.0Hz ($C^2$); 53.3, 53.2 ($CO_2\underline{C}H_3$); 43.1 ($N(CH_3)_2$); 29.2 ($C^4$); 28.1 d 2.5Hz ($C^3$).$\delta_F$: -141.0 d 48.5Hz.$\nu_{max}$: 1741cm$^{-1}$ (C=O); 1607cm$^{-1}$ (C=N).**m/z(FAB)**: 341 (100%, $[M\{^{79}Br\}+H]^+$), 343 (65%, $[M\{^{81}Br\}+H]^+$).**High Res.(FAB)**: Found ($[M+H]^+$) 341.0500; $[C_{11}H_{18}{}^{79}BrFN_2O_4+H]^+$ requires 341.0512.

**Preparation of (Dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-Diphenylhydrazone (128)**

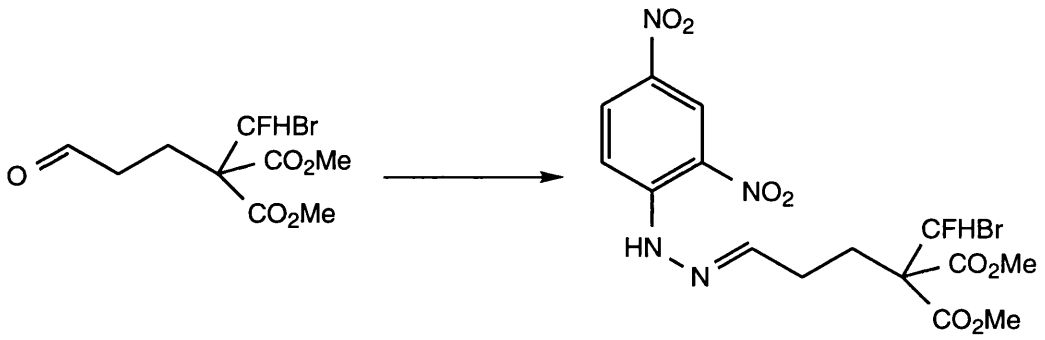



**113** **128**

To a stirred suspension of *N,N*-diphenylhydrazine hydrochloride (1.5g, 6.8mmol) in a mixture of water (25ml) and ether (150ml) was added sodium hydrogencarbonate (0.685g, 8.2mmol). After 5 minutes, stirring was stopped and the water removed by cannula. Magnesium sulphate was added, the mixture stirred for 5 minutes, then filtered and evaporated to give *N,N*-diphenylhydrazine as a red-brown oil. The *N,N*-diphenylhydrazine was added dropwise to a solution of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (223mg, 0.74mmol) in methanol (5ml) and the mixture stood for 2 days, then preadsorbed onto base washed silica. Column chromatography (base washed silica, 10-40% ether / petrol) gave (dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-diphenylhydrazone (128) as a colourless oil, which crystallised during extended storage in a refrigerator.Yield 326mg (0.70mmol, 94%).

**m.p.**73-73.5°C.$\delta_{\mathbf{H}}$: 7.35 t 8.0Hz 4H (*o*-ArH); 7.12 t 7.5Hz 2H (*p*-ArH); 7.06 d 7.5Hz 4H (*m*-ArH); 6.92 d 47.5Hz 1H ($C^1H$); 6.46 t 4.5Hz 1H (CH=N); 3.79 s 3H ($CO_2CH_3$); 3.76 s 3H ($CO_2CH_3$); 2.55-2.15 m 4H ($C^3H_2$ & $C^4H_2$).$\delta_C$: 167.0 ($CO_2Me$); 143.9 (C=N); 136.8 (C-N); 129.7 (*m*-C); 124.0 (*p*-C); 122.3 (*o*-C); 94.0 d 263.5Hz ($C^1$); 63.9 d 18.0Hz ($C^2$); 53.3, 53.2 ($CO_2\underline{C}H_3$); 28.5 ($C^4$); 27.9 d 2.5Hz ($C^3$).$\delta_F$: -141.5 d 47.0Hz.$\nu_{max}$: 1743cm$^{-1}$ (C=O); 1593cm$^{-1}$ (C=N).**m/z(FAB)**: 168 (100%, $[Ph_2N]^+$), 466 (48%, $[M\{^{81}Br\}]^+$), 464 (44%, $[M\{^{79}Br\}]^+$), 77 (11%, $[Ph]^+$).**High Res.(FAB)**: Found ($[M\{^{79}Br\}]^+$) 464.0740; $[C_{21}H_{22}{}^{79}BrFN_2O_4]^+$ requires 464.0747.

**Preparation of (Dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) 2',4'-Dinitrophenylhydrazone (129)**




**113** **129**

To 2,4-dinitrophenylhydrazine (0.25g, 1.3mmol) in ethanol (5ml) was added a few drops of concentrated sulphuric acid. The supernatent liquid was added dropwise to a solution of dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate (113) (148mg, 0.5mmol) in ethanol (5ml), which was then warmed for 5 minutes (50°C water bath). After cooling to 0°C the product was collected by filtration and recrystallised from methanol to give orange crystals of (dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) 2',4'-dinitrophenylhydrazone (129). Yield 205mg (0.43mmol, 85%).

**m.p.**141-142°C.$\delta_H$: 9.10 d 2.5Hz 1H ($C^{3'}H$); 8.30 dd 9.5Hz, 2.5Hz 1H ($C^{5'}H$); 7.92 d 9.5Hz 1H ($C^{6'}H$); 7.55 t 4.0Hz 1H (CH=N); 7.06 d 47.5Hz 1H ($C^1$); 3.82 s 3H ($CH_3$); 3.79 s 3H ($CH_3$); 2.80-2.60 m 1H (one of $CH_2$); 2.60-2.40 m 3H ($CH_2$ & one of $CH_2$).$\delta_C$: 166.6, 166.5 ($CO_2Me$); 150.3 (C=N); 145.0 ($C^{1'}$); 137.9, 128.9 (C-$NO_2$); 130.0 ($C^{5'}$); 123.4, 116.5 ($C^{3'}$ & $C^{6'}$); 94.0 d 262.5Hz ($C^1$); 63.5 d 18.5Hz ($C^2$); 53.5, 53.5 ($CO_2\underline{C}H_3$); 27.8 d 3.6Hz ($C^3$); 26.9 ($C^4$).$\delta_F$: -141.6 d 47.0Hz.$\nu_{max}$**(Nujol)**: 3295$cm^{-1}$ (NH); 1755$cm^{-1}$ (C=O); 1722$cm^{-1}$ (C=N).**m/z(FAB)**: 479 (100%, $[M\{^{79}Br\}+H]^+$), 481 (98%, $[M\{^{81}Br\}+H]^+$).**High Res.**: Found ($[M+H]^+$) 479.0220; $[C_9H_{12}{}^{79}BrFN_4O_5+H]^+$ requires 479.0214.

**Cyclisation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112)[100]**


**112** ***cis, trans* 135**

To a stirred solution of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (97mg, 325μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (5.5mg, 29μmol) and tri(*n*-butyl)tin hydride (97μl, 366μmol) in benzene (3.3ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (20% ether / petrol) gave an inseparable mixture of the two diastereomers of dimethyl 2-fluoro-3-methylcyclopentane-1,1-dicarboxylate (135), in the ratio *cis* : *trans* of 1 : 3, as a colourless oil. Yield 34mg (156μmol, 48%).

$\nu_{max}$: 1759cm$^{-1}$ (C=O); 1737cm$^{-1}$ (C=O).**m/z(FAB)**: 219 (100%, $[M+H]^+$).

Major diastereomer (*trans*): $\delta_H$: 5.10 dd 52.0Hz, 5.5Hz 1H ($C^2H$); 2.56 ddd 14.0Hz, 10.5Hz, 8.0Hz 1H (one of $C^5H_2$); 2.40-1.75 m 4H ($C^3H$, $C^4H_2$ & one of $C^5H_2$); 1.10 d 7.0Hz 3H ($CCH_3$).$\delta_C$: 168.5, 170.9 ($\underline{C}O_2Me$); 101.8 d 186Hz

($C^2$); 64.0 d 22.5Hz ($C^1$); 52.8 ($OCH_3$); 40.0 d 21.0Hz ($C^3$); 31.4 ($CH_2$); 29.6 d 5.5Hz ($CH_2$); 16.9 d 3.0Hz ($C\underline{C}H_3$).$\delta_F$: -183.4 dd 52.0Hz, 30.0Hz.

Minor diastereomer (*cis*): $\delta_H$: 5.18 dd 52.5Hz, 3.0Hz 1H ($C^2H$); 2.84-2.74 m 1H (one of $C^5H_2$); 1.75-2.40 m 4H ($C^3H$, $C^4H_2$ & one of $C^5H_2$); 1.07 dd 7.0Hz, 1.0Hz 3H ($CCH_3$).$\delta_C$: 170.8, 168.5 ($\underline{C}O_2Me$); 99.5 d 181Hz ($C^2$); 39.2 d 20.5Hz ($C^3$); 31.1, 30.2 ($CH_2$); 12.6 d 7.5Hz ($C\underline{C}H_3$).$\delta_F$: -202.7 dd 50.0Hz, 28.5Hz.

## Cyclisation of Dimethyl 1-bromo-1-fluoro-6-methyl-5-heptene-2,2-dicarboxylate (114)


**114** ***cis, trans* 136**

To a stirred solution of dimethyl 1-bromo-1-fluoro-6-methyl-5-heptene-2,2-dicarboxylate (114) (110mg, 342μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (6.8mg, 41μmol) and tri(*n*-butyl)tin hydride (104μl, 366μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (5% ether / petrol) gave an

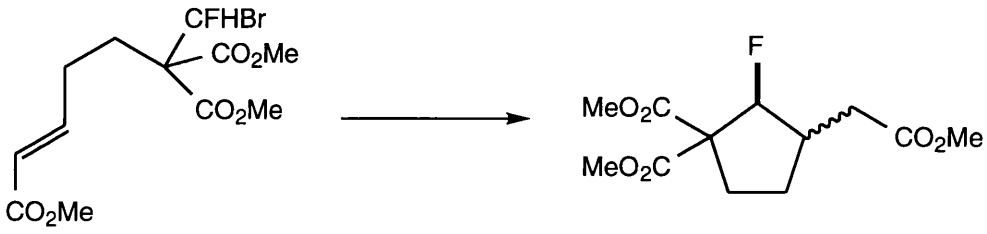
inseparable mixture of the two diastereomers of dimethyl 2-fluoro-3-*iso*propylcyclopentane-1,1-dicarboxylate (136), in the ratio *cis* : *trans* of 2 : 3, as a colourless oil. Yield 67mg (272μmol, 80%).

$\delta_C$: 170.7, 170.7 ($CO_2Me$); 52.8 ($OCH_3$); 31.4, 30.7, 27.8, 27.7, 27.4, 26.8, 26.7 ($Me_2CH$, $C^4$, $C^5$).$\nu_{max}$: 1735cm$^{-1}$ (C=O).**m/z(FAB)**: 107 (100%), 247 (90%, $[M+H]^+$).**High Res.(FAB)**: Found ($[M+H]^+$) 247.1360; $[C_{21}H_{22}FN_2O_4+H]^+$ requires 247.1346.

Major diastereomer (*trans*): $\delta_H$: 5.30 dd 47.0Hz, 5.0Hz 1H (CFH); 3.73 s 3H ($OCH_3$); 3.72 s 3H ($OCH_3$); 2.48 td 12.5Hz, 7.0Hz 1H (one of $C^4H_2$); 2.15-2.05 dd 13.5Hz, 8.0Hz 1H (one of $C^4H_2$); 2.0-1.5 m 3H ($C^3H$, one of $C^5H_2$ & $Me_2CH$); 1.25-1.05 m 1H (one of $C^5H_2$); 1.01 d 6.5Hz 3H ($CCH_3$); 0.87 d 6.5Hz 3H ($CCH_3$).$\delta_C$: 99.4 d 184Hz ($C^2$); 64.5 d 23.0Hz ($C^1$); 53.4 d 19.5Hz ($C^3$); 21.4, 20.8 ($C(CH_3)_2$).$\delta_F$: -178.2 dd 52.0Hz, 33.5Hz.

Minor diastereomer (*cis*): $\delta_H$: 5.35 dd 52.0Hz, 3.0Hz 1H (CFH); 3.73 s 3H ($OCH_3$); 3.70 s 3H ($OCH_3$); 2.85-2.75 m 1H (one of $C^4H_2$); 1.04 d 6.5Hz 3H ($CCH_3$); 0.89 d 6.5Hz 3H ($CCH_3$).$\delta_C$: 97.9 d 180Hz ($C^2$); 65.0 d 23.0Hz ($C^1$); 52.5 d 20.0Hz ($C^3$); 21.8, 21.4 ($C(CH_3)_2$).$\delta_F$: -202.5 dd 51.5Hz, 38.5Hz.

## Cyclisation of Trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115)[100]




**115** ***cis, trans* 137**

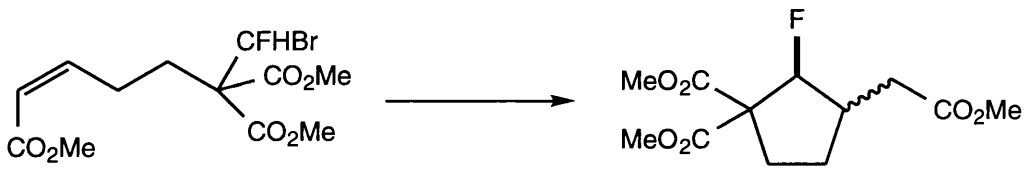
To a stirred solution of trimethyl *E* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (115) (126mg, 354μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (6.8mg, 41μmol) and tri(*n*-butyl)tin hydride (104μl, 393μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (40% ether / petrol) gave an inseparable mixture of the two diastereomers of dimethyl 2-fluoro-3-(methoxycarbonylmethyl)cyclopentane-1,1-dicarboxylate (137), in the ratio *cis* : *trans* of 1 : 2, as a colourless oil. Yield 64mg (231μmol, 65%).

$\delta_H$: 3.7-3.4 m 9H ($CO_2CH_3$); 2.70-2.45 m 4H ($C^4H_2$, $C\underline{H}_2CO_2Me$); 2.45-2.30 m 1H (one of $C^5H_2$).$\delta_C$: 172.5, 172.2, 170.5, 170.4, 167.9, 167.9 ($\underline{C}O_2Me$); 52.9, 52.8, 52.8, 51.7 ($CH_3$); 31.2, 30.6, 28.3, 27.9 ($CH_2$).$\nu_{max}$: 1731cm$^{-1}$ (C=O). **m/z(FAB)**: 277 (100%, $[M+H]^+$).

Major diastereomer (*trans*): $\delta_H$: 5.25 dd 51.5Hz, 4.0Hz 1H (CFH); 2.76 t 10.0Hz 1H ($C^3H$); 2.20-2.00 m 1H (one of $C^5H_2$).$\delta_C$: 99.7 d 186Hz ($C^2$); 64.1 d 22.5Hz ($C^1$); 42.0 d 22.5Hz ($C^3$).$\delta_F$: -181.1 dd 50.0Hz, 29.5Hz.

Minor diastereomer (*cis*): $\delta_H$: 5.36 dd 52.0Hz, 3.0Hz 1H (CFH); 2.85 t 10.0Hz 1H ($C^3H$); 2.0-1.85 m 1H (one of $C^5H_2$).$\delta_C$: 98.7 d 181Hz ($C^2$); 64.9 d 22.0Hz ($C^1$); 40.6 d 19.5Hz ($C^3$).$\delta_F$: -200.5 dd 52.5Hz, 30.5Hz.

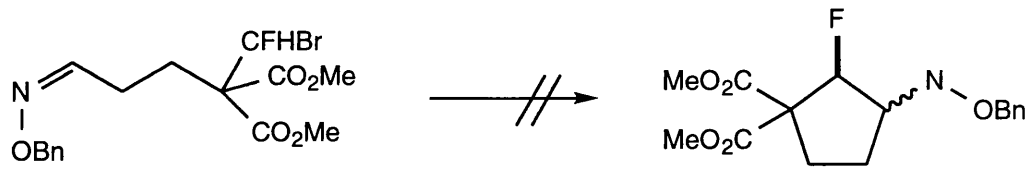
**Cyclisation of Trimethyl *Z* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (116)[100]**




**116** ***cis, trans* 137**

To a stirred solution of trimethyl *Z* 1-bromo-1-fluoro-5-hexene-2,2,6-tricarboxylate (116) (123mg, 346μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (7.1mg, 43μmol) and tri(*n*-butyl)tin hydride (105μl, 395μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (40% ether / petrol) gave an inseparable mixture of the two diastereomers of dimethyl 2-fluoro-3-(methoxycarbonylmethyl)cyclopentane-1,1-dicarboxylate (137), in the ratio *cis* : *trans* of 1 : 2, as a colourless oil with spectral characteristics identical to those previously described. Yield 54mg (195μmol, 56%).

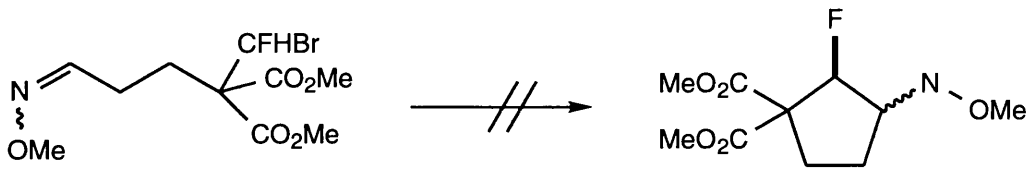
**Attempted Cyclisation of Dimethyl *Z* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118)**




***Z* 118**

To a stirred solution of dimethyl *Z* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) (141mg, 350μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (7.0mg, 42μmol) and tri(*n*-butyl)tin hydride (107μl, 407μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (5-30% ether / petrol) gave dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) as a mixture of isomers. Yield 103mg (73%).

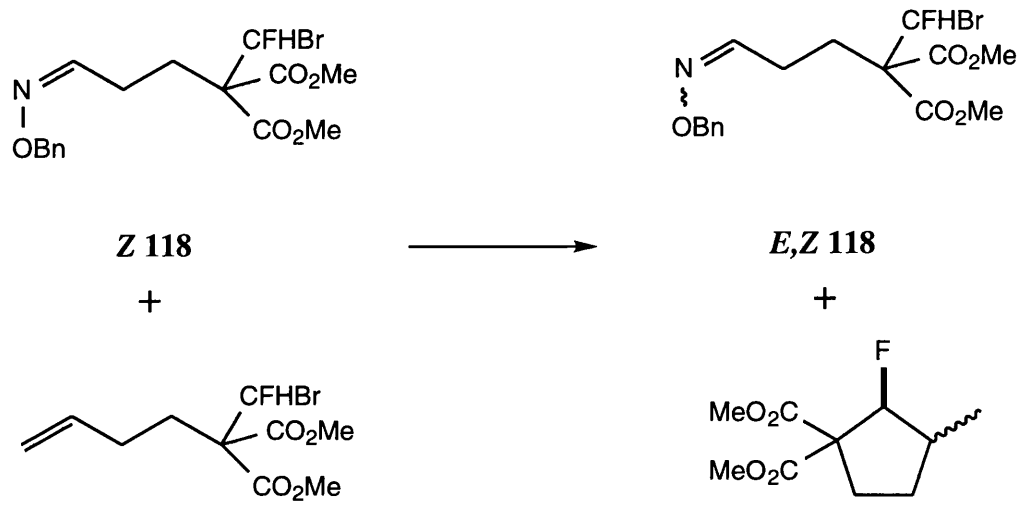
**Attempted Cyclisation of Dimethyl 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126)**




***E,Z* 126**

To a stirred solution of dimethyl *Z* 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126) (114mg, 345μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (7.0mg, 42μmol) and tri(*n*-butyl)tin hydride (107μl, 407μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (5-20% ether / petrol) gave dimethyl 1-bromo-1-fluoro-5-(methoxyimino)pentane-2,2-dicarboxylate (126) as a mixture of isomers. Yield 84mg (74%).

**Competitive Cyclisation of Dimethyl *Z* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) and Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112)**

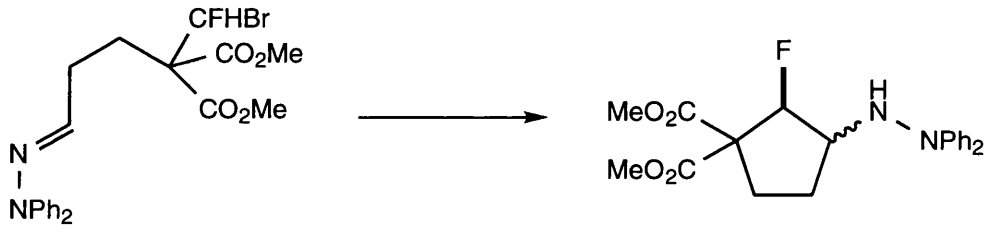



**112** **135**

To a stirred solution of dimethyl *Z* 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) (71mg, 177μmol) and dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (52mg, 174μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (7.1mg, 43μmol) and tri(*n*-butyl)tin hydride (106μl, 404μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. Column chromatography (10-40% ether / petrol) gave two colourless oils: an inseparable mixture of the two

diastereomers of dimethyl 2-fluoro-3-methylcyclopentane-1,1-dicarboxylate (135) (24mg, 110μmol, 62%), and dimethyl 5-(benzyloxyimino)-1-bromo-1-fluoropentane-2,2-dicarboxylate (118) (6mg, 8%) as a mixture of isomers.

## Cyclisation of (Dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-diphenylhydrazone (128)




**128** ***cis, trans* 138**

To a stirred solution of (dimethyl 1-bromo-1-fluoro-5-oxopentane-2,2-dicarboxylate) *N,N*-diphenylhydrazone (128) (156mg, 335μmol) in refluxing benzene (8ml) was added steadily over 20 hours *via* syringe pump a solution of AIBN (6.9mg, 42μmol) and tri(*n*-butyl)tin hydride (104μl, 393μmol) in benzene (3.4ml). After addition was completed, the mixture was allowed to reflux for a further 4 hours and then cooled. Carbon tetrachloride (10ml) was added, followed by a crystal of iodine to give a permanent pink colouration. The solvent was evaporated under reduced pressure, ethyl acetate (5ml) then aqueous potassium fluoride solution (sat., 20ml) were added, and this mixture stirred vigorously for 3 hours. The solution was filtered, the solid washed with ethyl acetate (3x25ml) and the combined organic phases separated and dried ($MgSO_4$), after which evaporation of the solvent under reduced pressure gave a milky oil. The product was preadsorbed onto base-washed silica, and column chromatography using base washed silica (20-50% ether / petrol) gave an inseparable mixture of the two

diastereomers of *N'*-[2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl]-*N*,*N*-diphenylhydrazine (138), in the ratio *cis* : *trans* of 7 : 3, as a colourless oil.Yield 92mg (238μmol, 71%).

$\nu_{max}$:1735cm$^{-1}$ (C=O), 3287 cm$^{-1}$ (NH), 3472cm$^{-1}$ (NH).**m/z(FAB)**: 386 (100%, $[M]^+$), 168 (61%, $[Ph_2N]^+$), 154 (47%, $[Ph_2]^+$), 136 (34%), 387 (32%, $[M+H]^+$).**High Res.(FAB)**: Found ($[M]^+$) 386.1642; $[C_{21}H_{23}FN_2O_4]^+$ requires 386.1642.

Major diastereomer (*cis*): $\delta_H$: 7.29 t 8.0Hz 4H (*o*-ArH); 7.20-6.95 m 6H (*p*-ArH and *m*-ArH); 5.50 dd 50.0Hz, 2.0Hz (CFH); 3.90 br s 1H exch. $D_2O$ (NH); 3.76 s 3H ($CO_2CH_3$); 3.73 s 3H ($CO_2CH_3$); 2.56 dt 13.5Hz, 8.0Hz 1H (one of $C^4H_2$); 2.40-2.30 m 1H ($C^3H$); 2.07 td 13.0Hz, 7.0Hz 1H (one of $C^4H_2$); 2.00-1.80 m 1H (one of $C^5H_2$); 1.65-1.55 m 1H (one of $C^5H_2$).$\delta_C$: 169.8, 167.9 ($CO_2Me$); 148.0 (Aromatic C-N); 129.2 (*m*-Aromatic C); 122.9 (*p*-Aromatic C); 120.7 (*o*-Aromatic C); 98.9 d 183Hz ($C^2$); 63.9 d 26.0Hz ($C^1$); 62.7 d 17.5Hz ($C^3$); 52.9 ($OCH_3$) 30.4, 27.7 ($CH_2$).$\delta_F$: -185.5 dd 52.5Hz, 23.5Hz.

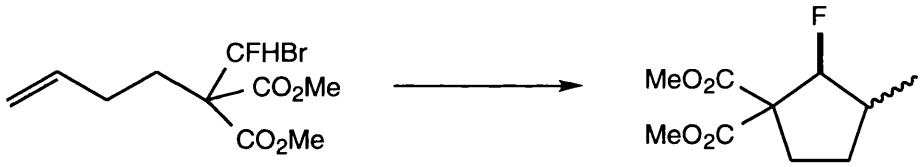
Minor diastereomer (*trans*): $\delta_H$: 5.16 dd 52.0Hz, 3.0Hz 1H (CFH); 4.21 br s 1H exch. $D_2O$ (NH).$\delta_C$: 169.9, 167.9 ($CO_2Me$); 95.0 d 183Hz ($C^2$); 64.5 d 22.0Hz ($C^1$); 63.1 d 21.5 Hz ($C^3$); 28.4, 27.6 ($CH_2$).$\delta_F$: -203.5 dd 56.0Hz, 28.5Hz.

## Attempted Cyclisation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) using 0.2eq Samarium diiodide


**112** ***cis, trans* 135**

A 0.1M solution of samarium diiodide in THF was prepared[163]. To a stirred solution of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (106mg, 335μmol) in THF / DMPU (9 : 1, 5ml) was added steadily a solution of samarium diiodide (0.1M) in THF until a purple colouration persisted (0.6ml, 60μmol). After 10 minutes the mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 20ml), extracted with ether (3x25ml) and the organic extracts washed with water (30ml) and brine (30ml) then evaporated to a yellow oil. Column chromatography (20% ether / petrol) gave dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (74mg, 70%) as a colourless oil, and a trace (~1mg) of dimethyl 2-fluoro-3-methylcyclopentane-1,1-dicarboxylate (135).

**Attempted Cyclisation of Dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) using 2eq Samarium diiodide**

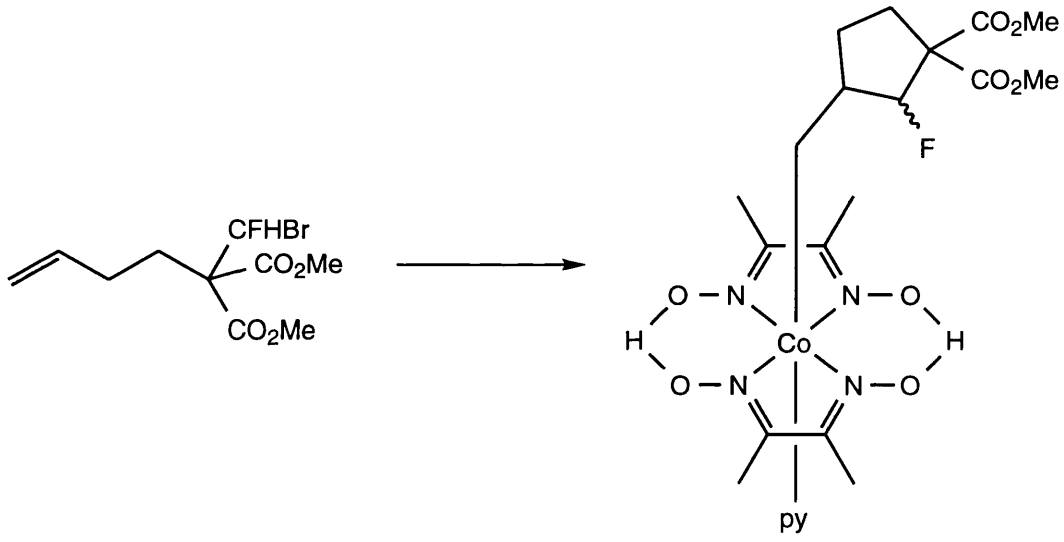



**112** ***cis, trans* 135**

A 0.1M solution of samarium diiodide in THF was prepared[163]. To a stirred solution of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (105mg, 333μmol) in THF / DMPU (9 : 1, 10ml) was added dropwise over 10 minutes a solution of samarium diiodide (0.1M, 6.7ml, 0.67mmol) in THF. After the first few drops, the solution was cloudy, and a persistent purple colouration was obtained after 0.3ml had been added. After 20 further minutes stirring the mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 20ml), extracted with ether (3x50ml) and the organic extracts washed with water (100ml)

and brine (100ml), dried ($MgSO_4$) then evaporated to a yellow oil. Column chromatography (20% ether / petrol) gave a mixture of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) and dimethyl 2-fluoro-3-methylcyclopentane-1,1-dicarboxylate (135) as a colourless oil, in the ratio 1 : 2.Yield of cyclised product 15mg (68mmol, 20%).

**Preparation of [(2-Fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl) methyl]-pyridine-cobaloxime (139)**




**112** ***cis, trans* 139**

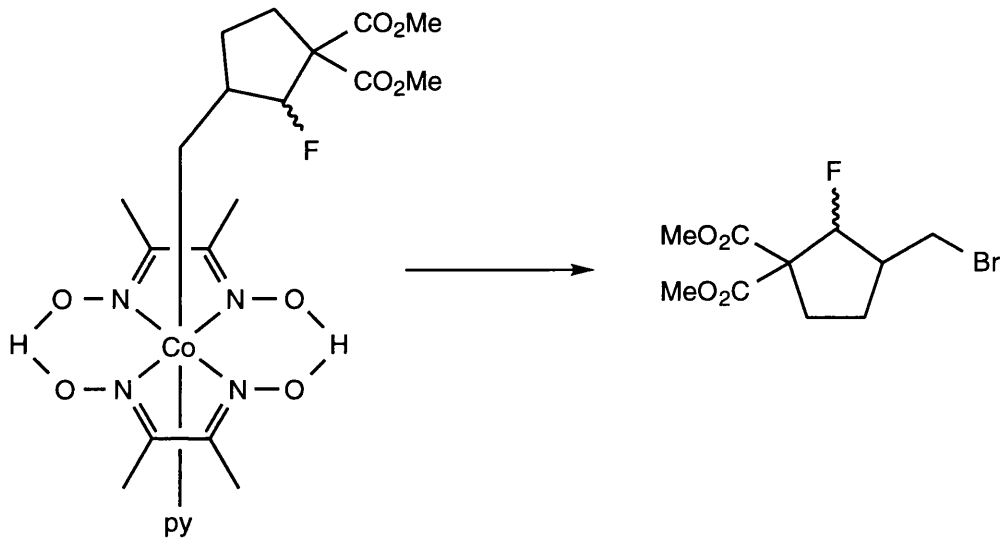
To a stirred, degassed solution of cobalt (II) chloride hexahydrate (238mg, 1.0mmol) and dimethyl glyoxime (240mg, 2.0mmol) in methanol (7ml) was added aqueous sodium hydroxide solution (12.5M, 160µl, 2.0mmol) and pyridine (82µl, 1.0mmol). Nitrogen was bubbled through the solution for 10 minutes, then sodium borohydride (70mg, 1.9mmol) added. After 10 minutes a degassed solution of dimethyl 1-bromo-1-fluoro-5-hexene-2,2-dicarboxylate (112) (297mg, 1.0mmol) in methanol (3ml) was added and the mixture stirred for 2 hours. Another portion of sodium borohydride (40mg, 1.1mmol) was added and stirring continued for 18

hours. Acetone (25ml) was added and the mixture preadsorbed onto silica. Column chromatography (10%, 50% and then 100% ethyl acetate / petrol) gave mainly *trans* [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) as a yellow solid. Yield 338mg (0.57mmol, 58%). Recrystallisation (ethyl acetate / petrol) gave yellow crystals.

**m.p.**174-176°C.$\nu_{max}$:1736cm$^{-1}$ (C=O), 1600cm$^{-1}$ (py C=C), 1555cm$^{-1}$, 1453cm$^{-1}$ (C=N).**m/z(FAB)**: 289 (100%), 506 (41%, [M-pyridine]$^+$), 585 (3.6%, [M]$^+$).**High Res.(FAB)**: Found ([M]$^+$) 585.1660; $[C_{23}H_{33}FN_5O_8Co]^+$ requires 585.1645.

Major diastereomer (*trans*):$\delta_H$: 18.25 br s 2H exch. $D_2O$ (N-OH); 8.54 dd 6.5Hz, 1.5Hz 2H (pyridine $H^{2'}$); 7.68 tt 7.5Hz, 1.5Hz 1H (pyridine $H^{4'}$); 7.28 ddd 7.5Hz, 6.5Hz, 1.0Hz 2H (pyridine $H^{3'}$); 4.97 dd 51.5Hz, 3.5Hz 1H (CFH); 3.67 s 3H ($CO_2CH_3$); 3.66 s 3H ($CO_2CH_3$); 2.65-2.55 m 1H (one of Co-$CH_2$); 2.40-2.25 m 1H (one of Co-$CH_2$); 2.10 s 6H (two of N=C-$CH_3$); 2.09 s 6H (two of N=C-$CH_3$); 2.05-1.95 m 2H (one of $C^4H_2$ and one of either $C^4H_2$ and $C^5H_2$); 1.85-1.70 br m 1H ($C^3H$); 1.35-1.25 m 1H (one of either $C^4H_2$ or $C^5H_2$); 1.05-0.95 m 1H (one of $C^5H_2$).$\delta_C$: 170.5 ($\underline{C}O_2Me$); 168.6 d 5.0Hz ($CO_2Me$); 149.9 (pyridine $C^{2'}$); 149.7 (N=C-Me); 149.6 (N=C-Me); 137.5 (pyridine $C^{4'}$); 125.2 (pyridine $C^{3'}$); 100.6 d 185.5Hz ($C^2$); 64.5 d 22.5Hz ($C^1$); 52.6 ($OCH_3$); 47.0 d 21.0Hz ($C^3$); 31.4 ($CH_2Co$); 30.7 ($CH_2$); 30.7 ($CH_2$).$\delta_F$: -141.5 dd 51.5Hz, 32.0Hz.

**Photolysis of [(2-Fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) Using Bromotrichloromethane**




***cis, trans* 139** ***cis, trans* 140**

A solution of [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) (*cis* : *trans* ratio 1 : 8, 132mg, 0.23mmol) and bromotrichloromethane (77mg, 38µl, 0.39mmol) in degassed benzene (17ml) in the standard photolysis cell was irradiated for 20 hours then evaporated and preadsorbed. Column chromatography (0-40% ether / petrol) gave an inseparable mixture of diastereomers of dimethyl 3-(bromomethyl)-2-fluorocyclopentane-1,1-dicarboxylate (1140) in the ratio *cis* : *trans* of 1 : 8, as a colourless oil.Yield 48mg (161µmol, 72%).

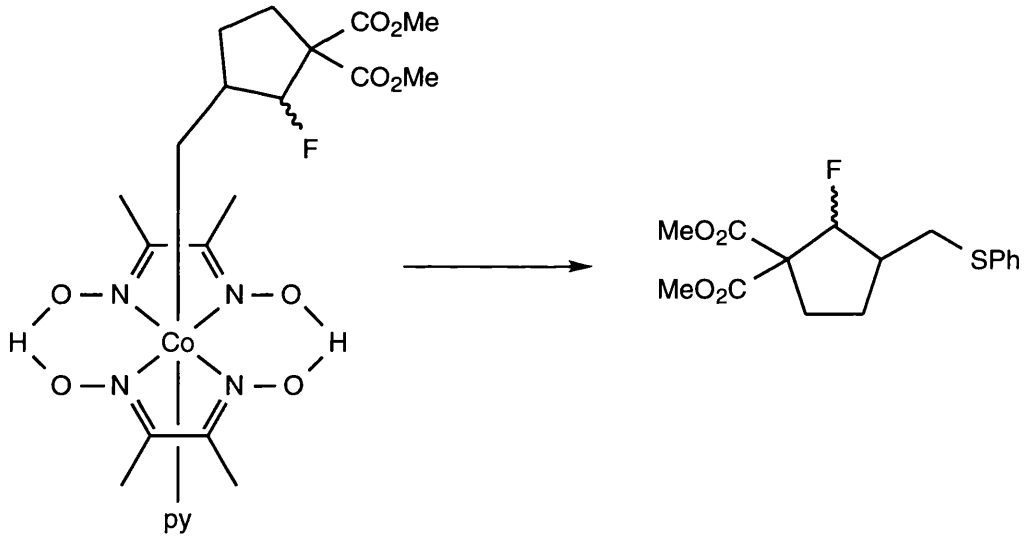
$\nu_{max}$: 1734cm$^{-1}$ (C=O).**m/z(FAB)**: 299 (100%, [M{$^{81}$Br}]$^+$), 297 (99%, [M{$^{79}$Br}]$^+$), 267 (61% [M{$^{81}$Br}-MeOH]$^+$), 265 (61% [M{$^{79}$Br}-MeOH]$^+$).**High Res.(FAB)**: Found ([M{$^{79}$Br}]$^+$) 297.0150; $[C_{10}H_{14}F^{79}BrO_4]^+$ requires 297.0138.

Major diastereomer (*trans*): $\delta_H$**(750MHz)**: 5.32 dd 51.5Hz, 4.5Hz 1H (CFH); 3.75 s 6H ($CH_3$); 3.56 dd 10.5Hz, 7.0Hz 1H (one of $CH_2Br$); 3.41 dd 9.5Hz,

7.0Hz 1H (one of $CH_2Br$); 2.75-2.60 m 1H ($C^3H$); 2.60-2.50 ddd 19.5Hz, 11.0Hz, 8.0Hz (one of $C^4H_2$); 2.20-2.10 m 2H (one of $C^5H_2$ and one of $C^4H_2$); 1.40-1.25 m 1H (one of $C^5H_2$).$\delta_C$: 170.3, 167.9 ($CO_2Me$); 98.4 d 185Hz ($C^2$); 64.2 d 22.5Hz ($C^1$); 53.0, 52.9 ($CH_3$); 48.1 d 22.5Hz ($C^3H$); 33.3 d 4.5Hz ($CH_2$); 31.1 ($CH_2$); 27.4 d 3.5Hz ($CH_2$).$\delta_F$: -179.4 dd 52.0Hz, 32.0Hz.

Minor diastereomer (*cis*): $\delta_H$**(750MHz)**: 5.42 dd 51.5Hz, 3.0Hz 1H (CFH); 3.51 dd 10.0Hz, 9.0Hz 1H (one of $CH_2Br$); 3.41 ddd 10.0Hz, 8.5Hz, 1.5Hz 1H (one of $CH_2Br$).$\delta_C$: 97.2 d 182Hz ($C^2$).$\delta_F$: -203.1 dd 52.5Hz, 32.0Hz.

**Photolysis of [(2-Fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) Using Diphenyl disulphide**




***cis, trans* 139** ***cis, trans* 141**

A solution of [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) (*cis* : *trans* ratio 1 : 8, 127mg, 0.22mmol) and diphenyl disulphide (85mg, 0.39mmol) in degassed benzene (17ml) in the standard photolysis cell was irradiated for 20 hours, then evaporated and preadsorbed.

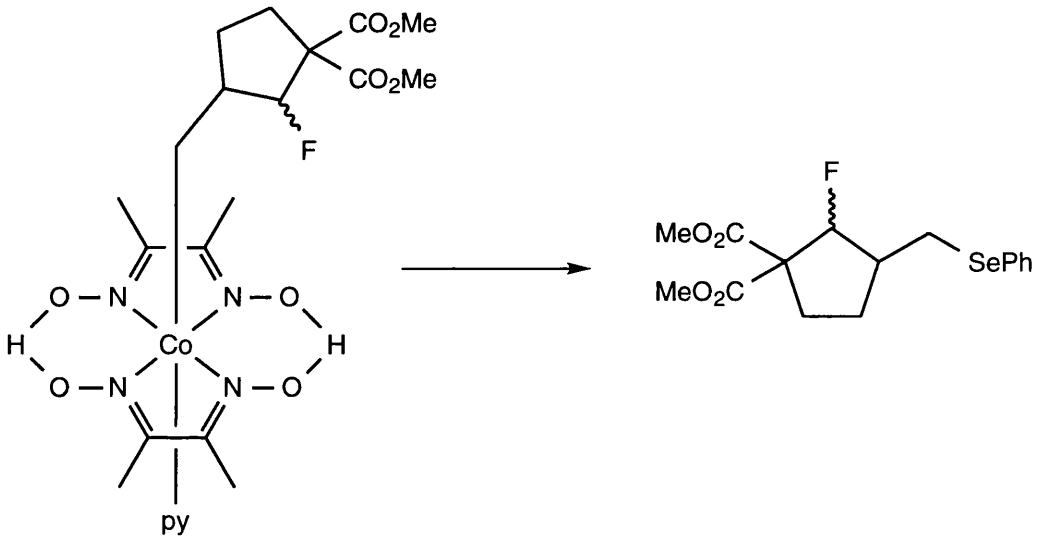
Column chromatography (0-20% ether / petrol) gave an inseparable mixture of diastereomers of [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl] phenyl sulphide (141) in the ratio *cis* : *trans* of 1 : 8, as a colourless oil.Yield 47mg (144μmol, 66%).

$\nu_{max}$: 1732cm$^{-1}$ (C=O), 1583cm$^{-1}$ (C=C).**m/z(FAB)**: 123 (100%, $[PhSCH_2]^+$), 326 (77%, $[M]^+$).**High Res.(FAB)**: Found ($[M]^+$) 326.0970; $[C_{16}H_{19}FSO_4]^+$ requires 326.0988.

Major diastereomer (*trans*): $\delta_H$**(750MHz)**: 7.40-7.30 m 2H (*o*-ArH); 7.30-7.25 m 2H (*m*-ArH); 7.18 tt 6.5Hz, 2.0Hz 1H (*p*-ArH); 5.36 dd 51.5Hz, 4.0Hz 1H (CFH); 3.73 s 6H ($CH_3$); 3.16 dd 13.0Hz, 7.5Hz 1H (one of $CH_2S$); 2.92 ddd 13.0Hz, 8.0Hz, 1.5Hz 1H (one of $CH_2S$); 2.60-2.50 m 1H (one of $C^4H_2$); 2.50-2.40 m 1H ($C^3H$); 2.20-2.05 m 2H (one of $C^4H_2$ and one of $C^5H_2$); 1.35-1.20 m 1H (one of $C^5H_2$).$\delta_C$: 170.5, 167.8 ($CO_2Me$); 135.6 (Aromatic CS); 129.9, 129.0 (*o*- and *m*- Aromatic CH); 126.4 (*p*- Aromatic CH); 99.6 d 185Hz ($C^2$); 64.5 d 23.5Hz ($C^1$); 52.9, 52.8 ($CH_3$); 45.6 d 22.0Hz ($C^3H$); 36.3 d 4.5Hz ($CH_2$); 31.4 ($CH_2$); 28.2 d 4.0Hz ($CH_2$). $\delta_F$: -179.4 dd 52.0Hz, 32.0Hz.

Minor diastereomer (*cis*): $\delta_H$: 5.43 dd 52.0Hz, 3.0Hz 1H (CFH).$\delta_C$: 97.6 d 181.5Hz ($C^2$). $\delta_F$: -201.7 dd 52.0Hz, 33.5Hz.

**Photolysis of [(2-Fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl) methyl]-pyridine-cobaloxime (139) Using Diphenyl diselenide**




*cis, trans* **139** *cis, trans* **142**

A solution of [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl]-pyridine-cobaloxime (139) (*cis* : *trans* ratio 1 : 7, 138mg, 0.24mmol) and diphenyl diselenide (122mg, 0.39mmol) in degassed benzene (17ml) in the standard photolysis cell was irradiated for 21 hours, then evaporated and preadsorbed onto silica. Column chromatography (0-16% ether / petrol) gave an inseparable mixture of diastereomers of [(2-fluoro-1,1-di(methoxycarbonyl)cyclopent-3-yl)methyl] phenyl selenide (142) in the ratio *cis* : *trans* of 1 : 7, as a colourless oil.Yield 74mg (198μmol, 84%).

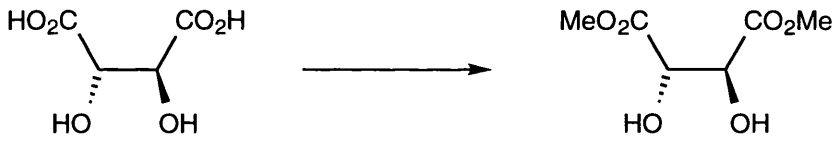
$\nu_{max}$: 1735cm$^{-1}$ (C=O), 1579cm$^{-1}$ (C=C).**m/z(FAB)**: 217 (100%), 374 (84%, ([M{$^{80}$Se}]$^+$).**High Res.(FAB)**: Found ([M{$^{80}$Se}]$^+$) 374.0420; $[C_{16}H_{19}F^{80}SeO_4]^+$ requires 374.0433.

Major diastereomer (*trans*): $\delta_H$: 7.55-7.45 m 2H (*o*-ArH); 7.35-7.20 m 3H (*m*-ArH & *p*-ArH); 5.33 dd 51.5Hz, 4.0Hz 1H (CFH); 3.73 s 6H ($CH_3$); 3.12 dd 12.0Hz, 7.5Hz 1H (one of $CH_2Se$); 2.92 ddd 12.0Hz, 8.0Hz, 1.0Hz 1H (one of

$CH_2Se$); 2.60-2.30 m 2H ($C^3H$ and one of $C^4H_2$); 2.20-2.00 m 2H (one of $C^4H_2$ and one of $C^5H_2$); 1.35-1.15 m 1H (one of $C^5H_2$).$\delta_C$: 170.5, 167.9 ($CO_2Me$); 133.1, 129.1 (*o*- and *m*- Aromatic CH); 129.5 (Aromatic CSe); 127.1 (*p*- Aromatic CH); 100.0 d 186.0Hz ($C^2$); 64.4 d 23.0Hz ($C^1$); 52.9, 52.8 ($CH_3$); 46.2 d 22.0Hz ($C^3H$); 31.4 ($CH_2Se$); 29.9 d 4.5Hz ($CH_2$); 28.8 d 4.0Hz ($CH_2$).$\delta_F$: -179.7 dd 51.0Hz, 31.0Hz.

Minor diastereomer (*cis*): $\delta_H$: 5.44 dd 52.0Hz, 3.0Hz 1H (CFH).$\delta_C$: 99.0 d 181.5Hz ($C^2$); 45.3 d 19.5Hz ($C^3H$); 30.7 ($CH_2Se$).$\delta_F$: -201.9 dd 52.0Hz, 34.5Hz.

## Preparation of Dimethyl (2S,3S)-2,3-dihydroxybutan-1,4-dioate (172)



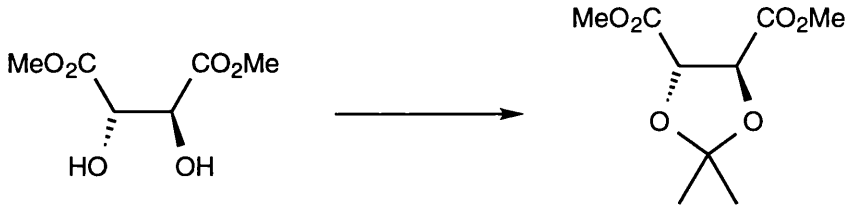

**171** **172**

A solution of (-)-(D)-tartaric acid (171) (19g, 0.13mol) and concentrated sulphuric acid (1ml) in methanol (80ml) was refluxed beneath a soxhlet extractor packed with molecular sieves (3Å, 25g) for 18 hours. The mixture was cooled, neutralised with sodium carbonate, filtered and evaporated. The crude brown oil was distilled, when the distillate, dimethyl (2S,3S)-2,3-dihydroxybutan-1,4-dioate (172), appeared as colourless crystals. Yield 16.6g (93.5 mmol, 74%).

**m.p.**57.5-58.5°C (Lit[165] 61.5°C).**b.p.**~100°C at 0.1mmHg.$[\alpha]_D^{20}$= -4.7° (c=25, acetone) (Lit[166]$[\alpha]_D^{20}$= -4.6° (c=25, acetone)).$\delta_H$: 4.55 d 4.5Hz 2H (CH); 3.85 s 6H ($CH_3$); 3.34 d 5.5Hz 2H exch. $D_2O$ (OH).$\delta_C$: 171.9 ($\underline{C}O_2Me$); 72.0 (CHOH); 53.1 ($CH_3$).$\nu_{max}$(**Nujol**): 3527$cm^{-1}$ (br, OH), 1740$cm^{-1}$

($CO_2Me$).**m/z(FAB)**: 179 (100%, $[M+H]^+$), 119 (59%, $[M-CH_3]^+$), 43 (52%, $[MeCO]^+$).

**Preparation of (4S,5S)-2,2-Dimethyl-4,5-di(methoxycarbonyl)-1,3-dioxolane (173)**[136]

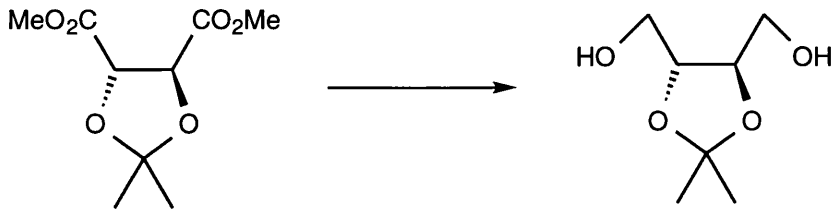



**172** **173**

A solution of dimethyl (2S,3S)-2,3-dihydroxybutan-1,4-dioate (172, (-)-dimethyl-(D)-tartrate, 20.0g, 225mmol), 2,2-dimethoxypropane (17.7g, 0.17mol) and *p*-toluenesulphonic acid (68mg) in benzene (150ml) was refluxed beneath a soxhlet extractor packed with molecular sieves (4Å, 25g) for 3 hours. The sieves were changed after 90 minutes. The mixture was cooled, potassium carbonate (100mg) added, and stirred overnight. The solution was filtered and evaporated under reduced presure. Distillation gave (4S,5S)-2,2-dimethyl-4,5-di(methoxycarbonyl)-1,3-dioxolane (173) as a green oil. Yield 24.2g (111mmol, 99%).

**b.p.**~100°C at 0.2mmHg.$[\alpha]_D^{20}$= +55.4° (c=1, acetone) (Lit[136]$[\alpha]_D^{20}$= +54.8° (c=1, acetone)).$\delta_H$: 4.76 s 2H (CH); 3.78 s 6H ($OCH_3$); 1.45 s 6H ($C(CH_3)_2$).$\delta_C$**($d_6$-DMSO)**: 170.0 ($\underline{C}O_2Me$); 113.0 ($\underline{C}Me_2$); 76.4 ($C^2$ & $C^3$); 52.4 ($OCH_3$); 26.3 ($C(\underline{C}H_3)_2$).$\nu_{max}$: 1762$cm^{-1}$ ($CO_2Me$), 1385$cm^{-1}$ ($CMe_2$).**m/z(FAB)**: 219 (100%, $[M+H]^+$), 203 (31%, $[M-CH_3]^+$).

**Preparation of (4R,5R)-2,2-Dimethyl-4,5-*bis*-hydroxymethyl-1,3-dioxolane (174)[136]**

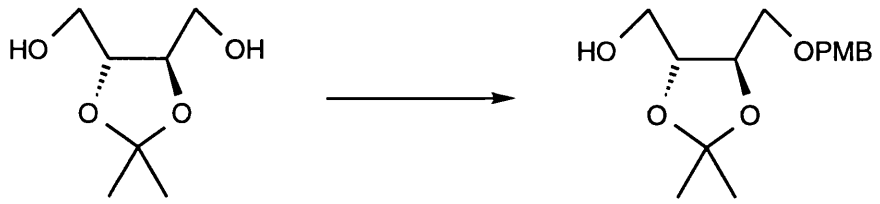



**173** **174**

To a stirred solution of (4S,5S)-2,2-dimethyl-4,5-di(methoxycarbonyl)-1,3-dioxolane (173) (46.9g, 0.21mol) in methanol (not dried, 800ml) at 0°C was added sodium borohydride (12.5g, 0.33mol) over 1 hour. Another portion of sodium borohydride (4.3g, 115mmol) was added, the mixture stirred at room temperature for 12 hours and then evaporated under reduced pressure. Water (290ml) was added and this extracted with ethyl acetate (5x750ml). The combined organic layers were dried ($Na_2SO_4$) and evaporated. Column chromatography (50-100% ethyl acetate / petrol) gave (4R,5R)-2,2-dimethyl-4,5-*bis*-hydroxymethyl-1,3-dioxolane (174) as a colourless, viscous oil. Yield 26.2g (164mmol, 76%).

$[\alpha]_D^{20}$= -4.5° (c=5, $CHCl_3$) (Lit[167] $[\alpha]_D^{20}$= -4.1° (c=5, $CHCl_3$)).$\delta_H$: 3.96 t 2.0Hz 2H (CH); 3.72 dd 11.5Hz, 1.5Hz 4H ($CH_2$); 2.51 s 2H exch. $D_2O$ (OH); 1.40 s 6H ($CH_3$).$\delta_C$: 109.3 ($\underline{C}Me_2$); 78.0 ($C^2$ & $C^3$); 62.0 ($CH_2OH$); 53.1 ($CH_3$).$\nu_{max}$: 3405$cm^{-1}$ (br, OH), 1377$cm^{-1}$ ($CMe_2$).**m/z(FAB)**: 59 (100%, $[Me_2COH]^+$), 163 (69%, $[M+H]^+$).

**Preparation of (4R,5R)-2,2-Dimethyl-4-hydroxymethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (175)[168]**



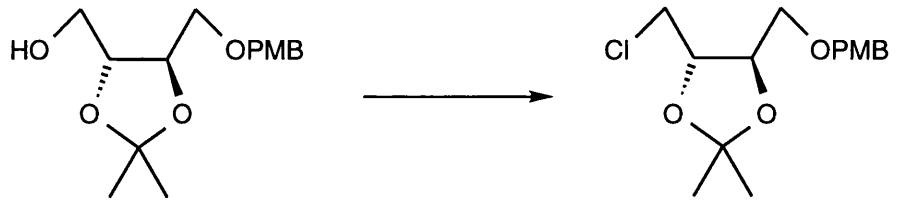

**174** **175**

To a vigorously stirred mixture of (4R,5R)-2,2-dimethyl-4,5-*bis*-hydroxymethyl-1,3-dioxolane (174) (18.8g, 0.12mol), DMF (220ml), and hexane (85ml) at -15°C was added in 3 portions over 15 minutes sodium hydride (60% dispersion in mineral oil, 5.55g, 0.14mol) then the mixture stirred or a further 30 minutes. A solution of *p*-methoxybenzyl chloride (23.5g, 0.15mol) in DMF (55ml) was added dropwise over 50 minutes, the mixture stirred for 20 minutes then warmed to room temperature. After 1 hour, the mixture was heated (hexane to reflux) for 3 hours, cooled and poured into water (550ml). The mixture was extracted with ether (4x220ml) and the combined organic layers washed with brine (3x55ml), dried ($MgSO_4$) and evaporated under reduced pressure. Residual DMF was removed under vacuum, then column chromatography (5-20% ether / petrol) gave (4R,5R)-2,2-dimethyl-4-hydroxymethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (175) as a colourless oil. Yield 23.7g (84mmol, 73%).

$[\alpha]_D^{20}$= -8.9° (c=5, $CHCl_3$) (Lit[168] $[\alpha]_D^{30}$= -10.6° (c=1.06, $CHCl_3$)).$\delta_H$: 7.22 d 8.5Hz 2H (Aromatic CH); 6.85 d 8.5Hz 2H (Aromatic CH); 4.49 s 2H ($ArCH_2$); 4.05-3.95 m 1H; 3.95-3.85 m 1H; 3.78 s 3H ($OCH_3$); 3.72 dd 11.5Hz, 4.5Hz 1H; 3.68-3.60 m 2H; 3.49 ddd 10Hz, 6Hz, 1.5Hz 1H; 2.23 br s 1H exch. $D_2O$ (OH); 1.39 s 6H ($C(CH_3)_2$).$\delta_C$: 159.3 (C-OMe); 129.5 (Aromatic C-$CH_2$); 129.4, 113.8 (Aromatic CH); 109.3 ($CMe_2$); 79.8, 76.7 ($C^2$ & $C^3$); 73.3, 70.0 ($CH_2OCH_2$); 62.4 ($CH_2OH$); 55.2 ($OCH_3$); 26.9 ($C(CH_3)_2$).**m/z(FAB)**: 121

(100%, $[MeOC_6H_4CH_2]^+$), 122 (10%, $[MeOC_6H_4CH_3]^+$), 282 (7%, $[M]^+$).**High Res.**: Found ($[M]^+$) 282.1460; $[C_{15}H_{22}O_5]^+$ requires 282.1467.

**Preparation of (4S,5R)-2,2-Dimethyl-4-chloromethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (176)**[138]



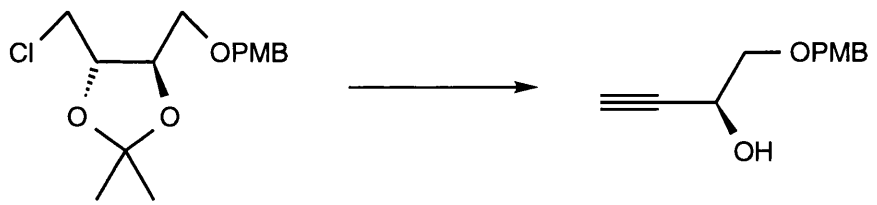

**175** **176**

A solution of triphenylphosphine (39g, 0.15mol) and (4R,5R)-2,2-dimethyl-4-hydroxymethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (175) (28.0g, 99mmol) in carbon tetrachloride (500ml) was refluxed for 3 days, then evaporated. The residue was dissolved in DCM (100ml), filtered and the filtrite washed with DCM (2x20ml). The combined organic washings were pre-adsorbed onto silica, and column chromatography (5-25% ether / petrol) gave (4S,5R)-2,2-dimethyl-4-chloromethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (176) as a colourless oil. Yield 24.9g (82.9mmol, 84%).

$[\alpha]_D^{20}$= -2.3° (c=10.2, $CHCl_3$),$[\alpha]_D^{20}$= -2.3° (c=2.5, $CHCl_3$)$\delta_H$: 7.25 dt 6.5Hz, 1.5Hz 2H (ArH); 6.85 dt 6.5Hz, 2.0Hz 2H (ArH); 4.51 s 2H ($ArCH_2$); 4.1-4.0 m 2H; 3.80 s 3H ($OCH_3$); 3.7-3.5 m 4H; 1.43 s 3H ($C(CH_3)_2$); 1.42 s 3H ($C(CH_3)_2$).$\delta_C$: 159.3 (C-OMe); 129.8 (Aromatic C-$CH_2$); 129.3, 113.8 (Aromatic CH); 110.0 ($CMe_2$); 78.2, 77.9 ($C^2$ & $C^3$); 73.2, 70.1 ($CH_2OCH_2$); 55.2 ($OCH_3$); 44.5 ($CH_2Cl$); 27.1, 26.9 ($C(CH_3)_2$).**m/z (FAB)**: 121 (100%,

$[MeOC_6H_4CH_2]^+$), 207 (17%), 300 (8%, $[M\{^{35}Cl\}]^+$).**High Res.**: Found ($[M]^+$) 300.1128; $[C_{15}H_{21}O_4Cl]^+$ requires 300.1120.

**Preparation of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-ol (177)[137]**




**176** **177**

To a stirred solution of (4S,5R)-2,2-dimethyl-4-chloromethyl-5-(*p*-methoxybenzyloxy)methyl-1,3-dioxolane (176) (0.9g, 3.1mmol) in THF (12ml) at -78°C was added *n*-butylithium (1.6M in hexanes, 13.4ml, 21mmol) over 5 minutes. After 3 hours the orange solution was brought to approximately -30°C and water (15ml) added cautiously. The green mixture was then diluted with water (50ml) and extracted with ether (3x70ml). The combined organic extracts were washed with brine (50ml), dried ($Na_2SO_4$) and evaporated under reduced pressure to give a yellow oil. Column chromatography (25-40% ether / petrol) gave (S) (*p*-methoxybenzyl)oxy-3-butyn-2-ol (177) as a colourless oil. Yield 0.54g (2.57mmol, 84%).

$[\alpha]_D^{20}$= +5.3° (c=2, $CHCl_3$) (Lit[138] $[\alpha]_D^{20}$= +4.8° (c=2, $CHCl_3$)).$\delta_H$: 7.28 d 8.5Hz 2H (ArH); 6.89 d 8.5Hz 2H (ArH); 4.65-4.50 m 3H ($C^2H$ and *p*-$MeOC_6H_4C\underline{H}_2$); 3.82 s 3H ($OCH_3$); 3.64 dd 10.0Hz, 3.5Hz 1H (ABX, one of $C^1H_2$); 3.56 dd 10.0Hz, 7.0Hz 1H (ABX, one of $C^1H_2$); 2.55 d 5.0Hz 1H exch. $D_2O$ (OH); 2.46 d 2.0Hz 1H ($C^4H$).$\delta_C$: 159.5 (C-OMe); 131.4 (Aromatic C-$CH_2$); 129.5, 113.9 (Aromatic CH); 81.7 ($C^3$); 73.7, 73.2, 73.1, 61.5 ($PhCH_2$, $C^1$, $C^2$

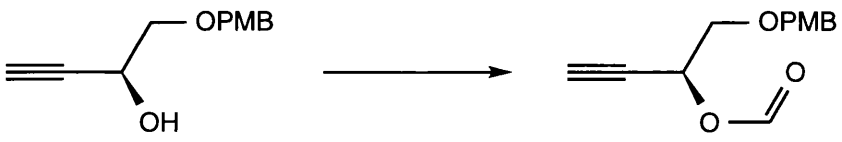
& $C^4$); 55.3 ($OCH_3$).$\nu_{max}$: 3422$cm^{-1}$ (br, OH), 3286$cm^{-1}$ (alkyne C-H), 2117$cm^{-1}$ (alkyne C-C), 1612$cm^{-1}$, 1586$cm^{-1}$, 1514$cm^{-1}$ (Aromatic C=C).**m/z(FAB)**: 121 (100%, $[MeOC_6H_4CH_2]^+$), 149 (16%), 137 (14%), 206 (7%, $[M]^+$).**High Res.**: Found ($[M]^+$) 206.0950; $[C_{12}H_{14}O_3]^+$ requires 206.0943.

**Preparation of Acetic Formic Anhydride[169]**

To a vigorously stirred suspension of sodium formate (21.1g, 0.31mol) in ether (17ml), in a room temperature water bath, was added over 2 minutes acetyl chloride (20.7g, 18.7ml, 0.26mol). After stirring for 20 hours the solution was filtered, the filtrite washed quickly with ether (20ml) and the washing added to the original filtrate. Careful evaporation of the ether under reduced pressure gave acetic formic anhydride, containing traces of formic and acetic anhydrides, which was used without further purification. Yield 19.5g (0.22mol, 85%).

$\delta_H$: 9.07 s 1H (HCO); 2.26 s 3H ($CH_3$).$\delta_C$: 167.9 ($CH_3\underline{C}$); 156.2 ($H\underline{C}$=O); 21.2 ($CH_3$).$\nu_{max}$: 1794$cm^{-1}$, 1771$cm^{-1}$ (C=O), 1055$cm^{-1}$ (C-O-C).**m/z(FAB)**:

**Preparation of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl methanoate (178)**

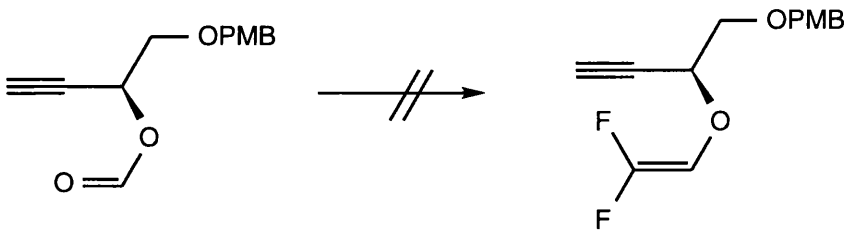


**177** **178**

To a stirred solution of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-ol (177) (140mg, 0.66mmol) and acetic formic anhydride (176mg, 2.0mmol) in THF (5ml) at 0°C was added pyridine (0.16ml, 2.0mmol). After 35 minutes the mixture was allowed to come to room temperature and stirred for a further 2 hours. The mixture was refluxed for 30 minutes, when tlc showed starting alcohol was still present. More acetic formic anhydride (60 mg, 0.6mmol) was added and refluxing continued for 5 hours. The mixture was cooled, poured into aqueous sodium hydrogencarbonate solution (40ml) and extracted with ether (50ml). The organic phase was washed with brine (20ml), dried ($Na_2SO_4$) and evaporated. Column chromatography (10-20% ether / petrol) gave (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl methanoate (178) as a colourless oil. Yield 115mg (0.49mmol, 74%).

$[\alpha]_D^{20}$= +8.2° (c=2.5, $CHCl_3$).$\delta_H$: 8.09 s (HC=O); 7.26 d 8.5Hz 2H (ArH); 6.89 d 8.5Hz 2H (ArH); 5.65 dddd 7.0Hz, 4.0Hz, 2.0Hz, 1.0Hz 1H ($C^2H$); 4.54 m 2H (*p*-$MeOC_6H_4C\underline{H}_2$); 3.80 s 3H ($OCH_3$); 3.75-3.65 m 2H ($C^1H_2$); 2.52 d 2.0Hz 1H ($C^4H$).$\delta_C$: 159.7 (C=O); 159.5 (<u>C</u>-OMe); 129.5, 113.9 (Aromatic CH); 129.4 (Aromatic <u>C</u>-$CH_2$); 77.9 ($C^3$); 75.2, 73.1, 70.4, 62.4 ($PhCH_2$, $C^1$, $C^2$ & $C^4$); 55.3 ($OCH_3$).$\nu_{max}$: 3282$cm^{-1}$ (alkyne C-H), 2126$cm^{-1}$ (alkyne C-C), 1732$cm^{-1}$ (C=O), 1612$cm^{-1}$, 1586$cm^{-1}$, 1514$cm^{-1}$ (Aromatic C=C).**m/z(FAB)**: 121 (100%, [*p*-$MeOC_6H_4CH_2$]$^+$), 136 (18%, [*p*-$MeOC_6H_4CHO$]$^+$), 154 (15%), 137 (14%), 122 (11%), 107 (9%), 234 (7.5%, $[M]^+$).**High Res.(FAB):** Found ($[M]^+$) 234.0880; $[C_{13}H_{14}O_4]^+$ requires 234.0892.

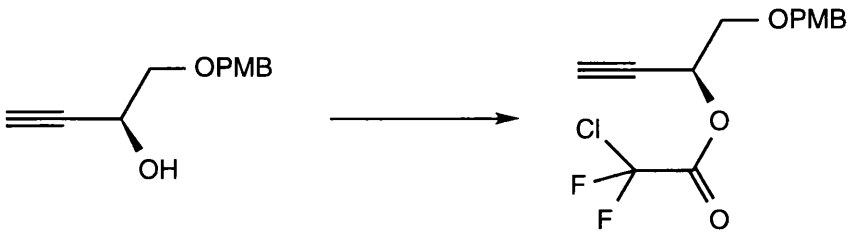
**Attempted Synthesis of (S) 4-(*p*-methoxybenzyloxy)-3-(2',2'-difluoroethenyloxy)butyne (170)**




**178** **170**

To a stirred solution of dibromodifluoromethane (1.6ml, 3.7g, 18mmol) in triglyme (12ml) at 0°C was added a solution of *tris*(dimethylamino)phosphine (4.42ml, 3.9g, 24.3mmol) in triglyme (7ml) and the mixture stirred for 15 minutes then brought to room temperature and stirred for another 20 minutes. A solution of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl methanoate (178) (345mg, 1.5mmol) in triglyme (4ml) was added, and after 15 minutes stirring the mixture heated to 85°C for 4 hours, cooled, dissolved in hexane (180ml) and stirred vigorously with aqueous copper sulphate solution (sat., 100ml) for 6 hours. The mixture was filtered through celite, the layers separated and the organic phase dried ($Na_2SO_4$) and evaporated under reduced pressure to give (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl methanoate (178) as a colourless oil.

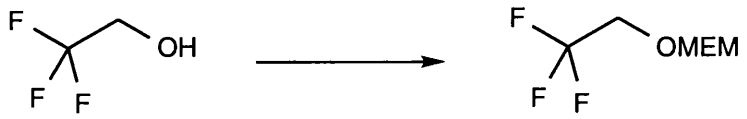
**Preparation of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl chlorodifluoroethanoate (197)**




**177** **197**

To a stirred solution of (S) (*p*-methoxybenzyl)oxy-3-butyn-2-ol (177) (640mg, 3.1mmol) and DMAP (476mg, 3.9mmol) in THF (40ml) at 0°C was added chlorodifluoroethanoic anhydride (0.66ml, 920mg, 3.9mmol). After 1 hour the mixture was allowed upto room temperature and stirring continued for another 5 hours. The mixture was filtered, the filtrite washed with ether (10ml) and the combined organic phases evaporated under reduced pressure. Column chromatography (20% ether / petrol) gave (S) (*p*-methoxybenzyl)oxy-3-butyn-2-yl chlorodifluoroethanoate (197) as a colourlesss oil. Yield 808mg (2.5mmol, 82%). $[\alpha]_D^{20}$= +5.0° (c=2.5, $CHCl_3$).$\delta_H$: 7.25 d 9.0Hz 2H (Aromatic CH); 6.89 d 8.5Hz 2H (Aromatic CH); 5.68 ddd 6.5Hz, 4.0Hz, 2.0Hz 1H ($C^2H$); 4.54 s 2H (*p*-$MeOC_6H_4C\underline{H}_2$); 3.82 s 3H ($OCH_3$); 3.80-3.75 m 2H ($C^1H_2$); 2.62 d 2.0Hz 1H ($C^4H$).$\delta_C$: 159.5 (Aromatic C-OMe); 158.2 t 35.0Hz (C=O); 130.6 (Aromatic C-$CH_2$); 129.4, 113.9 (Aromatic CH's); 116.6 t 301.0Hz ($CClF_2$); 75.9 ($C^3$); 73.1, 70.0, 69.8, 67.0 ($PhCH_2$, $C^1$, $C^2$ & $C^4$); 55.3 ($OCH_3$).$\delta_F$: -64.5.$\nu_{max}$: 3293$cm^{-1}$ (alkyne C-H), 2130$cm^{-1}$ (alkyne C-C), 1786$cm^{-1}$ (C=O), 1612$cm^{-1}$, 1586$cm^{-1}$, 1515$cm^{-1}$ (Aromatic C=C).**m/z(FAB)**: 121 (100%, [*p*-$MeOC_6H_4CH_2$]$^+$), 318 (7.5%, $[M]^+$).**High Res.(FAB):** Found ($[M]^+$) 318.0450; $[C_{14}H_{13}ClF_3O_4]^+$ requires 318.0470.

**Preparation of 2-[(2'-Methoxyethoxy)methoxy]-1,1,1-trifluoroethane (185)**[141]

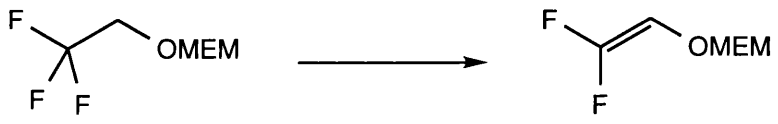



**185**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with 2x20ml toluene, 7.48g, 0.19mol) in THF (18ml) at 0°C was added dropwise over 90 minutes 2,2,2-trifluoroethanol (13.8ml, 18.9g, 0.19mol) in THF (18ml). After stirring for 1 hour, 2-(chloromethoxy)methoxyethane (28.0ml, 25.7g, 0.21mol) in THF (30ml) was added dropwise over 2 hours, the mixture stirred at room temperature for 16 hours, water (180ml) added and the resulting mixture extracted with ether (3x75ml). The combined organic extracts were washed with water (2x160ml), dried ($MgSO_4$) and cautiously evaporated under reduced pressure. Reduced pressure distillation (at ~100°C) of the resulting oil gave 2-[(2'-methoxyethoxy)methoxy]-1,1,1-trifluoroethane (185) as a colourless oil. Yield 24.7g (0.13mol, 71%).

$\delta_H$: 4.78 s 2H ($OCH_2O$); 3.91 q 9.0Hz 2H ($CF_3CH_2$); 3.75-3.65 m 2H ($OC\underline{H}_2CH_2OCH_3$); 3.60-3.50 m 2H ($OCH_2C\underline{H}_2OCH_3$); 3.38 s 3H ($CH_3$).$\delta_C$: 123.9 q 278Hz, ($CF_3$); 95.5 ($OCH_2O$); 71.5, 67.4 ($OCH_2CH_2O$); 64.4 q 34.5Hz, ($CF_3\underline{C}H_2$); 58.9 d 3.0Hz ($OCH_3$).$\delta_F$: -74.9 t 9.0Hz.**m/z(TS)**: 206 (100%, $[M+NH_4]^+$).**High Res.(ES):** Found ($[M+NH_4]^+$) 206.100268; $[C_6H_{15}F_3NO_3]^+$ requires 206.100403.

**Preparation of 1,1-Difluoro-2-[(2'-methoxyethoxy)methoxy]ethene (186)**[141]

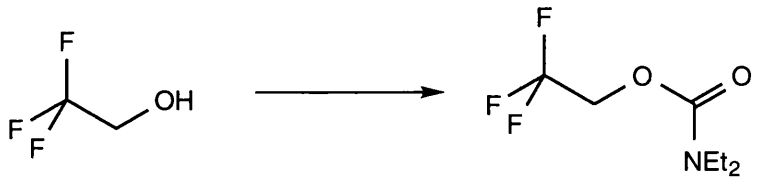



**185** **186**

To a freshly prepared solution of LDA (DIPA 4.0ml, 2.9g, 28.5mmol and *n*-butyllithium 1.5M in hexane, 17.8ml, 28.5mmol) in THF (15ml) at -78°C was added dropwise over 15 minutes 2-[(2'-methoxyethoxy)methoxy]-1,1,1-trifluoroethane (185) (2.56g, 13.6mmol) in THF (10ml). After stirring for a further 30 minutes, a saturated solution of ammonium chloride in methanol (15ml) was added dropwise, the mixture warmed to room temperature then poured into water (100ml). The mixture was extracted with ether (3x100ml), and the combined organic extracts washed with water (200ml), aqueous copper sulphate solution (sat., 3x40ml), water (50ml) and dried ($MgSO_4$). Cautious evaporation of the solvent under reduced pressure, followed by reduced pressure distillation (at room temperature) of the resulting oil gave 1,1-difluoro-2-[(2'-methoxyethoxy)methoxy] ethene (186) as a colourless oil. Yield 2.1g (12.6mmol, 93%).

$\delta_H$: 5.81 dd 16.0Hz, 3.0Hz 1H (=CH); 4.81 s 2H ($OCH_2O$); 3.75-3.70 m 2H ($OC\underline{H}_2CH_2OCH_3$); 3.55-3.50 m 2H ($OCH_2C\underline{H}_2OCH_3$); 3.37 s 3H ($CH_3$).$\delta_C$: 155.4 dd 287.5Hz, 275.5Hz ($CF_2$); 105.3 dd 53.5Hz, 15.5Hz (=CH); 96.1 ($OCH_2O$); 71.4, 67.7 ($OCH_2CH_2O$); 58.9 s ($OCH_3$).$\delta_F$: -100.4 dd 77.0Hz, 16.0Hz (*cis*-F); -119.5 d 77.0Hz (*trans*-F).**m/z(TS)**: 186 (100%, $[M+NH_4]^+$).**High Res.(ES):** Found ($[M+NH_4]^+$) 186.094660; $[C_6H_{14}F_2NO_3]^+$ requires 186.094175.

**Preparation of 2-(*N*,*N*-diethylcarbamoyloxy)-1,1,1-trifluoroethane (187)**[142]

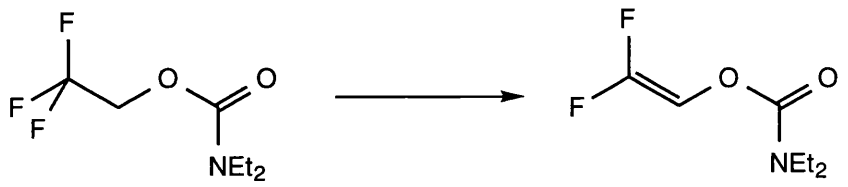



**187**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with 1x60ml then 2x20ml toluene, 4.0g, 0.10mol) in THF (20ml) at 0°C was added dropwise over 80 minutes 2,2,2-trifluoroethanol (7.3ml, 10.0g, 0.1mol). After stirring for another hour, *N*,*N*-diethylcarbamoyl chloride (12.7ml, 13.6g, 0.1mol) was added dropwise over 90 minutes, the mixture warmed to room temperature, stirred for 16 hours, and quenched with aqueous sodium hydrogencarbonate solution (sat., 50ml). Water (100ml) was added and the mixture extracted with ether (3x100ml). The combined organic extracts were washed with aqueous ammonium chloride solution (sat., 100ml), aqueous sodium hydrogencarbonate solution (sat., 100ml) and water (100ml) before being dried ($MgSO_4$) and cautiously evaporated under reduced pressure. Reduced pressure distillation (at ~50°C) of the resulting oil gave 2-(*N*,*N*-diethylcarbamoyloxy)-1,1,1-trifluoroethane (187) as a colourless oil. Yield 15.9g (80mmol, 80%).

$\delta_H$: 4.40 q 8.5Hz 2H ($CF_3CH_2$); 3.45-3.15 m 4H ($NCH_2$); 1.11 t 7.0Hz 6H ($CH_3$).$\delta_C$: 153.8 (C=O); 123.3 q 277.5Hz, ($CF_3$); 61.1 q 36.0Hz ($CF_3\underline{C}H_2$); 42.4, 41.5 ($N\underline{C}H_2$); 13.8, 13.2 ($CH_3$).$\delta_F$: -74.9 t 10.0Hz.$\nu_{max}$: 1724$cm^{-1}$ (C=O).**m/z(FAB)**: 227 (100%), 154 (49%), 136 (35%).

**Preparation of 1,1-Difluoro-2-(*N*,*N*-diethylcarbamoyloxy)ethene (188)**[142]



**187** **188**

To a freshly prepared solution of LDA (DIPA 8.3ml, 6.0g, 63.1mmol and *n*-butyllithium 1.6M in hexane, 37.9ml, 60.6mmol) in THF (65ml) at -78°C was added dropwise over 15 minutes 2-(*N*,*N*-diethylcarbamoyloxy)-1,1,1-trifluoroethane (187) (6.03g, 30.3mmol). After stirring for a further 25 minutes, a solution of ammonium chloride in methanol (sat., 6.5ml) was added, and stirring continued for 45 minutes when the mixture was warmed to room temperature and more ammonium chloride in methanol (sat., 250ml) added. The mixture was extracted with ether (3x75ml), and the combined organic extracts washed with aqueous copper sulphate solution (sat., 50ml), water (100ml), brine (50ml) and dried ($MgSO_4$). Cautious evaporation of the solvent under reduced pressure, followed by reduced pressure distillation (at room temperature) of the resulting oil gave 1,1-difluoro-2-(*N*,*N*-diethylcarbamoyloxy)ethene (188) as a colourless oil. Yield 5.2g (28.9mmol, 95%).

$\delta_H$: 6.61 dd 16.0Hz, 3.0Hz 1H (=CH); 3.35-3.20 m 4H ($NCH_2$); 1.10 t 8.0Hz 6H ($CH_3$).$\delta_C$: 154.5 dd 288.5Hz, 275.0Hz ($CF_2$); 152.3 s (C=O); 101.2 dd 60.5Hz, 13.0Hz (=CH); 42.4, 41.7 ($NCH_2$); 13.8, 13.1 ($CH_3$);.$\delta_F$: -97.7 dd 61.5Hz, 16.5Hz (*cis*-F); -118.1 d 72.0Hz (*trans*-F).$\nu_{max}$: 1733$cm^{-1}$ (C=O).**m/z(FAB)**: 180 (100%, $[M+H]^+$).

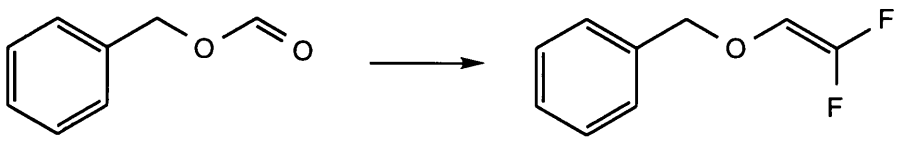
**Preparation of Benzyl Formate (191)**[170]

**191**

To a stirred solution of benzyl alcohol (4.3g, 40mmol) and formic acetic anhydride (9.8g, 0.14mol) in DCM (170ml) at 0°C was added pyridine (9.0ml, 8.8g, 112mmol) and the mixture stirred for 2 hours. The mixture was allowed upto room temperature and stirring continued for a further 2 hours before the mixture was poured into aqueous sodium hydrogencarbonate solution (sat., 300ml). The layers were separated, the organic layer washed with aqueous sodium hydrogencarbonate solution (sat., 300ml), dried ($Na_2SO_4$) and evaporated to a pale yellow oil. Column chromatography (0-4% ether / petrol) gave benzyl formate (191) as a colourless oil. Yield 4.5g (33.3mmol, 84%)

$\delta_H$: 8.12 s 1H (H-C=O); 7.45-7.25 m 5H (aromatic CH); 5.19 s 2H ($CH_2$).$\delta_C$: 160.8 (C=O); 135.1 (aromatic C-$CH_2$); 128.6, 128.3 (*m*-CH & *o*-CH); 128.5 (*p*-CH); 65.7 ($CH_2$).$\nu_{max}$: 1725$cm^{-1}$ (C=O).**m/z(FAB)**: 136 (100%, $[M]^+$).

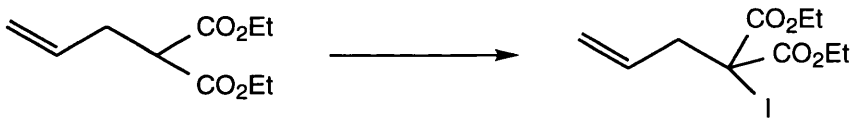
**Attempted Preparation of 1,1-Difluoro-2-(benzyloxy)ethene (192)**[170]



**191** **192**

To a stirred solution of dibromodifluoromethane (1.6ml, 3.7g, 18mmol) in triglyme (12ml) at 0°C was added a solution of *tris*(dimethylamino)phosphine (4.4ml, 3.9g, 24.3mmol) in triglyme (7ml) and the mixture stirred for 15 minutes then brought to room temperature and stirred for another 20 minutes. A solution of benzyl formate (191) (223mg, 1.5mmol) in triglyme (4ml) was added, and after 15 minutes stirring the mixture heated to 85°C for 4 hours, cooled, dissolved in hexane (180ml) and stirred vigorously with aqueous copper sulphate solution (sat., 100ml) for 6 hours. The mixture was filtered through celite, the layers separated and the organic phase dried ($Na_2SO_4$) and evaporated under reduced pressure to give a colourless volatile oil which was not characterised.

**Preparation of Diethyl allyliodomalonate (207)**[164]

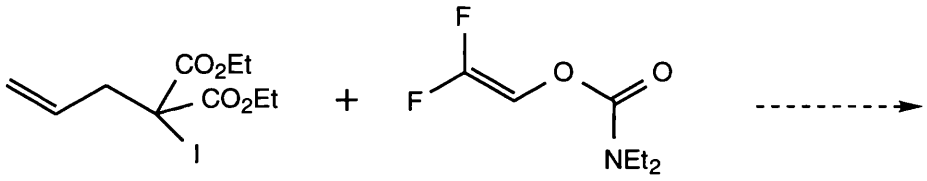



**207**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, washed with 2x50ml pentane, 1.2g, 30mmol) in THF (90ml) was added dropwise a solution of diethyl allylmalonate (4.23g, 21mmol) in THF (20ml). After stirring for 15 minutes, a colourless solution had been obtained. The flask was covered with foil and then a solution of NIS (7.4g, 33mmol) in THF (40ml) added and stirring continued for 50 minutes. The solution was filtered, evaporated under reduced pressure and the residue filtered through a short silica column, eluting with ether. Evaporation under reduced pressure gave diethyl allyliodomalonate (207) as an orange oil. Yield 6.0g (18.3mmol, 87%).

$\delta_H$: 5.78 m 1H ($CH_2$=C<u>H</u>); 5.25-5.15 m 2H (C<u>$H_2$</u>=CH); 4.26 q 7.0Hz 4H ($OCH_2$); 2.99 d 7.0Hz 2H ($CH_2$); 1.28 t 7.0Hz 6H ($CH_3$).$\delta_C$: 167.8 s (C=O); 133.3 ($CH_2$=<u>C</u>H); 120.1 (<u>C</u>$H_2$=CH); 63.1 ($OCH_2$); 44.4 ($CCH_2$); 43.8 (C-I); 13.9 ($CH_3$).$\nu_{max}$: 1736$cm^{-1}$ (C=O); 1643$cm^{-1}$ (C=C).**m/z(FAB)**: 327 (100%), 174 (100%), 200 (97%), 168 (49%, $[M]^+$).

## Attempted Atom Transfer Reaction of Diethyl allyliodomalonate (207) and 1,1-Difluoro-2-(*N*,*N*-diethylcarbamoyloxy)ethene (188)




**207** **188**

### Method A

To a stirred solution of 1,1-difluoro-2-(*N*,*N*-diethylcarbamoyloxy)ethene (188) (183mg, 1.02mmol) and diethyl allyliodomalonate (207) (989mg, 3.0mmol) in benzene (10ml) was added hexabutylditin (0.25ml, 0.5mmol) and the mixture irradiated for 1 hour. The solvent was removed under reduced pressure, the residue dissolved in carbon tetrachloride (10ml) and shaken with aqueous potassium fluoride solution (sat., 10ml). The organic phase was separated, dried ($Na_2SO_4$) and the solvent evaporated under reduced pressure. Column chromatography (30% ether / petrol) gave unknown compound (209) (50mg), and diethyl allylmalonate (220mg, 35%).(209) contained no fluorine.

**Method B**

To a stirred solution of 1,1-difluoro-2-(*N*,*N*-diethylcarbamoyloxy)ethene (188) (190mg, 1.06mmol) and diethyl allyliodomalonate (207) (979mg, 3.0mmol) in benzene (10ml) was added hexabutylditin (0.25ml, 0.5mmol) and iodoethane (0.28ml, 3.5mmol) and the mixture irradiated for 1hour. The solvent was removed under reduced pressure. Column chromatography (30% ether / petrol) gave no fluorinated material, traces of unknown compound (209), and diethyl allylmalonate (250mg, 40%).

# Chapter 4

# References

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