Generating Structural Diversity in α,α-Difluoromethyl Ketones

by

Jeremy Jon Fullbrook

A thesis submitted to the
Faculty of Science
of the
University of Birmingham
for the Degree of
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School of Chemical Sciences
University of Birmingham
Edgbaston
Birmingham
B15 2TT
UK

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2008 Addendum/Corrigenda

This document represents a re-publication of a 2002 doctoral thesis submitted to the Faculty of Science of the University of Birmingham.

Publications Update

As of April 2008, work from this thesis has been published as the following peer-reviewed articles:

a) Deboos, G.A.; Fullbrook, J.J.; Owton, W.M.; Percy, J.M.; Thomas, A.C., *Synlett* **2000**, *7*, 963-966.

b) Deboos, G.A.; Fullbrook, J.J.; Percy, J.M., *Org. Lett*. **2001**, *18*, 2859-2861.

c) Cox, L.R.; Deboos, G.A.; Fullbrook, J.J.; Owton, W.M.; Percy, J.M.; Spencer, N.S.; Tolley, M., *Org. Lett*. **2003**, *3*, 337-339.

d) Cox, L.R.; Deboos, G.A.; Fullbrook, J.J.; Owton, W.M.; Percy, J.M.; Spencer, N.S., *Tetrahedron:Asymmetry* **2005**, *16*, 347-359.

Typographical and Grammatical Corrections

Several typographical and grammatical errors have been corrected, but in no way alter the meaning of the contents of the accepted thesis.

Nomenclature Errors/Omissions

The R/S configurations in the names for compounds **199**, **200**, **214** and **215** in the experimental section should be (4*R*,5*S*), not (2*R*,3*S*).

The correct names for compounds **202** and **203** in the experimental section using R/S terminology are, respectively:

Ethyl 2S-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2R'-yl)-propionate;

Ethyl 2R-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2R'-yl)-propionate

The systematic name using carbohydrate nomenclature for compound **201** in the experimental section is 2,3-*O*-isopropylidene-1-deoxy-1,1-difluoro-β-D-xylulo-furanose

Assignment of Anomeric Configuration in Sugars **155** and **173**

The assignments of the α/β anomers for sugars **155** and **173** may well cause much confusion, especially in light of those used in the subsequent publications c) and d) referred to above. I was not involved in the preparation of these papers for publication.

I have subsequently found that there has been much confusion within the carbohydrate field itself as to the rules surrounding the assignment of anomeric configuration. This has been highlighted in the publication "On the Assignment of Anomeric Configuration", Lee, Yuan; Lee, Reiko, *J. Chin. Chem. Soc*., **1999**, Vol. 46, No. 3, 283, which can be found on the internet as a downloadable pdf file.

The assignment of configuration in my original thesis was based upon the comparison of the configurations for the anomeric centre and the anomeric reference carbon atom, which is defined as the highest-numbered chiral carbon atom in the sugar. The resulting assignment to α or β was based upon the definition of α and β anomers as described in the textbook McMurry 4th edition Organic Chemistry. This procedure was correctly applied for sugar **155** but incorrectly for sugar **173**.

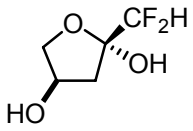
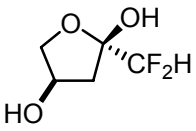
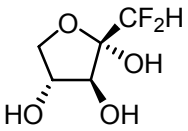
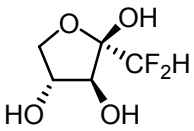
However, according to the Chinese paper above, the assignment method described in McMurry is incorrect in any case. In addition, the use of R/S configurations has also been mentioned to be misleading, especially when some fluorinated sugars are used, as the presence of the fluorine atom can alter the R/S configuration when compared to its non-fluorinated analogue. This comment, however, deems that the use of the α and β notation reflects a specific structural feature rather than simply a means of distinguishing the two anomers for the purpose of nomenclature, which is in contradiction both to logic and the recommended IUPAC protocol (see below).

It should also be said that, as highlighted in the Chinese paper, the assignment of the anomers should not be done by direct comparison to α/β-glucose (i.e α means "down" at the anomeric centre) or by using the relative stereochemical relationships in Haworth representations (i.e α means trans), especially when this is further

complicated by issue of the chirality of the ring-closing hydroxyl-bearing carbon atom (i.e ring-size).

The IUPAC recommendation of 1996, as described in "Nomenclature of Carbohydrates", *Pure & Appl. Chem.,* Vol. 68, No. 10, pp. 1919-2008, 1996, states that the assignment should be done on the basis of the ***relative*** configurations of the ***anomeric centre*** and the ***anomeric reference atom***, when drawn in a ***Fischer projection***; "in the α anomer, the exocyclic oxygen atom at the anomeric centre is formally ***cis,*** in the Fischer projection, to the oxygen attached to the anomeric reference atom; in the β anomer these oxygen atoms are formally ***trans***".

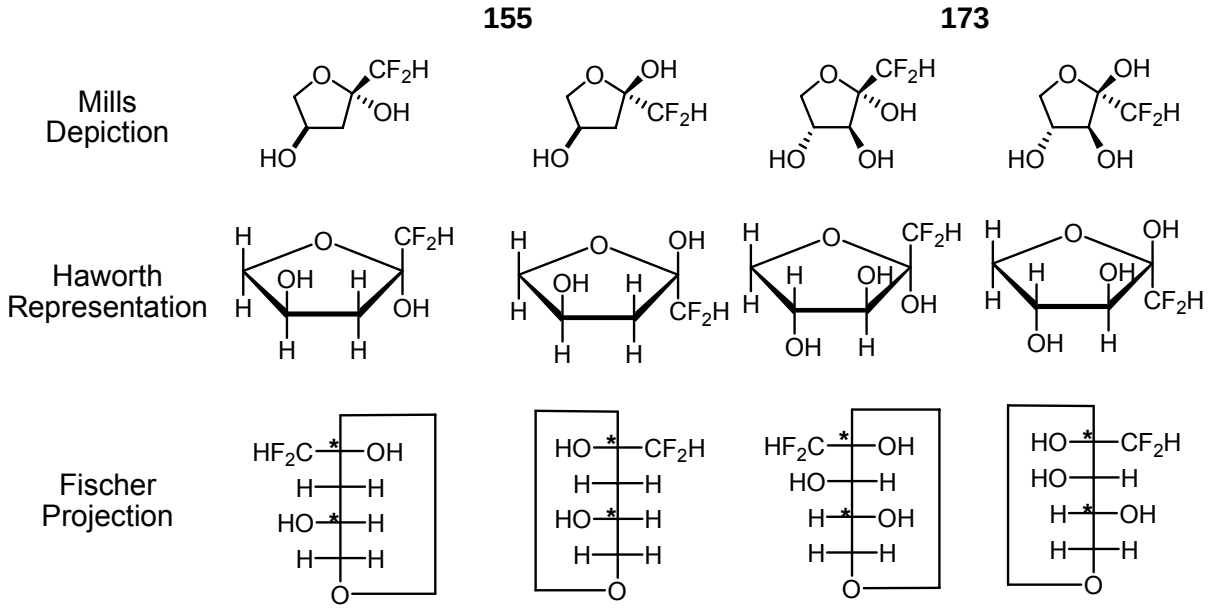
As a summary, the following table shows the results of applying different rules to the assignment of the anomers in sugars **155** and **173**. The correct assignments, based upon the IUPAC recommendations, are highlighted in bold.

	155		**173**	
				
Thesis 2002	α	β	β	α
R/S McMurry	α	β	α	β
R/S	β	α	β	α
α-Glucose OH	α (down)	β (up)	α (down)	β (up)
α-Glucose (Haworth)	α (trans)	β (cis)	β (cis)	α (trans)
Fischer	**β**	**α**	**α**	**β**

*As such, within this thesis, in reference to sugars **155** and **173**, the α and β designations should be interchanged in all cases. This discrepancy does not alter in any way the conclusions regarding the absolute stereochemistry or anomeric ratios of the anomers as elucidated by NMR, but merely reflects a conflict in how to assign α or β to a particular absolute stereoisomer.*

Stereo Representation for Sugars **155** and **173**

There are several methods for depicting the stereochemistry of a carbohydrate. In this thesis, the Mills depiction was used as the work is not primarily associated with carbohydrate chemistry and hence carbohydrate nomenclature. However, in light of the issues above regarding assignment of anomeric configurations, the corresponding Haworth representations and Fischer projections for the two anomers of the two sugars are shown below for ease of comparison.



Comments

Section 2.1.2

It should be said that, given the evidence for tin to copper transmetallation under the conditions used in these couplings, that the use of CuI may well be deleterious to the yields, due to homocoupling of any organocopper reagent and subsequent decomposition of the iodide or related palladium complexes.

Section 2.1.3

It is possible that the large amount of reduced product is as of a result of slow coupling and that the reaction was in fact incomplete. The use of the organozinc reagent in coupling was published in Arany et al., *Org. Biomol. Chem*., 2004, 2, 455 – 465.

Section 2.2.3

In the section regarding attempts to trap the diol utilising boronate ester formation, it should have been said that the method was abandoned primarily because this procedure was only documented at that time for use with achiral ligands and not for use using Sharpless Asymmetric Dihydroxylation with the AD mixes.

In addition, it should have been stressed further that whilst the enantiomeric excess for asymmetric dihydroxylation was measured under standard conditions, the material used for the synthesis was produced under pH-controlled conditions. Thus there is an unproven assumption that the *ee* is not affected by pH control.

Finally, it should be mentioned that monodefluorination of alcohol **200** was attempted in an effort to synthesise sugar **169**. The monofluoroalcohols were observed but the procedure was not investigated further due to a lack of time.

Section 2.2.4

It should be said that the O-C transfer of the MEM protecting group was not tested using trimethylsilyl triflate in the carbonate **214** due to the large amount of ketone **213** that was observed in the test reaction, associated with a high lability of the TMS enol ether.

Chapter 3

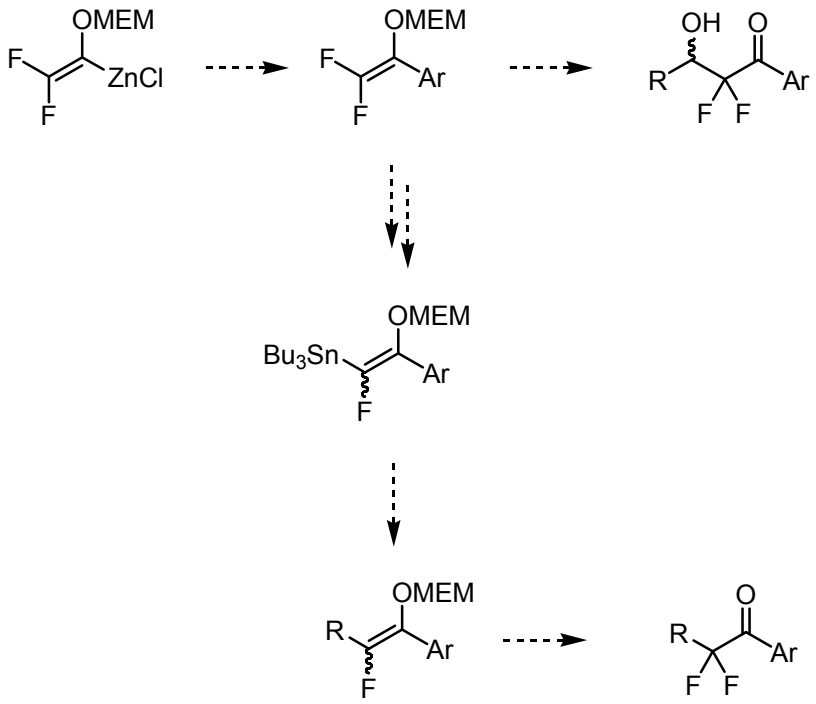
The discussion of future avenues for the work was insufficiently outlined in the conclusions and did not give justice to the success of the initial results within this thesis.

I have therefore taken this opportunity to expand upon these omissions in the orginial thesis for the benefit of interested readers.

Firstly, in the synthesis of α,α-difluoroketones, the initial success of using the corresponding difluorovinylzinc reagent provides promise for the omission of toxic tin compounds in the coupling protocol and simplification of purification of the products. Moreover, the initial successes in cleaving the MEM group under Mukaiyama-aldol

conditions suggest a method for generating larger structural diversity in these compounds.

Furthermore, monodefluorination of the coupling products provides the intruiging possibility of synthesising a novel fluorovinylstannane or fluorovinylzinc reagent which can further the scope of the diversity surrounding the CF_2 group after electrophilic cleavage with fluoride (**Scheme A**).



Scheme A: Future directions in the synthesis of α,α-difluoroketones using coupling technology

Some specific targets which utilise the methodology developed to date are shown in **Figure A**, representing either known compounds with use in drug discovery or novel compounds which are current targets.

The requisite difluoroaryl difluoroenol ether has already been synthesised and all that is required is the testing of *alkyl*sulfenium chlorides as the electrophile. For the benzoxazole derivative, initial attempts at coupling with 2-iodobenzoxazole were met with failure. However, in hindsight, it would be more prudent to use 2-bromobenzoxazole as this should be more stable and coupling with brominated heterocycles was achieved in the orginal thesis.

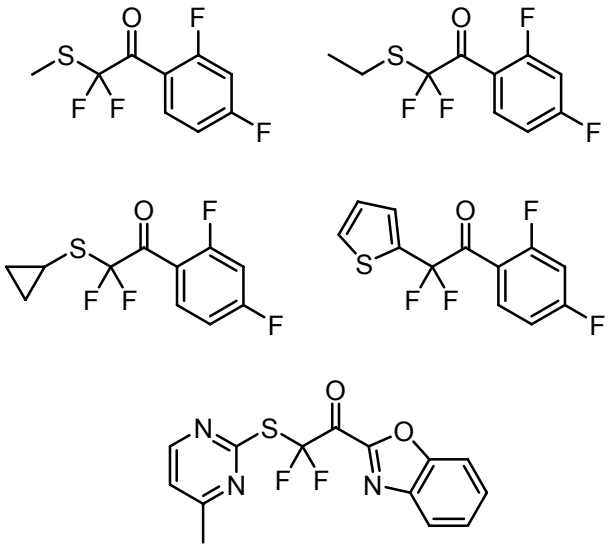
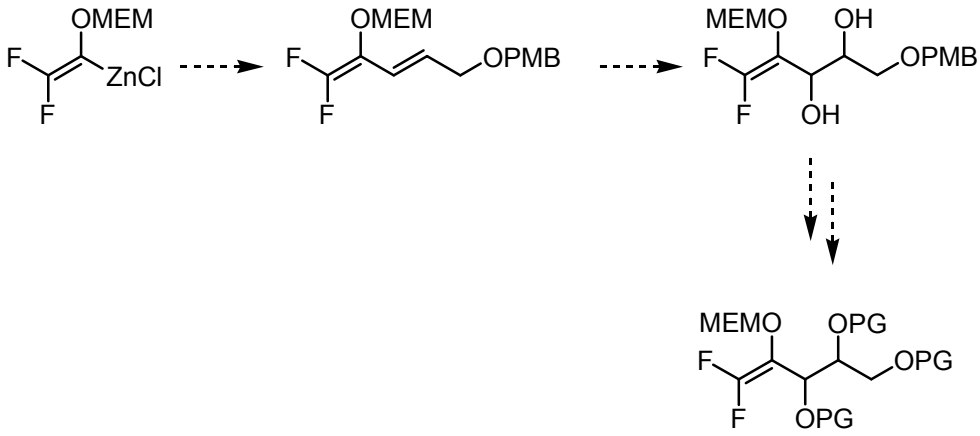


Figure A: Possible targets for coupling/cleavage methodology

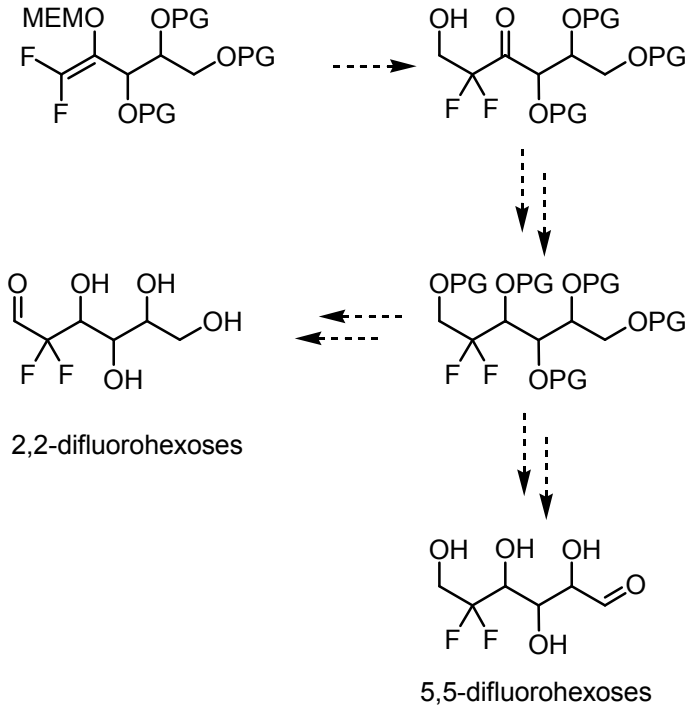
In the synthesis of fluorinated sugars, there are many avenues which can be tested using the initial findings within this thesis.

As eluded to in the original thesis, the use of the difluorovinylzinc reagent should resolve the issues surrounding the synthesis of the key diene. The use of the *para*-methoxybenzyl group should also provide greater stability to the basic conditions used during dihydroxylation. A suitable protecting group strategy could deliver the key triol shown in **Scheme B**.



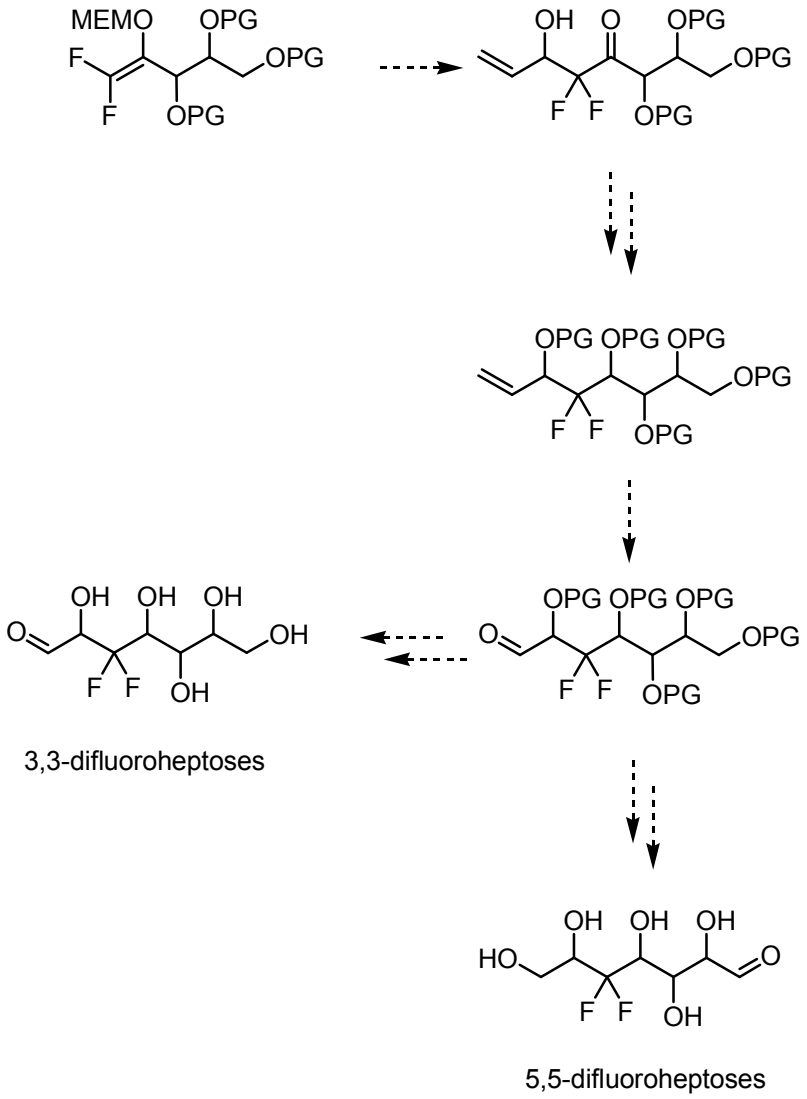
Scheme B: Future delivery of pivotal triol using modified procedures

The development of a Mukaiyama-aldol procedure using this difluoroenol ether should open the way for the synthesis of a range of sugars. For instance, trapping with formaldehyde should provide a route to 2,2- and 5,5-difluorohexoses using appropriate protecting group strategies (**Scheme C**).



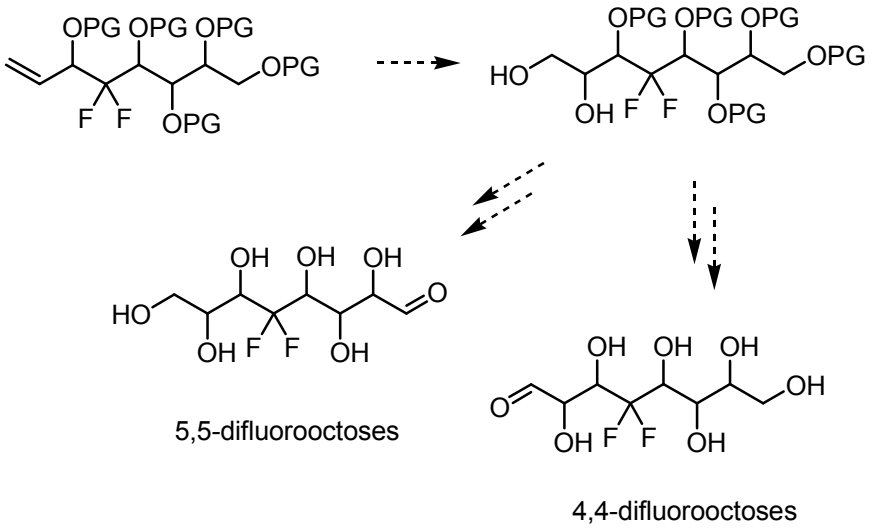
Scheme C: Route to difluorohexoses using key triol

Furthermore, coupling of the enol ether with acrolein provides a potential route to difluoroheptoses and difluorooctoses. Cleavage of the alkene using ozonolysis delivers an aldehyde which can be processed into 3,3- and 5,5-difluoroheptoses (**Scheme D**).



Scheme D: Possible route to difluoroheptoses

Dihydroxylation of the alkene unit provides a possible entry into difluorooctoses after oxidation of the C-1 or C-8 primary alcohols using a suitable protecting group strategy (**Scheme E**).

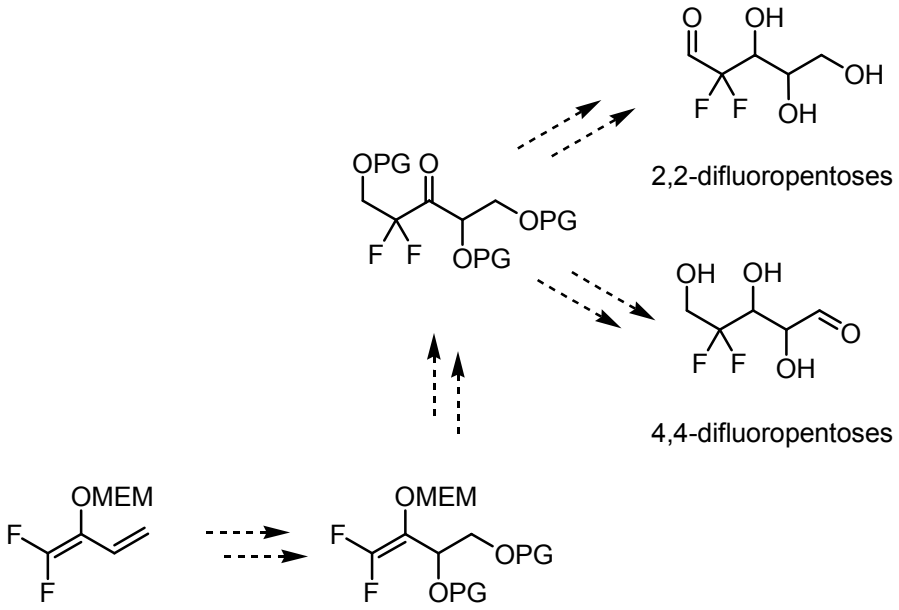


Scheme E: Possible route to difluorooctoses

A further development would involve the synthesis of 1,1-difluoro-1,3-butadiene bearing the methoxyethoxymethoxy protecting group. The synthesis of this diene would have to be attempted using the stannane as the corresponding iodide is unstable. The coupling would require the use of bromoethene and more reactive palladium catalysts would probably have to be employed. If this material can be synthesised then this could become a key building-block to pentoses, hexoses and heptoses.

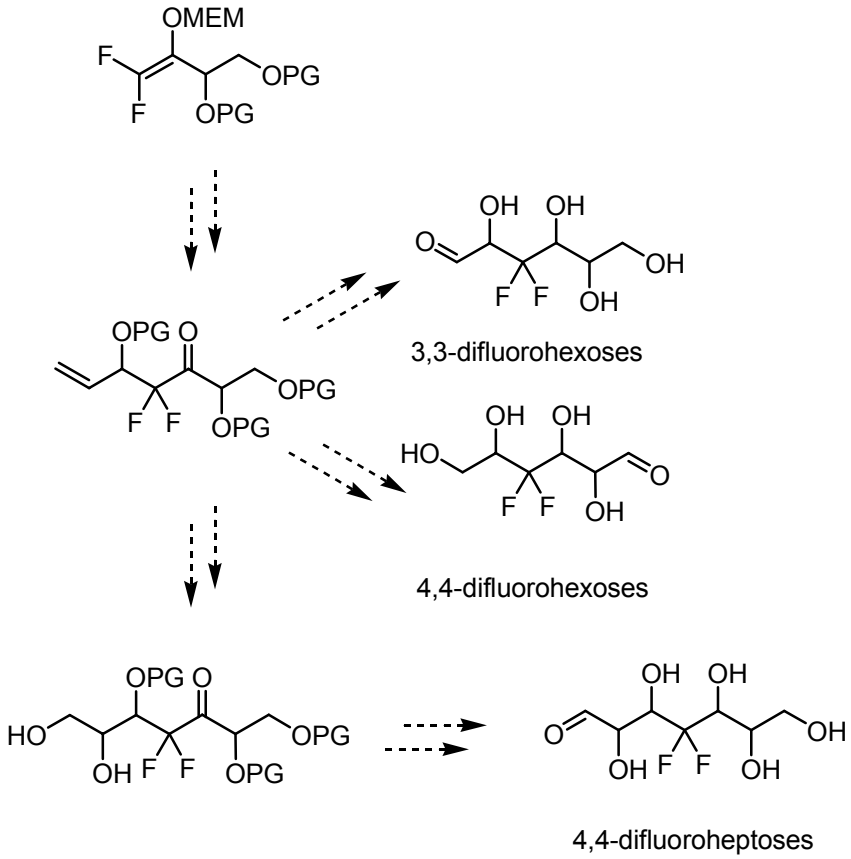
Dihydroxylation of the alkene would be difficult but the observation of diol with the analogous DEC diene suggests that reaction is not impossible and the development of the improved pH-controlled protocol may be able to deliver the required diol. If so, then this diol could deliver a range of sugars.

Firstly, protection and cleavage of the enol ether with formaldehyde allows a facile synthesis of difluoropentoses (**Scheme F**).



Scheme F: Possible synthesis of difluoropentoses from a 1,1-difluoro-1,3-butadiene derivative

In addition, the application of the same strategies as proposed before, using acrolein as the aldol partner could provide a route to difluorohexoses and difluoroheptoses (**Scheme G**).



Scheme G: Possible route to difluorohexoses and difluoroheptoses from diol building-block

As can be seen, the results in this thesis provide encouraging results that a strategy has been found which could deliver powerful methods to the synthesis of a large range of difluoro- pentoses, hexoses, heptoses and octoses.

In toto, these strategies could deliver 2,2-, 3,3-, 4,4-, or 5,5-difluorohexoses in a concise manner from trifluoroethanol with variable control of the absolute stereochemistry of the sugars.

April 2008, Dr Jeremy J Fullbrook

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Abstract

This thesis describes attempts to use palladium-catalysed cross-coupling methodology in the synthesis of α,α-difluoroketones contained within a diverse array of molecular motifs. [241]

1-(*N*,*N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene undergoes Stille cross coupling with a variety of aryl, heteroaryl, vinyl and allyl organic electrophiles. Conditions, which promote *in situ* transmetallation to a more reactive copper intermediate, were essential for obtaining significant quantities of product. 1-(*N*,*N*-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene also underwent coupling with a range of aryl, heteroaryl and vinyl stannanes. Due to the difficulties with cleavage of this protecting group, the synthesis and potential application of an *N*-ethyl-*N*-(2-methylallyl)carbamate has been studied. A 2-methoxyethoxymethyl (MEM) protecting group strategy proved very successful for the synthesis of a range of difluoromethyl aryl ketones. Two consecutive coupling reactions were possible from a difluoroenol stannane, in which coupling of initial styrene products bearing a triflate group afforded a range of biarylethenes. Cleavage occurred under mild electrophilic conditions with protic, halogen, sulfur and carbon electrophiles.

Diene products have been tested for reactivity in Sharpless Asymmetric Dihydroxylation. A 1,4-diene has been converted through to a fluorinated analogue of a dideoxyxylulose. A 1,3-diene has been successfully converted through to a difluorodeoxyxylulose of current interest. Key points involve regioselective and highly enantioselective dihydroxylation of the non-fluorinated olefin. Application of a special protecting group for the allylic alcohol was essential, as was control of the pH of the reaction medium.

Acknowledgments

I would like to thank Professor Jonathan Percy and Dr Liam Cox for supervision and guidance during the course of this PhD. I would also like to thank Dr Gareth Deboos of Avecia Ltd for contributions to this project as well as Avecia for support.

I would also like to thank the technical staff at the School of Chemical Sciences for their invaluable contribution: Dr Neil Spencer and Malcolm Tolley for providing an excellent NMR unit; Peter Ashton, Nick May and Lianne Hill for mass spectrometry; Lianne Hill for elemental analysis; and Graham Burns for excellent GC and HPLC services. Gratitude also goes to Dr Heather Tye for the use of the chiral HPLC column.

I am grateful to the EPSRC and Avecia Ltd for funding this research and to the University of Birmingham for funding my third year as well as providing the necessary laboratory and sporting facilities.

I would also like to thank all the past members of the JMP research group for their academic and social support. Thanks also go to the current members at Leicester. A big thankyou must also go to the members of the LRC group for putting up with me for the last year.

Lastly, but certainly not least, I wish to thank all friends and family who have helped me over the entire course of my education. Your contributions, however inapparent, have been vital to my success. Special thanks go to Mom and Dad.

Abbreviations

Abs.	absolute
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobis*iso*butyronitrile
AIDS	Acquired Immunodeficiency Syndrome
All	allyl
Ar	aryl
aq.	aqueous
Bn	benzyl
BOC	*t*-butoxycarbonyl
BPO	benzoyl peroxide
Bu	*n*-butyl
BuLi	*n*-butyllithium
Bz	benzoyl
ca.	circa, approximately
cat.	catalytic
Cbse	*N*-(*tert*-butyldiphenylsilyloxyethyl)-*N*-*iso*propylcarbamoyl
CDI	1,1-carbonyldiimidazole
CoA	coenzyme A
Conc.	concentrated
COSY	Correlation Spectroscopy
Cy	cyclohexyl

d	days
DAC	*N*,*N*-diallylcarbamoyl
DAST	diethylaminosulfur trifluoride
dba	*trans*,*trans*-dibenzylideneacetone
DBU	1,8-diazabicyclo[4.3.0]undec-7-ene
DCM	dichloromethane, methylene chloride
DEC	*N*,*N*-diethylcarbamoyl
DHQ	dihydroquinine
DHQD	dihydroquinidine
Dibal-H	di*iso*butylaluminium hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane, ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
E.coli	*Escherichia coli*
ee	enantiomeric excess
Emac	*N*-ethyl-*N*-(2-methylallyl)carbamoyl
EPR	Electron Paramagnetic Resonance
Eq.	equivalents

er	enantiomeric ratio
ES	electrospray
Et	*n*-ethyl
FDA	Food and Drug Administration (US)
1-F-DX	1-deoxy-1-fluoro-D-xylulose
1,1-F_2-DX	1-deoxy-1,1-difluoro-D-xylulose
G	group
GC	gas chromatography
GOESY	Gradient Nuclear Overhauser Effect Spectroscopy
h	hours
Hetaryl	Heteroaryl
HIV	Human Immunodeficiency Virus
HMBC	Homonuclear Multiple Bond Correlation
HMG	hydroxymethylglutaryl
HMPA	hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
hrs	hours
HSQC	Heteronuclear Single Quantum Correlation
HWE	Horner-Wadsworth-Emmons
Hz	hertz
^{i}Pr	*i*sopropyl
Im	imidazolyl
IUPAC	International Union of Pure and Applied Chemistry
K	thousand

KHMDS	potassium *bis*(trimethylsilyl)amide
LDA	lithium di*iso*propylamide
LUMO	Lowest Unoccupied Molecular Orbital
M	molar
MAC	*N*-methyl-*N*-allylcarbamoyl
MBC	*N*-methyl-*N*-benzylcarbamoyl
Me	methyl
MEM	2-methoxyethoxymethyl
MHz	megahertz
Min(s)	minutes
Mmol	millimole(s)
Mol	mole(s)
MS	mass spectrometry
MTPA	2-methoxy-2-trifluoromethyl-2-phenylacetyl
NaHMDS	sodium *bis*(trimethylsilyl)amide
NCS	*N*-chlorosuccinimide
NMP	1-methyl-2-pyrrolidinone
NMO	4-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NOE	Nuclear Overhauser Effect
PDC	pyridinium dichromate
PG	protecting group
pH	-log $[H^+]$

Ph	phenyl
PHAL	phthalazine
*p*MBz	*para*-methoxybenzoyl
*p*NBz	*para*-nitrobenzoyl
PNP	pyridoxine phosphate
*p*TSA	*para*-toluenesulfonic acid
ppm	parts per million
pyr.	pyridine
R	undefined group
R_f	perfluoroalkyl group
Red-Al®	sodium *bis*(2-methoxyethoxy)aluminium hydride
Ra-Ni	Raney nickel
RT	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
S_N2	bimolecular nucleophilic substitution
$S_{RN}1$	unimolecular nucleophilic radical substitution
$t_{1/2}$	half-life
TA	transacylation
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
*t*Bu (^{t}Bu, ^{t}Bu)	*tert*-butyl
TC	2-thiophenecarboxylate

TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFP	trifurylphosphine
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMNO	trimethylamine *N*-oxide
TMS	trimethylsilyl
TOF	time of flight
Ts	*para*-toluenesulfonyl
TS	transition state
UV	ultraviolet
vide ante	see before
vide infra	see below
vide supra	see above
Z	benzyloxycarbonyl (Cbz)
μmol	micromole(s)

Contents

“To make an end is to make a beginning,
the end is where we start from”

Chapter One

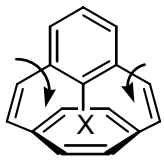
Introduction

1.1 Rationale for Fluorine Atom Introduction

Naturally occurring fluorinated molecules are very rare.[1] Organofluorine chemists are therefore interested in the possible effects on biological properties of molecules after introducing a limited number of highly electronegative fluorine atoms. Over the last thirty years, the interest and profile of selectively fluorinated biomolecules have risen dramatically. As such, much synthetic effort has been invested to synthesise biologically active organofluorine compounds.[2] The drive to develop methodology allowing improved access to such compounds has arisen after the demonstration of the useful physical and chemical properties possessed by this class of compound. The rationale for the selective introduction of a limited number of fluorine atoms into key sites of bioactive molecules is based upon several relevant properties of the fluorine atom:[3]

i) On steric grounds, exchanging a hydrogen atom for a fluorine atom involves the minimal possible change in molecular volume, thus minimising any change in complementarity between the substrate and the receptor site in the enzyme. Although it has often been claimed that the fluorine atom has a similar volume to the hydrogen atom, this is not the case. On comparing van der Waals radii, the fluorine atom is 23% larger than the hydrogen atom and so only the replacement of a small number of hydrogen atoms (one or two) with fluorine atoms will not greatly alter steric requirements. This difference is exemplified by comparing the conformational A value of the methyl (CH_3) and trifluoromethyl (CF_3) substituents (1.4 and 2.4 respectively). In fact, the CF_3 group is as sterically demanding as an *iso*propyl group. The largest F-steric effect recorded is illustrated in the rate differences between the *meta* ring-flip

(cradle effect of X over the lower planar benzene ring) of the molecule below in **Figure 1**.



X = H or F

$R_H/R_F = 10^{11}$

Figure 1: Steric differences between H and F

The ring-flip occurs 10^{11} times faster when X is hydrogen, compared to when it is fluorine. This is presumably due to the increase in electronic repulsion between X and the circulating electrons in the π-cloud of the benzene ring when X is a fluorine atom. From these facts, it is more correct to describe the fluorine atom as isosteric with the oxygen atom or a hydroxyl group, and this interchange is very common in the literature.[4]

ii) The high relative electronegativity of the fluorine atom (4.0 on the Pauling scale) compared to the hydrogen atom (2.1) may have a marked effect on the electronic surface of the molecule and may modify the behaviour of proximate functional groups. In addition, this property of fluorine is often used to stabilise a key linkage, by destabilising any positively charged intermediates or transition states (e.g acetal or glycosidic linkages).[5]

iii) The high bond dissociation energy of the C-F bond (489 kJ mol^{-1}) can effectively block metabolic oxidation at sites at which C-H bonds are cleaved by hydrogen atom abstraction.[6] This property also severely reduces the possibility of losing a high-energy fluorine atom during radical processes. However, though the C-F bond is strong, the fluoride ion may function as a leaving group in certain circumstances,

albeit with low nucleofugacity. It may also be displaced at or near to the active sites of enzymes, resulting in the covalent attachment of the organic moiety to the enzyme.[7]

iv) The introduction of fluorine atoms usually (but not always) increases lipid solubility (due to an increase in hydrophobicity), thereby enhancing the rate of absorption of drugs *in vivo* and hence bioavailability. This is an important therapeutic property as it allows the administration of lower doses of drugs. The CF_3 group is among the most lipophilic of all substituents, although, from limited data, it is apparent that mono- and trifluoromethylation reduces lipophilicity when the site of fluorination is separated from any heteroatom or π-bond by at least three carbon-carbon bonds. This is due to the relatively polar nature of these groups. Aromatic fluorination always increases lipophilicity and explains the ubiquitous presence of the fluorine atom (as fluoroarenes) in biocides.[8]

Fluorine-containing medicinal compounds have contributed significantly to advances in such areas as cancer chemotherapy, anti-inflammatory agents, anti-parasitic agents, antibiotics and the chemistry of mental health.[9] It is therefore clear that there is a great demand for new methodology allowing access to a range of fluorinated motifs, such that the full potential of fluorinated medicinals can be harnessed.

1.2 Current Methods for the Synthesis of Fluorinated Motifs

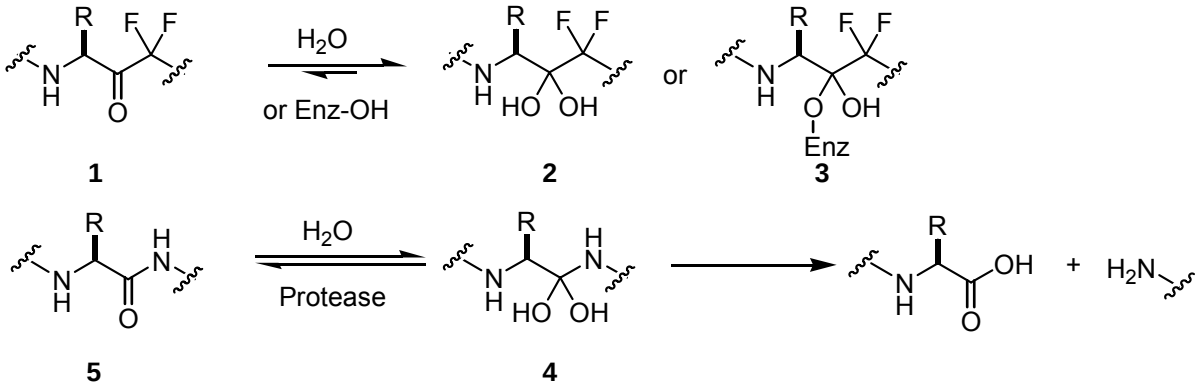
Many chemists, when targeting a fluorinated compound, utilise direct fluorination of a precursor at a late stage in the synthesis in order to reach their goal. This mode of fluorination takes place by a functional group transformation, notably of a ketone, an

alcohol or an epoxide. Chemists are currently able to utilise both electrophilic and nucleophilic sources of fluorine.

An alternative approach has become popular in which the fluorine atoms are present from the outset and the molecular dressing is added *via* adaptation of known synthetic methodology to the presence of the fluorine atom. The number of reactions studied is expanding and often highlights both the benefits and pitfalls of using this approach. The very nature of the initiative of fluorine atom introduction can cause severe synthetic limitations and it has become important to find improved strategies to subclasses of fluorinated molecules. This strategy is often denoted as the building-block approach.[10]

1.2.1 Current Methods for the Synthesis of (Aryl) Difluoromethyl Ketones

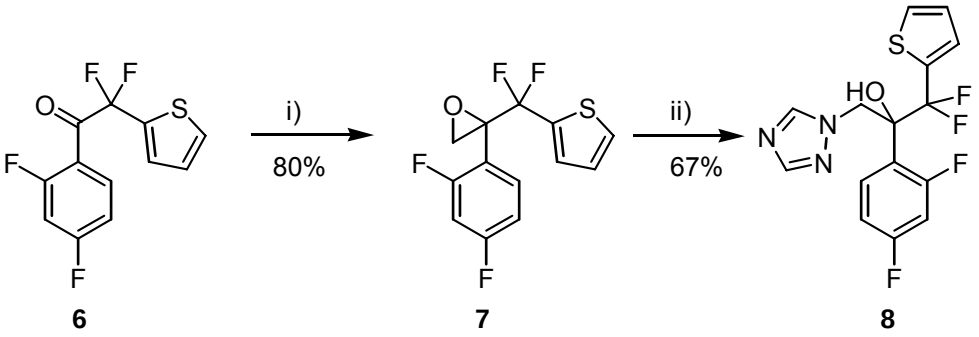
α,α-Difluoromethyl ketones are ubiquitous targets in the literature. The continuing interest in this moiety has arisen from the activating effects of the fluorine atoms on the electrophilicity of the carbonyl, arising from a lowering of the LUMO energy level.[11] This mode of action is frequently adopted in the field of drug discovery in which selected peptide linkages are replaced by a difluoroketone moiety to form a competitive inhibitor **1** of, for example, disfunctioning protease enzymes. Active site nucleophiles (such as a water molecule or a hydroxyl group of a serine residue) competitively react with the fluoroketone to form the stable hydrate **2** or hemiketal **3**, respectively. The process occurs through mimicry of the intermediate **4** traversed during hydrolysis of a peptide linkage **5** by protease enzymes (**Scheme 1**).



Scheme 1: Use of α-fluoro-α-peptidyl ketones as competitive inhibitors of proteases through TS mimicry

Fluoroketones have been successfully used as inhibitors of renin,[12,16] HMG CoA reductase,[13] γ-secretase,[14] HCMV protease[15] and HIV-1 proteases.[16]

The application of a difluoroketone moiety within other molecular frameworks is far less well explored, due to the lack of availability of appropriate methodologies for incorporating this group. However, Eto and co-workers have recently shown an interest in the use of aryl difluoromethyl ketone derivatives in the synthesis of antifungal agents (**Scheme 2**).[17]



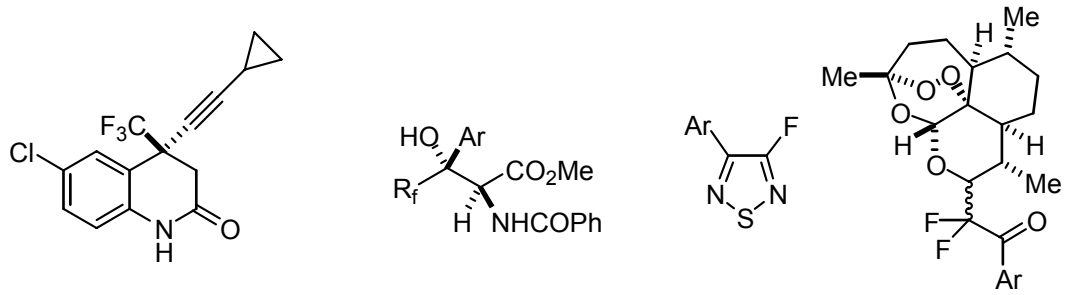
6 **7** **8**

Reagents and Conditions: i) $[Me_3SO]^+I^-$, NaH, DMSO;
ii) 1,2,4-triazole, K_2CO_3, DMF

Scheme 2: Antifungal synthesis using aryl difluoromethyl ketones

Treatment of difluoroketone **6** (prepared by addition of 2,4-difluorophenyllithium to the corresponding ester, formed by cross-coupling of ethyl bromodifluoroacetate with 2-iodothiophene with copper, 50% yield for two steps) with trimethylsulfoxonium iodide led to the formation of epoxide **7**. Ring opening with 1,2,4-triazole afforded the potent antifungal agent **8**. The (+)-isomer possessed significant *in vitro* activity against a range of yeasts and filamentous fungi. The same group has also described the synthesis and activity of similar compounds in which an alkylsulfanyl group has replaced the heteroaryl group (thienyl in **8**).[18]

Other uses of difluoro- and trifluoromethyl ketones include the synthesis of the Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) efavirenz **9**,[19] novel fluorinated amino acids[20] **10**, 3-aryl-4-fluoro-1,2,5-thiadiazoles[21] **11** which possess herbicidal and nematicidal properties and C-10 fluorinated derivatives[22] **12** of *epi*-dihydroartemisinin which may possess antimalarial properties (**Figure 2**).



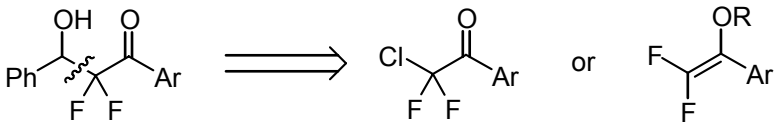
9 **10** **11** **12**

Figure 2: Potentially useful products from aryl difluoromethyl ketones

α-Halo-α,α-difluoromethyl ketones can also serve as useful building blocks to other mid-chain difluoroketones through Reformatsky reactions[23] or cross-coupling with aryl halides under nickel(0)[24] or copper(0) catalysis.[25]

A suitable methodology that is amenable to parallel synthesis should allow the generation of a diverse array of compounds, allowing structure-activity correlations to be made. In the future, other uses of aryl difluoromethyl ketones may be developed. In drug design, the aromatic rings may be applicable as a means of introducing conformational rigidity as well as directing units, a ploy used often in the pharmaceutical industry. It is clear that aryl difluoromethyl ketones are worthy targets for testing such molecular connections in future drug design.

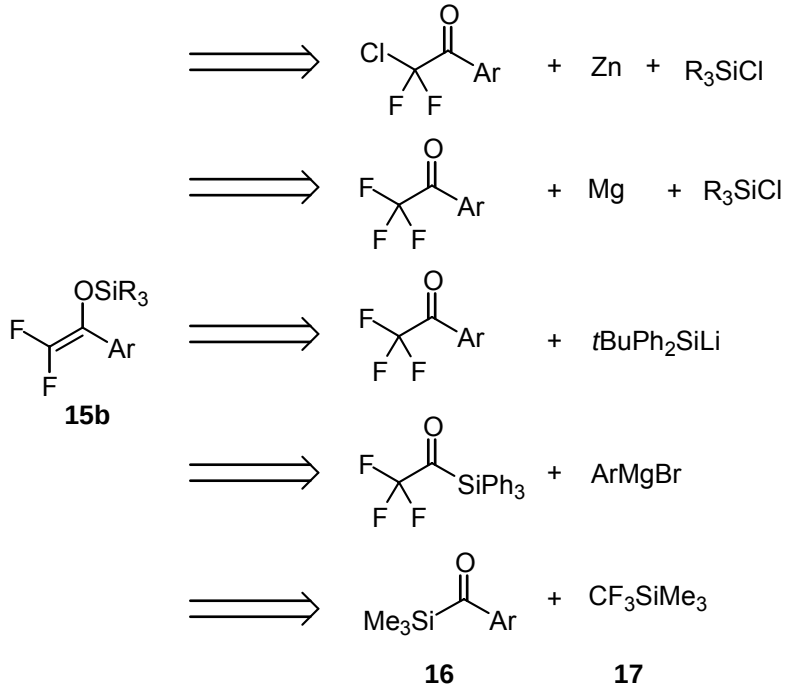
Retrosynthetic analysis of a typical target, aldol product **13** is shown in **Scheme 3**.



13 **14** **15a** R = Me
15b R = TMS

Scheme 3: Initial disconnection of an aldol target **13**

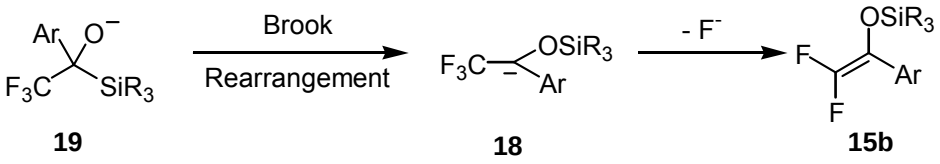
Disconnection of the CF_2-R bond can either lead to an α-chloro-α,α-difluoromethyl ketone **14** or a difluoroenol ether **15**. Ishihara has reported Reformatsky-type reactions of α-chloro-α,α-difluoromethyl ketones with ketones using a variety of metal catalyst systems.[23a,b] Alternatively, indium-mediated reaction of α-halo-α,α-difluoromethyl ketones (formed by halogenolysis of the corresponding silyl difluoroenol ethers) in aqueous media has been described by Welch.[23c] Taguchi has described the aldol condensation of 1,1-difluoroenol methyl ether derivatives **15a**,[26] whilst Portella has described an identical sequence using silyl difluoroenol ethers **15b**.[27] The enol ethers **15a** are available from chlorodifluoromethyl ketones **14** whilst several avenues to the corresponding silyl difluoroenol ethers **15b** have been investigated. **Scheme 4** shows the approaches studied.



Scheme 4: Approaches to silyl difluoroenol ethers **15b**

Ishihara has described the reaction of Zn(0) with chlorodifluoromethyl ketones in the presence of chlorotrimethylsilane to form the corresponding silyl difluoroenol ether.[28] A milder version, in which Mg(0) is employed, has been recently described by Uneyama.[29] This method is now the method of choice even though a large excess of Mg(0) and silane is required. However, the method has been put to good use by the sequential conversion of trifluoromethyl ketones to difluoromethyl ketones and then fluoromethyl ketones.[30] Such a conversion using Mg(0) has also been achieved electrochemically.[31]

The last three approaches all rely upon the elimination of fluoride from a carbanion **18**, resulting from Brook rearrangement of a 1-trifluoromethyl-1-aryl-1-trialkyl-silylmethoxide anion **19** (**Scheme 5**).

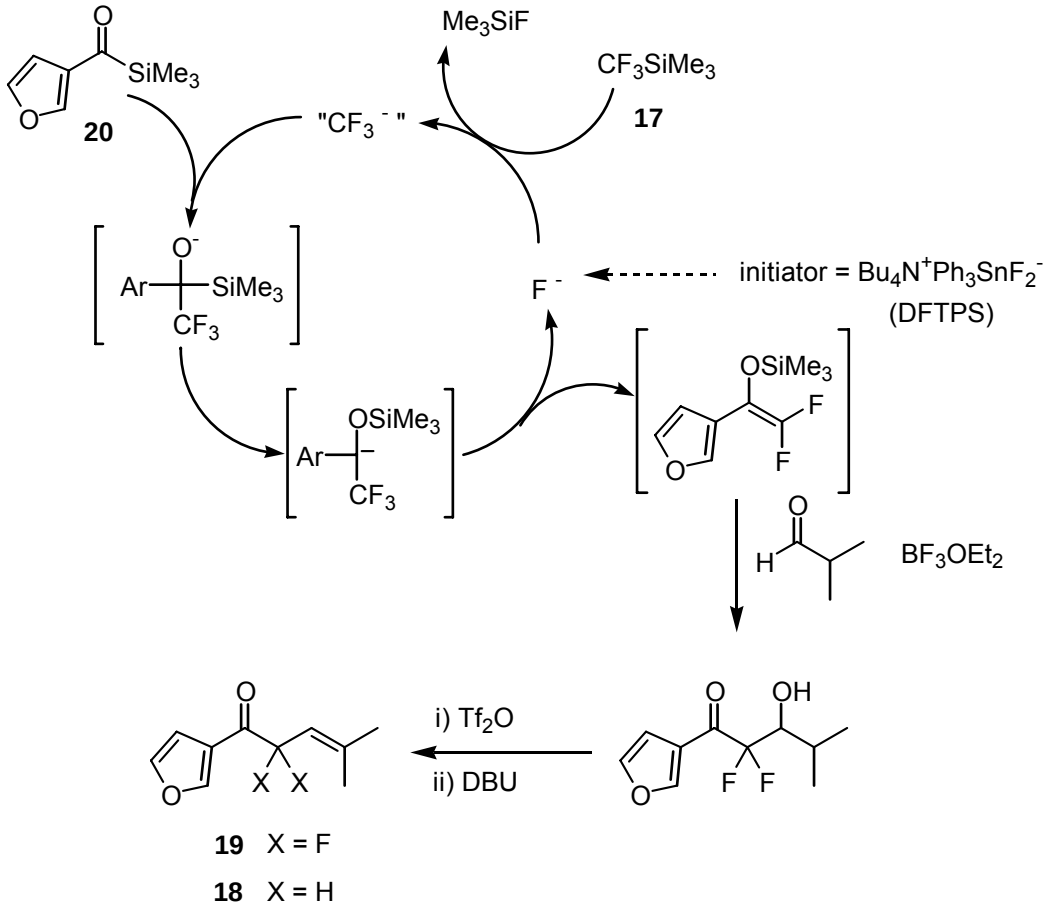


19 **18** **15b**

Scheme 5: A Brook rearrangement in the formation of silyl difluoroenol ethers **15b**

The three methods differ in the nature of the nucleophile used upon the carbonyl starting material. Fleming described the addition of *tert*-butyldiphenylsilyllithium to trifluoromethyl ketones.[32] The reaction, however, was difficult to control and the product **15b** (R_3=TBDP) was isolated in only moderate (51%) yield. Xu reported the reaction of Grignard reagents with trifluoroacetyltriphenylsilane to form the corresponding silyl difluoroenol ethers **15b** in high (88-99%) yield.[33] On the other hand, Portella has examined the use of acylsilanes[34] **16** in conjunction with Ruppert's reagent **17**, which acts as a source of trifluoromethylide in the presence of a catalytic

fluoride source.[27a,b] **Scheme 6** shows such an approach to a difluorinated analogue of egomaketone **18**.[27c] One major drawback of this approach is the high cost (£1.44 /mmol) of the Ruppert reagent **17**.

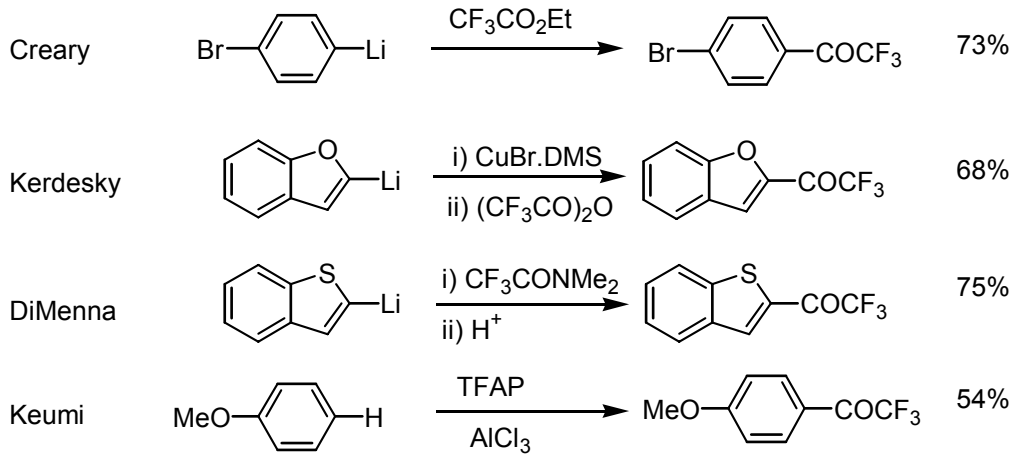


Scheme 6: Synthetic approach to difluoroegomaketone **19** using Ruppert's reagent **17** and acylsilane **20**

Many of the other approaches require the use of α-halo-α,α-difluoromethyl aryl ketones. Such materials are typically accessed through the addition of a suitable organometal, typically aryllithium and Grignard reagents, to commercially available carbonyl derivatives, such as esters or amides. All of the monofluoro-, difluoro- and trifluoroacyl (except those containing iodine) starting materials are commercially available. Limitations of this method exist in the cost of some of the starting materials

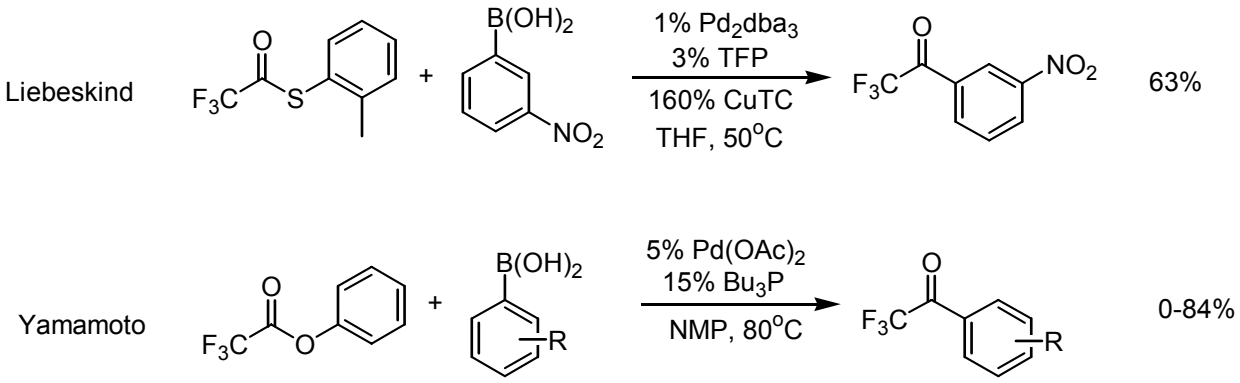
as well as the repetitive use of cold-temperature reactions for each aryl installation. More importantly, the nature of the reaction does not permit the presence of either acidic or electrophilic groups and therefore limits the degree of functionality present elsewhere in the product. As can be seen from **Scheme 4**, trifluoromethyl ketones[35] are a major source of difluoroenol derivatives, which can be transformed into other fluoromethyl ketone derivatives.

Creary has studied the addition of aryllithium reagents to ethyl trifluoroacetate and has shown that the desired ketones could be isolated in good yield.[36] Kerdesky utilised trifluoroacetic acid anhydride with heteroaryl copper reagents to afford products in good (65-85%) yield.[37] DiMenna reported a similar protocol in which *N*,*N*-trifluoroacetamide was used as the trifluoroacetylating agent with lithiated heterocycles.[38] In a more direct approach, Keumi and co-workers used 2-(trifluoroacetoxy)pyridine (TFAP) as an effective trifluoroacetylating agent for arenes in the presence of aluminium trichloride.[39] Though good yields were isolated, structural variation of the aromatic ring was not studied (**Scheme 7**).



Scheme 7: Various methods of trifluoromethyl aryl ketone synthesis

Srogl and Yamamoto have described improved protocols to trifluoromethyl aryl ketones based upon cross-coupling of trifluorothioacetic and trifluoroacetic acid derivatives with boronic acids, respectively (**Scheme 8**).

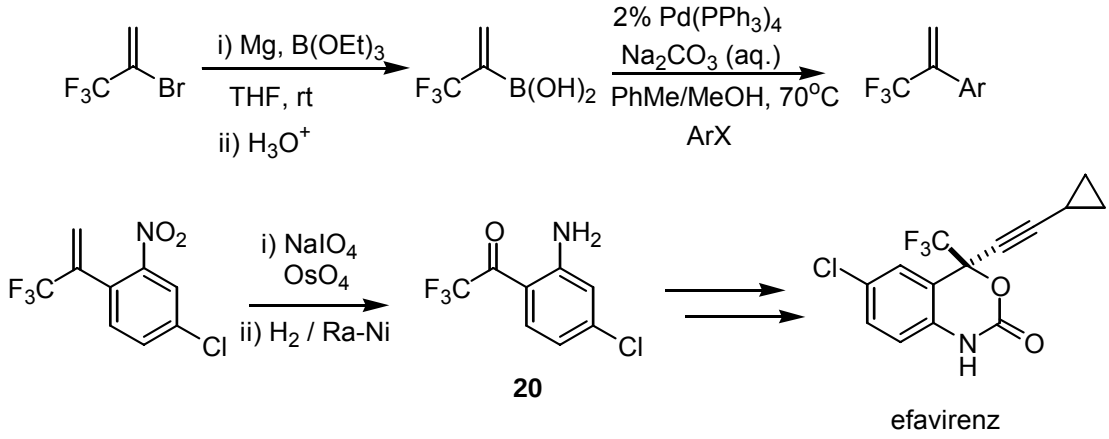


Scheme 8: Coupling strategies from trifluoro(thio)acetic acid derivatives

Liebeskind and Srogl described the efficient cross-coupling of *o*-tolyl trifluorothioacetate with boronic acids under palladium catalysis in the presence of copper(I) thiophene-2-carboxylate (CuTC) to afford the corresponding ketone.[40] However, only one example was provided and the starting thioester needs to be synthesised. The copper(I) salt is also used in excess. In addition, this methodology was superceded by the work of Yamamoto, in which inexpensive and commercially available phenyl trifluoroacetate could be used directly with boronic acids; heterocyclic boronic acids were unfortunately unable to undergo cross-coupling in addition to those substituted at the *ortho* positions.[41] Yamamoto has subsequently developed methodology that may allow the inexpensive trifluoroacetic anhydride and trifluoroacetic acid to be used as alternative starting materials.[42]

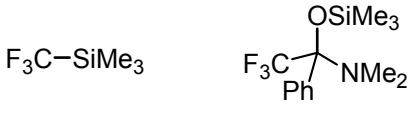
A less direct approach has been described by Jiang and co-workers in which α-(trifluoromethyl)vinyl boronic acid or the corresponding organozinc reagent have

been cross-coupled to iodo- and bromoarenes with excellent efficiency.[43,44] Synthesis of the requisite boronic acid was facile and a range of α-(trifluoromethyl)styrenes could be accessed. Osmium tetroxide/periodate could be used to install the ketone functionality in a synthesis of ketone **20**, used in the preparation of efavirenz, a potent NNRTI approved by the FDA for the treatment of AIDS (**Scheme 9**).



Scheme 9: Jiang's approach to trifluoromethyl aryl ketones

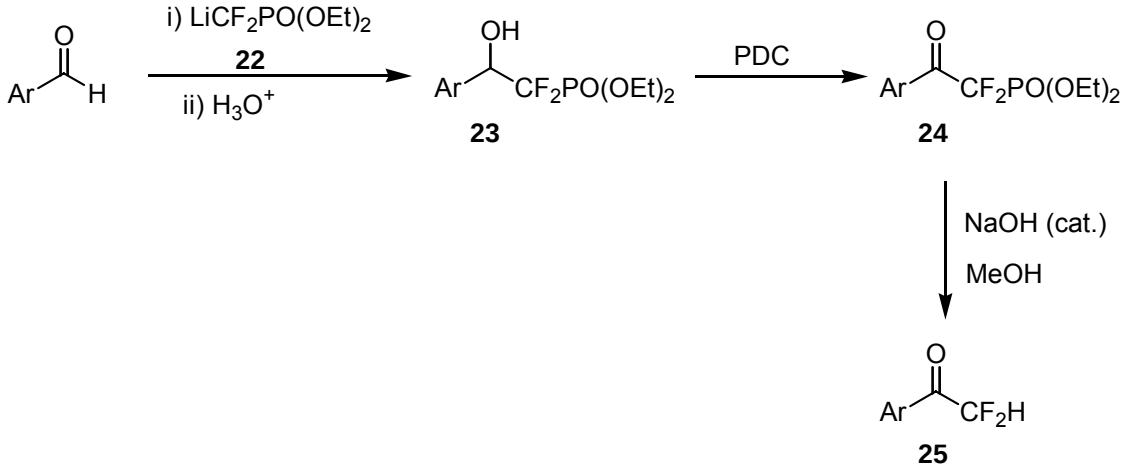
Other building-block methods have used nucleophilic trifluoromethylation[45] with either trifluoromethyltrimethylsilane[46] **17** or trifluoromethylacetophenone-*N*,*N*-dimethyltrimethylsilane[47] **21** (**Figure 3**). The latter reagent is considerably more stable and less expensive than Ruppert's reagent **17**.



17 **21**

Figure 3: Nucleophilic trifluoromethylating reagents

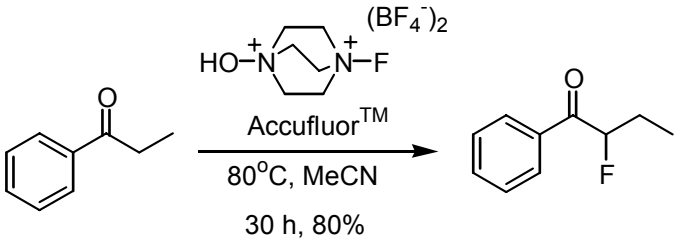
Piettre has reported the difluoromethylation of aromatic aldehydes with a lithiated difluorophosphonate **22** to afford alcohols **23**, which underwent oxidation to acyl phosphonates **24**.[48] Exposure to basic methoxide led to C-P bond cleavage and the subsequent formation of difluoromethyl ketones **25** (**Scheme 10**). This is one of the most useful methods for the formation of simple difluoromethyl aryl ketones, due to the large number of aldehydes available; however, the route does suffer for indirectness.



Scheme 10: Use of acyl phosphonates **24** to access difluoromethyl ketones **25**

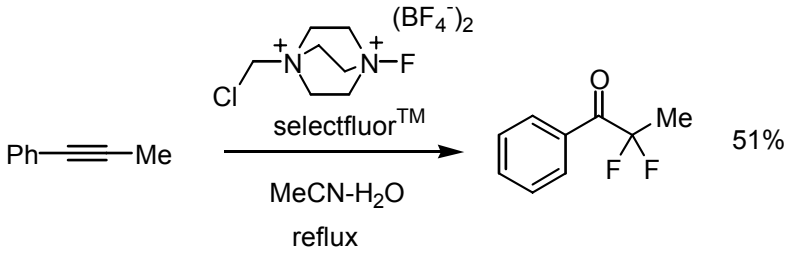
Several methods based upon fluorination have also been described. DesMarteau reported the fluorination of lithium enolates derived from benzophenones with *N*-fluoro-*bis*[(trifluoromethyl)sulfonyl]imide, which results in α-fluoromethyl aryl ketones as the major component, but in poor (26-38%) yield.[49] Difluoromethyl aryl ketones could be formed as the sole product by the use of imines with two equivalents of the fluorinating agent. Zupan has described the fluorination of propiophenone with Accufluor™ to afford the monofluorinated aryl ketone in good (80%) yield (**Scheme**

11). The reaction is slow however (30 h at 80°C) and does not appear to be general (acetophenone gave only 23% product).[50]



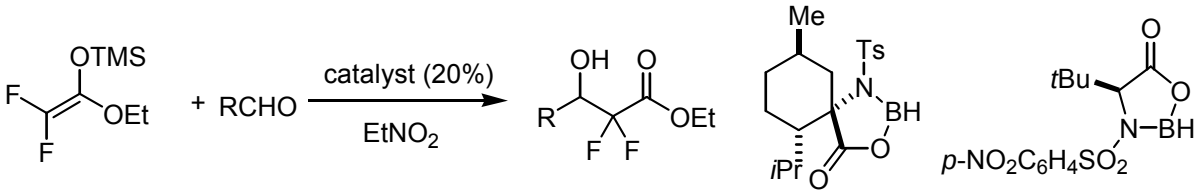
Scheme 11: Monofluorination using Accufluor™

Zupan has also described a more attractive approach, in which substituted phenylacetylenes underwent reaction with Selectfluor™ in the presence of water to form difluoromethyl aryl ketones in moderate (36-51%) yield (**Scheme 12**). The scope of the reaction has not been fully explored, however.[51]



Scheme 12: Fluorination of acetylenes to difluoroketones

It is also possible to access the target materials by reversing the sequence of events. Iseki[52] has described the catalytic asymmetric aldol condensation of silyl difluoroketene acetals **26** with aldehydes to afford β-hydroxy-α,α-difluoropropionates **27** in high (81-97%) *ee* using Masamune's catalyst **28** or Kiyooka's catalyst **29** (**Scheme 13**).



26 **27** **28** **29**

Scheme 13: Synthesis of optically active β-hydroxy-α,α-difluoro-propionates **27** from silyl difluoroketene acetals **26**

These materials can be transformed into the corresponding Weinreb amides with an enhancement of the *ee* by recrystallisation (typically to 100% *ee*). Treatment with Grignard reagents then affords the enantiomerically pure α,α-difluoro-β-hydroxyketones in high (80-98%) yield.[53] Protection of the hydroxyl group followed by exposure to a Grignard reagent should then deliver the desired materials. However, the same limitations already alluded to apply here (*vide ante*).

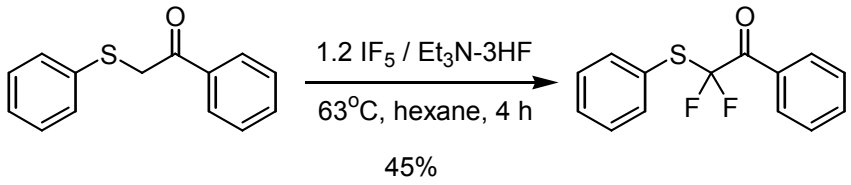
A similar reaction using silyl fluoroketene acetals and a range of aromatic aldehydes, in the presence of trimethylsilyl triflate, has been described by Chen.[54] Fluorination methods to these materials have also been reported; β-ketoesters reacted with *p*-iodotoluene difluoride and Olah's reagent (9HF-pyridine) at ambient temperature to afford the monofluorinated esters in good (72-80%) yield.[55]

A particularly rare motif is the α-(heteroarylthio)-α,α-difluoromethyl aryl ketone, a species which has been used as a building-block to antifungal agents (*vide ante*) or as possible NNRTI candidates.[56]

Few methods are available for this connection. Brigaud[57]and Fuchigami[58] have reported electrochemical methods, whilst Kuroboshi[59] used an oxidative fluorodesulfurisation approach using tetrabutylammonium dihydrogentrifluoride and

dimethylhydantoin with β-hydroxyorthothioesters at ambient temperature. However, the reaction gave variable yields of products and the reagents were required in excess.

Several authors have described fluorination methods employing α-(phenylsulfanyl)-acetates. Takeda and co-workers used a variety of *N*-fluoropyridinium salts to achieve the desired transformation, albeit under harsh (105°C) conditions.[60] Variable yields of products were also observed. Motherwell used difluoroiodotoluene as the fluoride source and both mono- and difluorination could be achieved by altering the stoichiometry.[61] Good (64-80%) yields were typically achieved. A similar approach using an IF_5/Et_3N-3HF fluorination regime was successful in moderate (45-55%) yield (**Scheme 14**).[62]



Scheme 14: Fluorination of (α-phenylthio)acetophenone using IF_5

The best method to date, however, involves the displacement of chloride from a chlorodifluoromethyl aryl ketone using a thiolate nucleophile.[63] In this manner, Médebielle was able to synthesise a small number of the target compounds for biological testing. However, the method does require the use of α-chloro-α,α-difluoromethyl aryl ketones, which have limited diversity in the aryl unit, as already outlined.

1.2.2 Fluorinated Carbohydrates

Much attention has been paid to the synthesis of selectively fluorinated carbohydrate analogues over the last fifty years.[64] During this period, many successful syntheses have been reported and the sugars have been used for probing glucose metabolism,[65] hydrogen-bonding patterns in binding specificity studies[66] and as drug candidates.[67]

Biological activity

The largest single field of study is that of fluorination at the 2'- and 3'- positions of deoxypentoses. The parent sugars are key nucleosides in the replication of viral DNA in herpes, hepatitis-B and HIV viruses. Considerable effort has been put into the synthesis of selectively fluorinated deoxypentoses as potential anti-HIV,[68] anti-hepatitis-B[69] and anti-herpes[70] viral agents .The design strategy is threefold:

i) Replication involves activation of the 5'-hydroxyl by phosphorylation followed by chain elongation at the 3'-hydroxyl group. Therefore, blockage of the 3'-group with a fluorine atom should lead to chain termination.

ii) Introduction of 2'-fluoro or 2',2'-difluoro substituents leads to significant stabilisation of the glycosidic linkage by inductive destabilisation of the oxacarbenium ion intermediate. This leads to higher activity, better bioavailability and lower dosage requirements.

iii) The presence of fluorine atoms can alter the conformation of the sugar ring, leading to a change in activity, resulting from a change in complementarity with the receptor site.[71]

The above points have been used to make a series of fluorinated sugar analogues, resulting in invaluable structure-activity correlation studies.[72]

Some fluorosugars of current interest are shown in **Figure 4**.

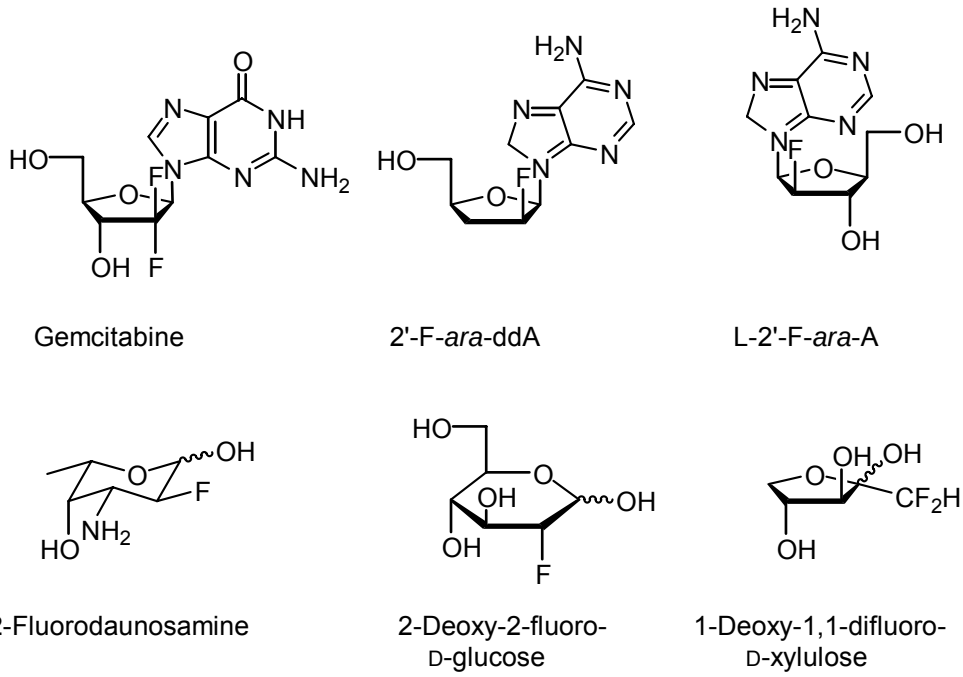


Figure 4: Fluorosugars of current interest

Current studies are also probing the use of unnatural L-nucleosides for incorporation into drug molecules.[68a,69a-b,72b-c,73] The use of fluorine in other carbohydrate systems is far less studied. *Gem*-difluorination at the 2'- position remains a key design point, improving stability to acidic conditions. Applications of 2-deoxy-2,2-difluorohexoses are rare in the literature. 2-Deoxy-2,2-[18-F]$_2$-difluoroglucose has attracted some attention as a possible alternative to 2-deoxy-2-[18-F]-fluoroglucose in the clinical study of glucose metabolism.[74] However, the short half-life ($t_{1/2}$ = 110 mins) precludes its synthesis by building-block approaches and the use of DAST remains the only viable option.

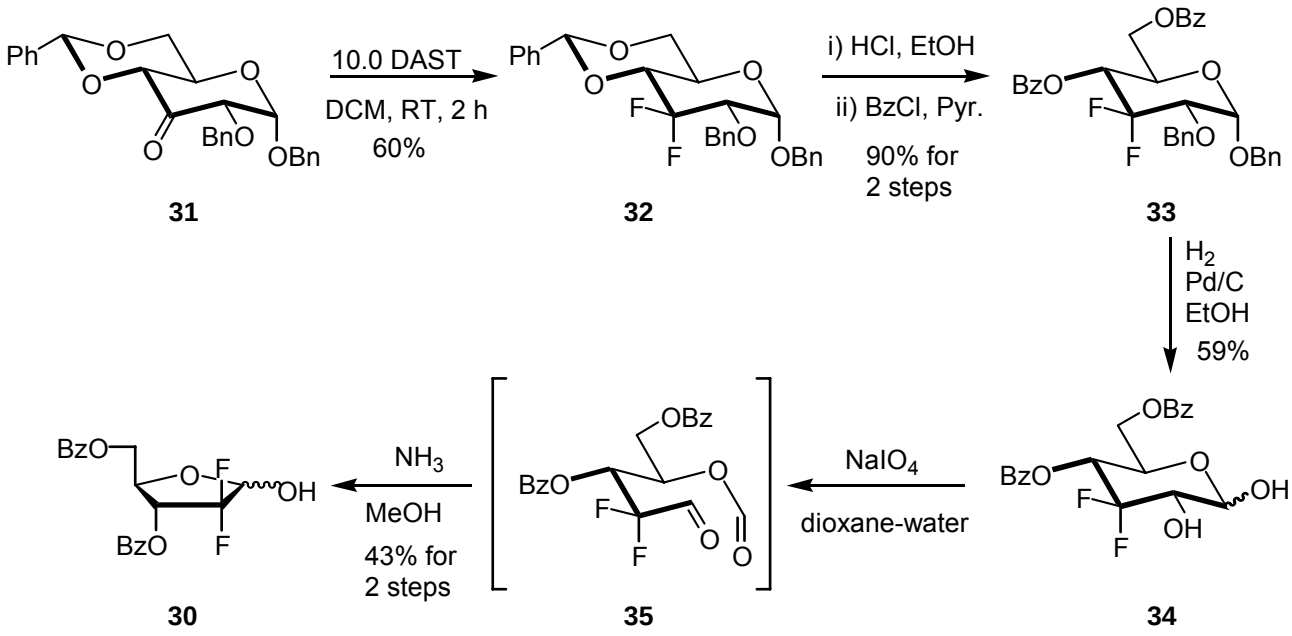
Synthesis using fluorination methodology

Nucleophilic fluorination

The introduction of fluorine atoms at a late stage in a synthesis can be achieved using either a nucleophilic or electrophilic fluorine source.

Nucleophilic sources consist of harsh regimes such as hydrofluoric acid, xenon(II) fluoride, sulfur(IV) fluoride and the family of alkylaminosulfur trifluorides (DAST, Morph-DAST, Deoxo-Fluor). Alkali metal fluorides have also been extensively used, especially in the developing years of the field.

The synthesis of 2-deoxy-3,5-di-*O*-benzyl-2,2-difluoro-D-ribose **30** by Castillón and co-workers exemplifies the use of DAST in the synthesis of fluorosugars (**Scheme 15**).[75]

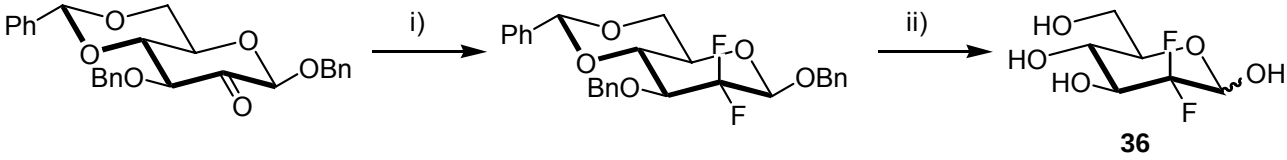


Scheme 15: Use of DAST in 2-deoxy-2,2-difluoro-D-ribose synthesis

Treatment of protected D-glucose **31** with an excess of DAST in dichloromethane at ambient temperature afforded the desired protected 3,3-difluoro-D-glucose **32** in

good (60%) yield. Deprotection of the benzylidene acetal with acid followed by double benzoylation afforded **33**. Hydrogenolysis over palladium/charcoal gave glucose **34** in moderate (59%) yield as a mixture of anomers. Finally, oxidative cleavage of the diol, using periodate, afforded the target 2-deoxy-2,2-difluoro-D-ribose sugar **30** after hydrolysis of the intermediate 4-formyl derivative **35** with methanolic ammonia.

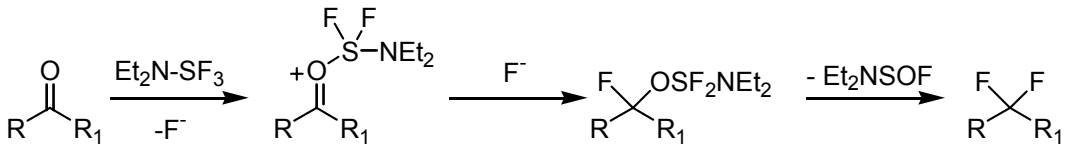
A similar ulose deoxyfluorination with DAST was used by Castillón and co-workers in an efficient synthesis of 2-deoxy-2,2-difluoro-D-arabinohexose **36** (**Scheme 16**).[74]



Reagents and Conditions: i) 6.0 DAST, PhMe, 110^{o}C, 5 min, 80%; ii) 20% $Pd(OH)_2$ /C, 35-kg pressure H_2, 7 min, 81% (total time = 35 min, 65%)

Scheme 16: Ulose deoxyfluorination with DAST

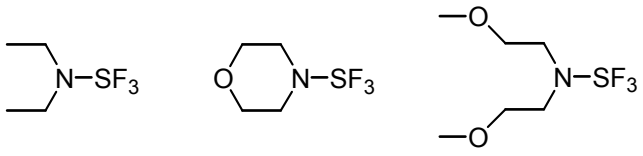
The general mechanism for deoxyfluorination using DAST is shown in **Scheme 17**.



Scheme 17: Mechanism of DAST deoxyfluorination

However, whilst many successful applications have been documented, several problems with DAST **37** are apparent. The material is expensive (£1.47 / mmol for small amounts) and decomposes upon storage for extended periods. In addition, many equivalents are often required in order to achieve the desired transformation. A

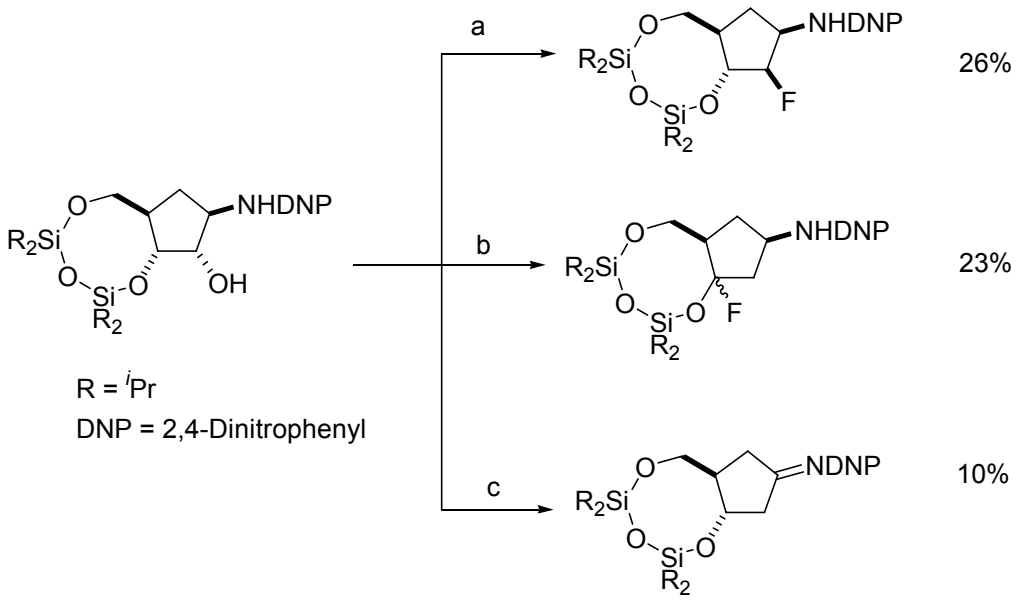
major drawback to scale-up is the knowledge that under forcing conditions or on large scale the reagent is liable to explode or detonate. More stable analogues have consequently been developed such as Morph-DAST[76] **38** and *bis*(2-methoxyethoxy)aminosulfur trifluoride[77] (Deoxo-Fluor^{TM}) **39** (**Figure 5**). Even though these analogues are less prone to thermal decomposition, they are also less chemically active than DAST.



DAST, **37** Morph-DAST, **38** **39**

Figure 5: Family of alkylaminosulfur trifluorides

It is also important to appreciate that reaction occurs *via* pathways with high carbenium ion character and several undesired pathways can be activated leading to elimination, rearrangement, 1,2-hydride shifts and neighbouring group participation (**Scheme 18**).[78]



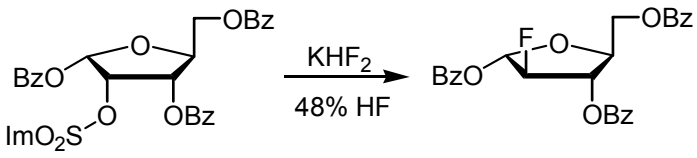
Scheme 18: Typical side reactions when using DAST

Apart from the desired fluorodeoxygenation pathway (a), two significant side reactions compete effectively; 1,2-hydride shift (b) and elimination of HF (c). Other more conventional amine protecting groups like BOC or Z lead to the formation of products arising from neighbouring group participation. Importantly, reactions involving DAST and similar reagents are highly sensitive to steric and conformational factors and reaction outcomes can be highly unpredictable.

Another popular approach is the use of metal fluorides as sources of nucleophilic fluoride. Reaction sequences typically involve *trans*-diaxial ring opening of epoxides or S_N2 displacement of a reactive hydroxyl leaving group, such as a mesylate or tosylate.

Ma *et al.* have described the use of potassium hydrogendifluoride as a nucleophilic source of fluoride in a synthesis of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)-pyrimidine nucleosides as potential anti-hepatitis B viral agents.[69b] The key synthetic

step involved the protection of the hydroxyl group as an imidazolyl sulfonate, primed for S_N2 displacement by fluoride (**Scheme 19**).

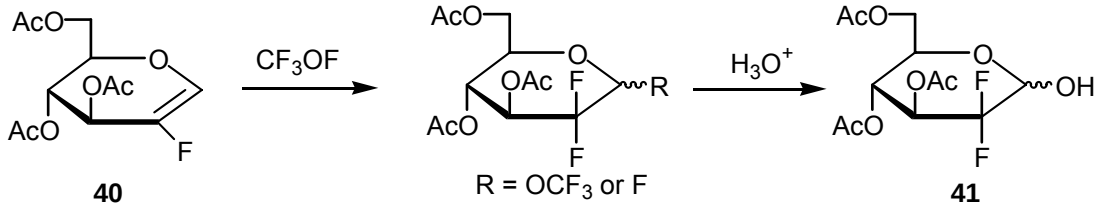


Scheme 19: Installation of a fluorine substituent using S_N2 displacement of a sulfonate

Electrophilic fluorination

Although the term electrophilic fluorination suggests the generation of a positively charged fluorine atom, it merely indicates the reactivity of the reagents used. Such reactivity can be achieved by attachment to an electronegative element such as oxygen or nitrogen.

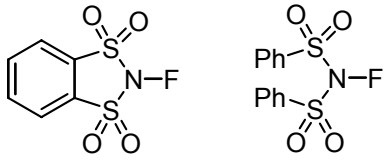
Trifluoromethyl hypofluorite (CF_3OF) has been used as an electrophilic source of fluorine whereby *cis*-addition occurs to a glycal. The intermediate carbenium ion is quenched either by the trifluoromethoxide ion or by fluoride to afford the saturated sugar. Adamson *et al.* used this approach in the conversion of 3,4,6-tri-*O*-acetyl-D-glucal **40** to 2-deoxy-2,2-difluoro-D-glucose **41** (**Scheme 20**).[79]



40 **41**

Scheme 20: Fluorination of a glycal using CF_3OF

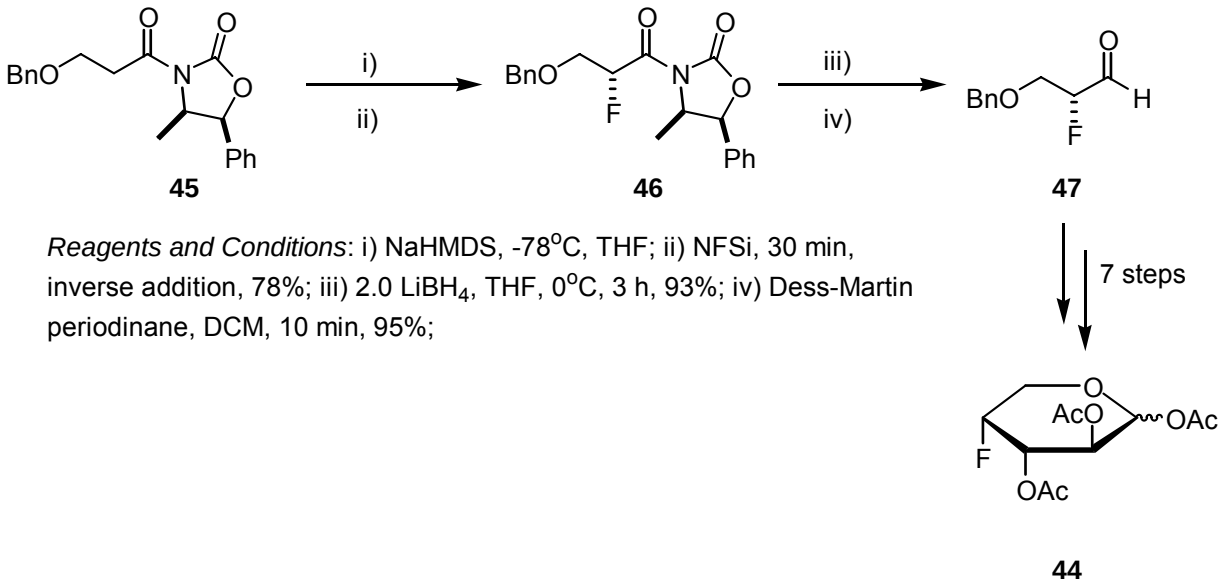
The handling problems of CF_3OF have been overcome by the use of N-F reagents such as *N*-fluoro-*O*-benzenedisulfonamide[80] **42** (NFOBS) and *N*-fluorobenzene-sulfonimide[81] **43** (NFSi) (**Figure 6**).



NFOBS, **42** NFSi, **43**

Figure 6: Electrophilic sources of fluorine

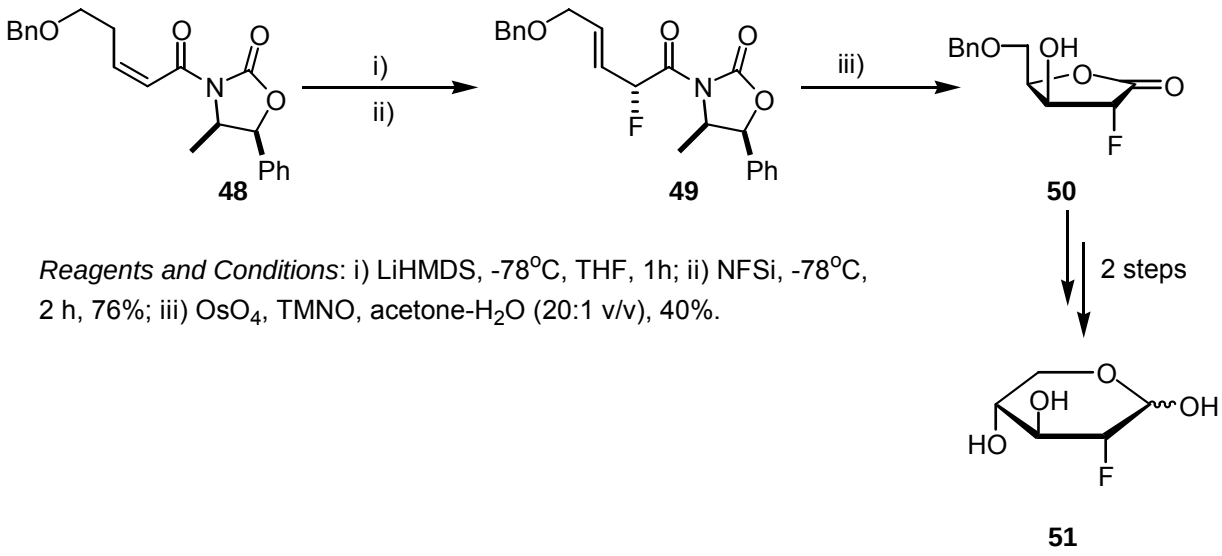
Davis and co-workers have utilised these reagents in the facially selective fluorination of enolates. In their synthesis of 4-deoxy-4-fluoro-D-arabinopyranose **44**, chiral amide **45** was treated with sodium hexamethyldisilazide to generate the sodium enolate, followed by quenching with NFSi to afford α-fluoroamide **46** in 94% *de*. Removal of the auxiliary group with lithium borohydride followed by Dess-Martin oxidation afforded the pivotal aldehyde **47** in 94% *ee*. This was then converted in 7 steps to the desired peracetylated sugar **44** (**Scheme 21**).[82]



Reagents and Conditions: i) NaHMDS, -78^{o}C, THF; ii) NFSi, 30 min, inverse addition, 78%; iii) 2.0 $LiBH_4$, THF, 0^{o}C, 3 h, 93%; iv) Dess-Martin periodinane, DCM, 10 min, 95%;

Scheme 21: Asymmetric synthesis of a 4-deoxy-4-fluoroarabinose using NFSi

A similar approach was used to synthesise 2-deoxy-2-fluoro-γ-aldonolactones, which were converted to 2-deoxy-2-fluoropentoses.[83] Treatment of unsaturated imide **48** with lithium hexamethyldisilazide led to an extended enolate, which was quenched with NFSi to afford the chiral imide **49** as a single diastereoisomer. Dihydroxylation with low selectivity (1:2.3) afforded the aldonolactone **50** as the minor product. **50** was converted in two steps to 2-deoxy-2-fluoro-D-xylopyranose **51** (**Scheme 22**).



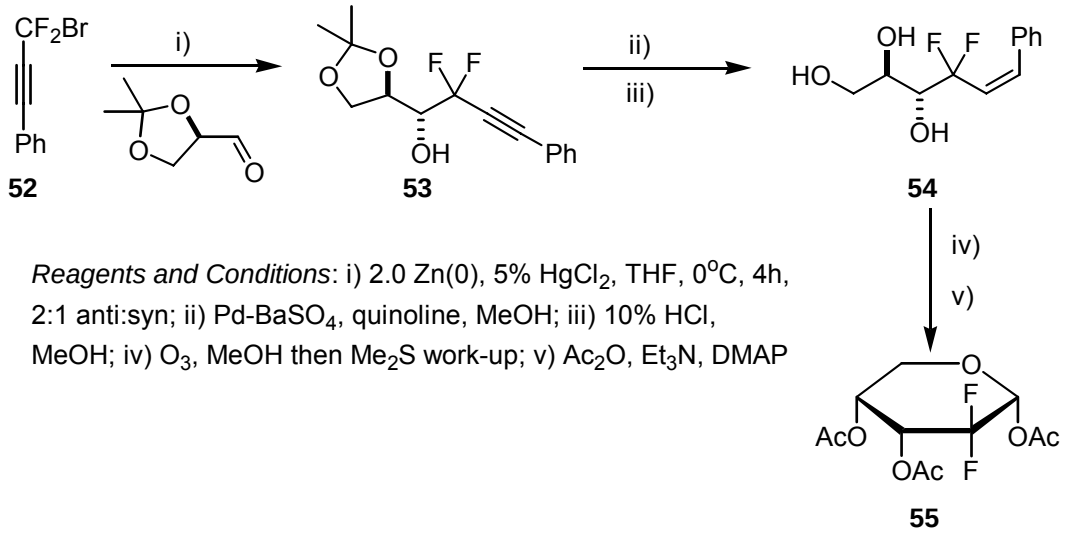
Reagents and Conditions: i) LiHMDS, -78°C, THF, 1h; ii) NFSi, -78°C, 2 h, 76%; iii) OsO_4, TMNO, acetone-H_2O (20:1 v/v), 40%.

Scheme 22: Asymmetric synthesis of a 2-deoxy-2-fluoroxylose using NFSi

Building-block methodology

There are relatively few building-block methods to fluorinated sugars. One well-researched approach is the use of the Reformatsky reaction of ethyl bromodifluoroacetate or a synthetic equivalent.

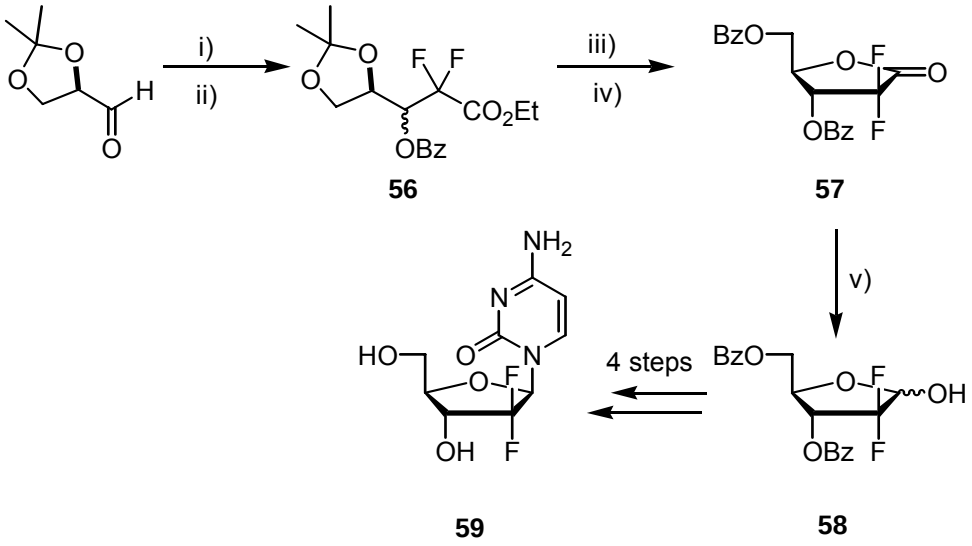
Kobayashi utilised bromodifluoromethylalkyne **52** in a Reformatsky-like reaction with D-*iso*propylideneglyceraldehyde to form the alcohols **53** with poor diastereo-selectivity.[84] Acetal deprotection and stereoselective alkyne reduction using Lindlar's catalyst afforded triol **54**, which underwent ozonolysis to afford the parent 2-deoxy-2,2-difluoro-D-ribose. The free sugar was peracetylated to **55** in order to aid characterisation (**Scheme 23**).



Reagents and Conditions: i) 2.0 Zn(0), 5% $HgCl_2$, THF, 0°C, 4h, 2:1 anti:syn; ii) Pd-$BaSO_4$, quinoline, MeOH; iii) 10% HCl, MeOH; iv) O_3, MeOH then Me_2S work-up; v) Ac_2O, Et_3N, DMAP

Scheme 23: Use of a variant of the Reformatsky reaction in fluorosugar synthesis

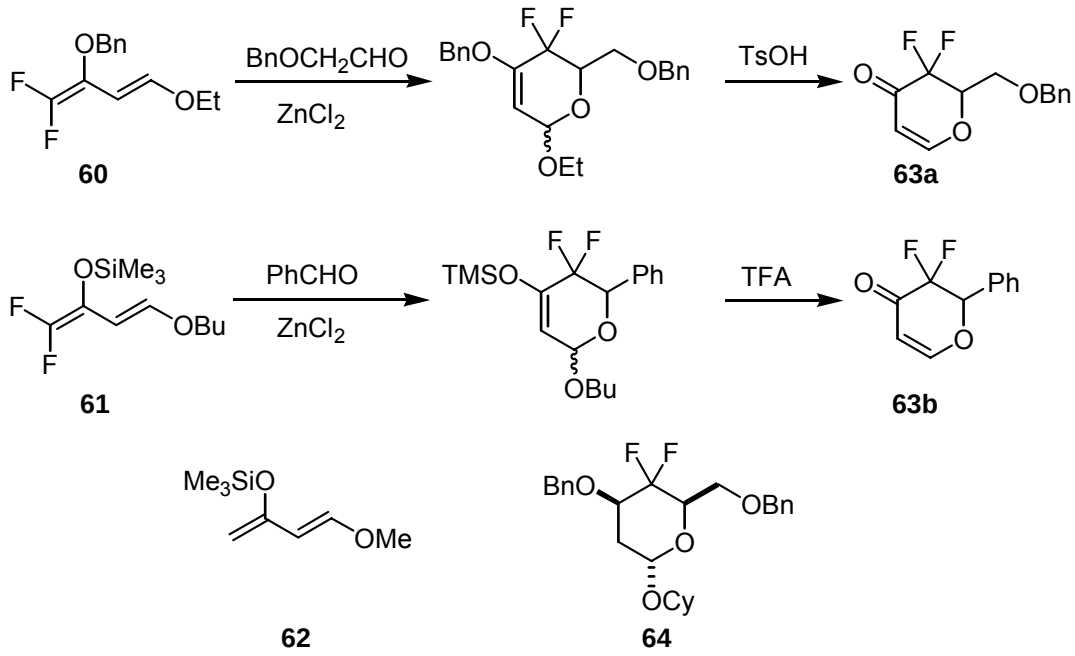
Chou and co-workers at Lilly utilised ethyl bromodifluoroacetate in their synthesis of gemcitabine.[68j] Addition of the corresponding zinc reagent of ethyl bromo-difluoroacetate to (*R*)-2,3-*O*-*iso*propylideneglyceraldehyde afforded alcohols as a mixture of diastereoisomers. The alcohols were protected as benzoate esters **56** and the acetal removed under acidic conditions to give diols which cyclised upon azeotropic removal of water to give lactones. Selective crystallisation gave pure lactone **57**, which was reduced to the lactol **58**. This was then converted into gemcitabine **59** in four steps (**Scheme 24**).



Reagents and Conditions: i) $BrCF_2CO_2Et$, Zn(0), Et_2O, THF, 3:1 anti:syn; ii) BzCl, lutidine, DMAP; iii) TFA, MeCN-H_2O then Dean-Stark; iv) BzCl, lutidine, DMAP, then selective crystallisation; v) $LiAl(OBu\text{-}t)_3H$

Scheme 24: Synthesis of gemcitabine using a Reformatsksy reaction

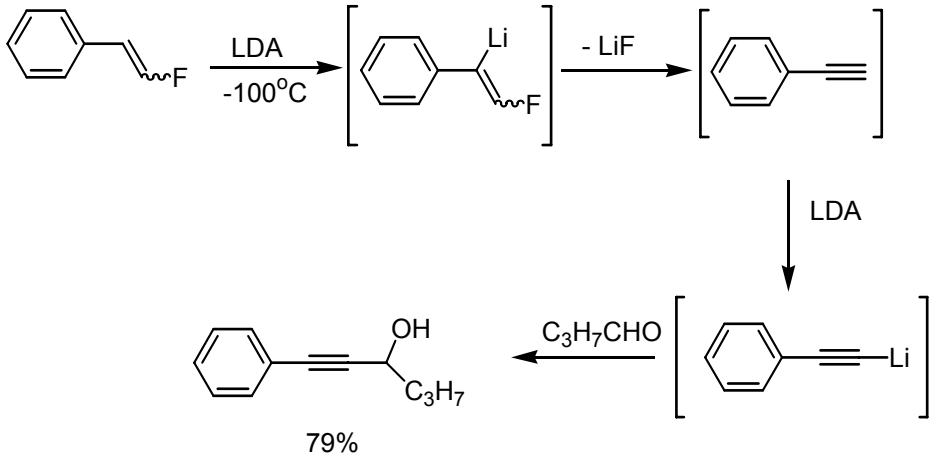
Other possible routes to fluorosugars have been described by Taguchi[85] and Uneyama,[86] both of which hinge upon the hetero Diels-Alder cycloaddition between fluorinated versions (**60** and **61**) of Danishefsky's diene **62** with aldehydes under Zn(II) catalysis to afford 2,3-dihydro-4*H*-pyran-4-one derivatives **63**. Taguchi has demonstrated how pyrones **63** could be converted into 4-deoxy-4,4-difluoro-pyranosides **64** (**Scheme 25**).



Scheme 25: Hetero Diels-Alder cycloaddition reaction in fluorosugar synthesis

1.3 Fluorovinyl Organometallics[87]

The application of organometallic reagents has had a profound effect upon modern organic chemistry and the use of vinyllithium or Grignard reagents is very common. However, a similar approach with lithiated fluorovinyl organometallics has been limited due to their thermal instability.[88] Typically, very low (-100°C) temperatures are required and isolated yields of products after quenching can be low due to significant decomposition. A clear example is shown in the attempted electrophilic trapping of lithiated fluorostyrenes. Exposure to lithium di*iso*propylamide at -100°C led to lithiation followed by spontaneous lithium fluoride expulsion to afford the acetylene. Further lithiation and trapping with aldehydes or ketones afforded the corresponding propargylic alcohols in good yields (**Scheme 26**).[89]

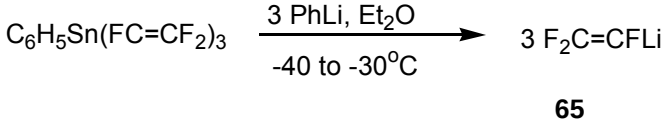


Scheme 26: Instability of a lithiated fluoroalkene

Synthesis and application of fluorovinyl organometallics[87]

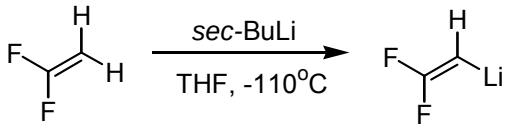
The thermal stability of lithiated fluoroalkenes can be increased by the attachment of inductively stabilising electronegative atoms such as fluorine,[90] chlorine[91] or oxygen.[92]

Several groups have reported the application of fluorovinyllithium reagents. Trifluoro-vinyllithium **65** was first generated by Seyferth and co-workers by exchange of phenyllithium with phenyl*tris*(trifluorovinyl)tin in diethyl ether at between -40 and -30°C (**Scheme 27**).[90a] The generation of **65** at a relatively high temperature indicates that the presence of three fluorine atoms imparts some extra stability on the vinyllithium reagent.



Scheme 27: Formation of trifluorovinyllithium **65**

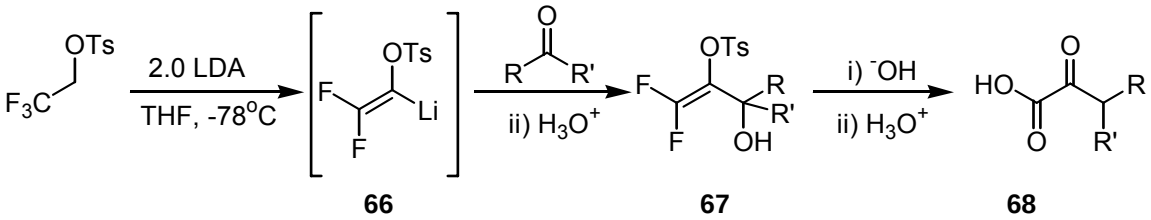
Normant and Sauvêtre have described the reaction of 1,1-difluoroethene with alkyllithium reagents at low temperature. In a solvent-dependent process, lithiation with *sec*-butyllithium in THF at very low temperature afforded the lithiated alkene in quantitative yield (**Scheme 28**).[93]



Scheme 28: Lithiation of 1,1-difluoroethene

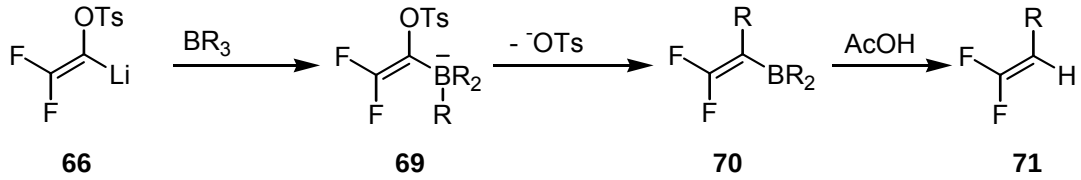
α-Metallated vinyl ethers are useful umpolung reagents[94] and the use of α-oxygen-substituted difluorovinyllithium reagents has received much attention as a means of both increasing the thermal stability of such species as well as for incorporating further functionality. Several groups have used trifluoroethanol as a starting material to lithiated difluoroenol derivatives.

In the first instance, Nakai and co-workers prepared 2,2-difluoro-1-tosyloxyvinyllithium **66** from the reaction of 2,2,2-trifluoroethyl tosylate with two equivalents of LDA in THF at -78°C. This intermediate reacted with carbonyl electrophiles to give allylic alcohols **67**, which afforded α-ketoacids **68** after hydrolysis (**Scheme 29**).[92d]



Scheme 29: Generation and use of a difluorovinyllithium reagent **66**

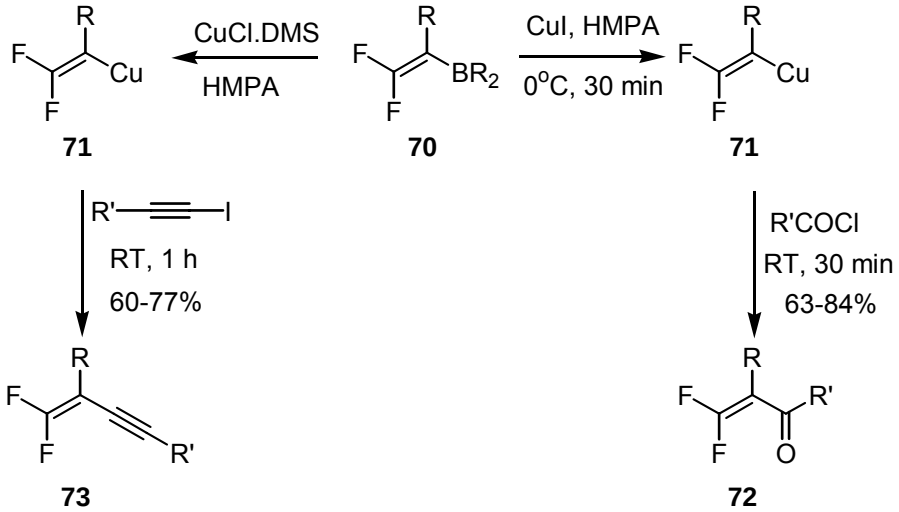
Ichikawa has utilised intermediate **66** in C-C bond formation *via* its interception with trialkylboranes to form intermediate boron-*ate* complexes **69**.[95] 1,2-Migration of the alkyl group from boron to the vinylic carbon, with the loss of tosylate, afforded vinylboranes **70**. Protonation afforded difluoroalkenes **71** in good yield (**Scheme 30**).



66 **69** **70** **71**

Scheme 30: Synthetic use of difluorovinylboranes **70**

Furthermore, boranes **70** could undergo transmetallation with copper(I) to form a vinylcopper reagent **71**.[95b] This reagent was capable of participating in coupling reactions with acid chlorides and iodoalkynes to form enones[96] **72** and enynes[97] **73**, respectively (**Scheme 31**).

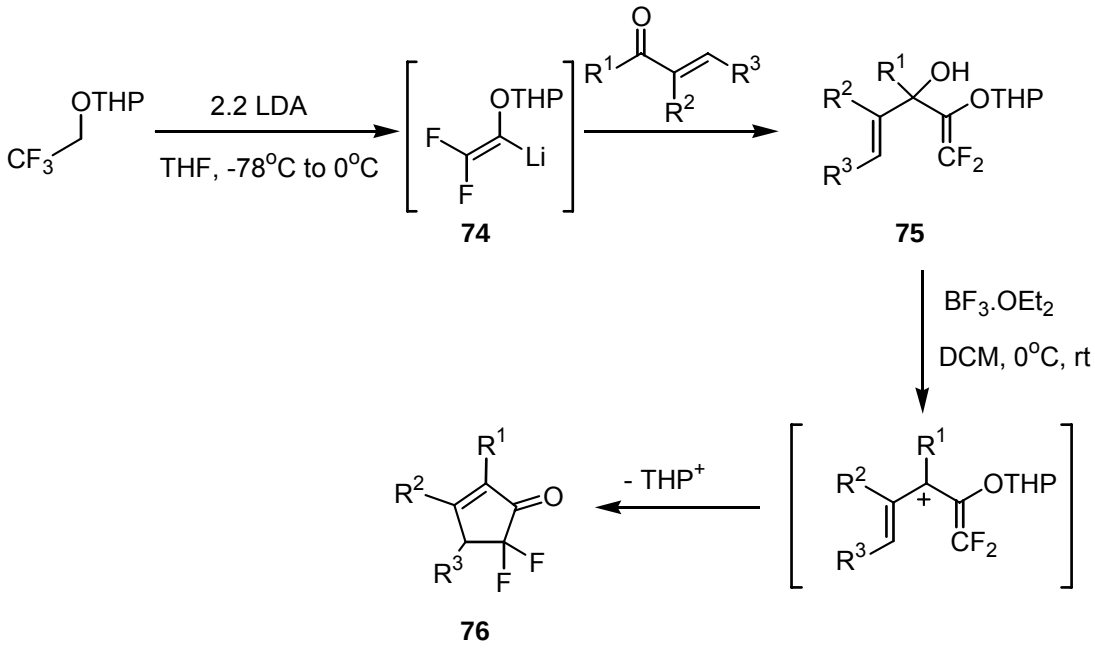


71 **70** **71**

73 **72**

Scheme 31: Synthetic use of a difluorovinylcopper reagent **71**

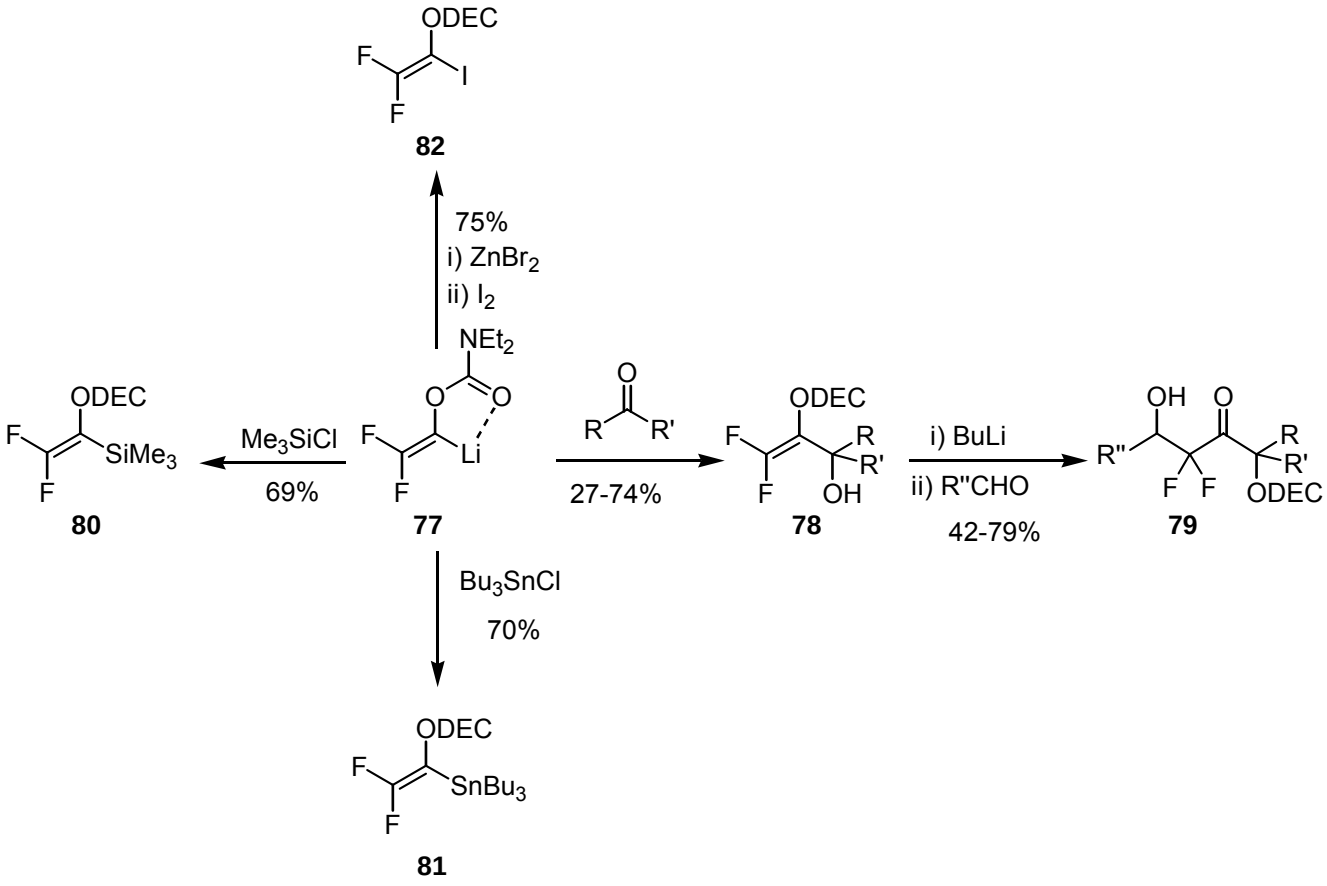
However, the requirement of trialkylboranes affords products of limited synthetic use due to the presence of a simple alkyl group attached to the olefin. Potentially more interesting chemistry has been developed within our group and that of Tius.[92e] In the case of Tius and co-workers, interception of vinyllithium reagent **74** with enones afforded *bis*-allylic alcohols **75** which underwent Nazarov cyclisation to afford novel difluorocyclopentenones **76** (**Scheme 32**).



Scheme 32: Difluorocyclopentenone synthesis by Nazarov cyclisation

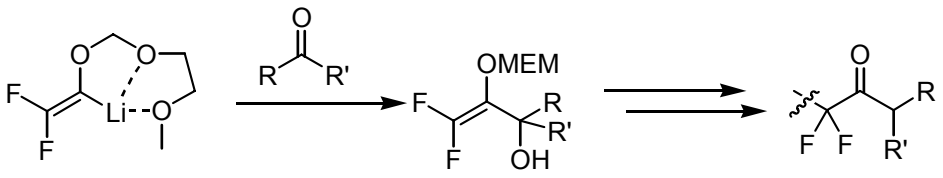
Patel, Howarth and Balnaves have achieved improved synthetic utility of the trifluoroethanol protecting-group strategy. Howarth used an *N*,*N*-diethylcarbamate (DEC) group in which the carbamate oxygen can co-ordinate to the lithium atom affording some degree of stabilisation. The vinyllithium reagent **77** has been used to generate allylic alcohols **78**, which can be used to generate the corresponding enolates *in situ*. These in turn undergo aldol condensation with non-enolisable aldehydes to afford a general route to molecules of class **79**.[98] Vinyllithium **77** could

also be trapped with chlorotrimethylsilane (to form silane **80**), chlorotributyltin (to form stannane **81**), and iodine, *via* a presumed vinylzinc intermediate (to form iodide **82**) (**Scheme 33**).[99]



Scheme 33: Use of a DEC protecting group in synthesis

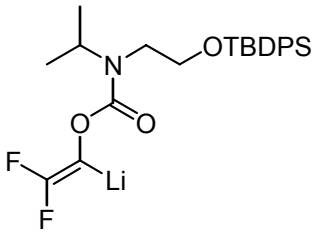
Percy and Patel subsequently developed a 2-methoxyethoxymethoxy[100] (MEM) derivative, in which double co-ordination to lithium can occur. Vinyllithium **83** has been trapped with Group(IV) halides as well as carbonyl species to afford allylic alcohols **84**.[101] These have been transformed into mid-chain difluoroketones using rearrangement methodologies (**Scheme 34**).[102]



83 **84**

Scheme 34: Use of a MEM group in rearrangement strategies to difluoroketones

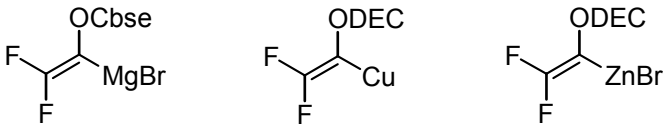
The DEC group has been shown to be difficult to remove, so an identical methodology was attempted using the lithiated Hoppe carbamate **85**. This protecting group proved successful in the synthesis of difluoropolyols (**Figure 7**).[103]



85

Figure 7: Vinyllithium reagent **85** derived from a Hoppe carbamate

Transmetallation of difluorovinyllithium reagents with zinc(II) bromide, magnesium bromide etherate or copper(I) iodide affords the corresponding organometallic reagent. These species have been shown to possess higher thermal stability than the corresponding organolithium species and are stable at or just below ambient temperature. Balnaves used Grignard **86** for coupling to aldehydes bearing α-oxygen functionality at -30°C.[103] Difluorovinylcopper reagent **87** has been used in allylation at ambient temperature[104] and zinc reagent **88** is formed at 0°C as an intermediate in the synthesis of iodide **82** (**Figure 8**).[99]



86 **87** **88**

Figure 8: Metallated difluoroenol derivatives with improved thermal stability

Thermal stability and ease of isolation and purification has been achieved through the development of difluorovinyltin reagents. These materials, although toxic, are stable at ambient temperature and can be stored without decomposition in a refridgerated (-5°C) environment for several months. They have played a central role in the use of fluorinated organometallics in palladium-catalysed cross-coupling methodology.

1.4 Palladium-catalysed Coupling Reactions

Introduction

Processes that construct C-C bonds hold a central role in organic synthesis. The use of metal-mediated C-C bond formation has had a revolutionary effect upon modern synthetic organic chemistry.[105]

The catalytic cycles involved consist of several discrete steps fundamental to organometallic chemistry. Low valent metals such as palladium(0) and nickel(0) undergo a process known as oxidative addition with organic electrophiles, in which overall insertion into the C-X (X = halogen, OTf etc.) bond occurs. This process is thought to occur *via* a three-membered transition state and has characteristics of a polar addition process, such that electron-deficient centres undergo more facile insertion. The nature of the leaving group in the electrophile is expanding constantly

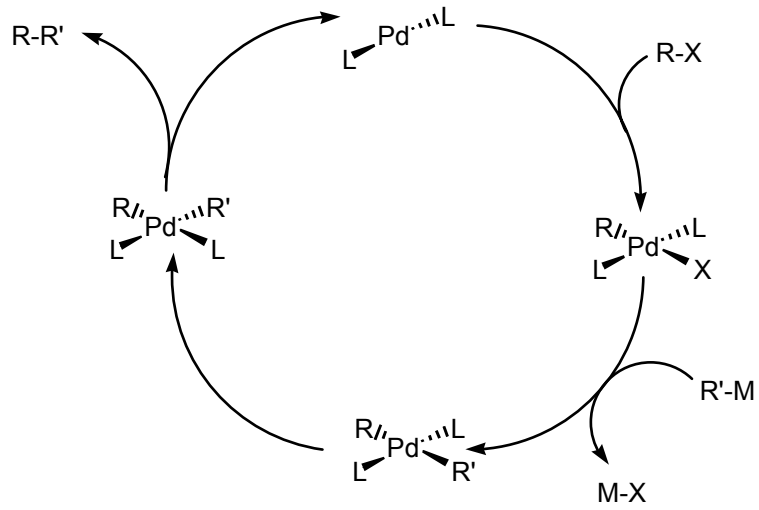
and now includes such groups as anhydrides,[42a] thiolates,[106] mesylates,[107] nonaflates,[108] fluorosulfonates[109] and carboxylic acids[42b] (*via* anhydride formation *in situ*) as well as the typical iodides, bromides, chlorides[110] and triflates.[111]

In order to make progress in expanding the scope of useful electrophiles, a greater understanding of catalyst structure has had to be developed. New methodologies include using better σ-donor ligands such as trifurylphosphine[112] as replacements for triphenylphosphine. In addition, softer ligands such as triphenylarsine[112] or triphenylantimony[113] have also been employed. The type of ligand has also changed dramatically; bidentate phosphorus ligands[114] (such as dppb, dppp, dppe and dppf) and also tetradentate phosphorus ligands[115] have been used to produce highly active catalysts. Other ligands include *bis*-carbenes,[116] phosphites,[117] 2-aryl-2-oxazolines[118] and fluorous dialkylsulfides.[119] Importantly, it has been shown that stoichiometry is a key issue, with reactivity being balanced with stability. It is not uncommon to see "naked" palladium as a catalyst.[120] In addition, the metal component of the catalyst is also being varied. Although palladium is by far the most commonly used,[121] procedures employing nickel,[122] copper,[123] manganese,[123c,124] platinum[125] and iron[126] have also been described.

The resulting organometal halide is susceptible to attack by another organometal in an overall transmetallation step. This occurs through a four-centre transition state and again portrays polar characteristics. The organopalladium halide is weakly electrophilic and nucleophilic species such as organozinc,[127] copper[128] or magnesium[129] reagents are required for coupling. Organotin[130] compounds will undergo coupling but often require high temperatures or additives in order to increase the electrophilicity of the palladium complex. Organosilicon[131] and

organoboron[132] reagents are usually insufficiently reactive to undergo unassisted coupling and nucleophilic additives have to be added in order to form silic*ate* or boron-*ate* complexes *in situ*. In the case of silicon this is achieved by adding a fluoride source; in the case of boronic acids a base (source of hydroxide or alkoxide) is added. Once again, the use of other organometals is being studied in order to investigate trends in reactivity, functional-group tolerance, toxicity and selectivity. Such metals studied include aluminium,[133] gallium,[134] zirconium[135] and tellurium.[136]

The final step in the cycle is reductive elimination in which the two organic fragments combine with the concomitant release of the palladium catalyst. The overall cycle is shown in **Scheme 35**.[229]



Scheme 35: Overall catalytic cycle for Pd(0)-catalysed cross-coupling

Once again, important insights into catalyst reactivity have resulted in the development of ligands with varying bite angles, a property directly affecting the rate of reductive elimination and the ability to turn over the cycle.[137]

Co-catalytic copper in Stille coupling

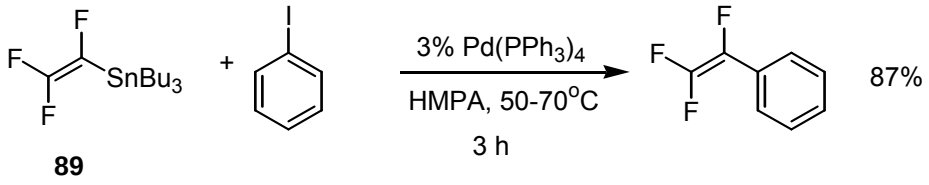
The use of co-catalytic copper(I) salts in the literature is becoming increasingly common.[138] Liebeskind and Farina were the first to study this effect and our understanding of the relevant roles has increased further over the last few years, although some uncertainty in the exact mechanisms in operation still remains. The seminal paper[139] was published in 1990 and describes the effect of added copper(I) iodide on the rate of two Stille couplings in apolar dioxane and polar aprotic NMP. The results in dioxane indicated that the addition of Cu(I) led to a rate enhancement in parallel with the Cu(I)/triphenylphosphine ratio until such time that the conversion to product was sacrificed at the expense of the initial rate, which in fact decreased slightly. When the softer triphenylarsine ligand was used, the initial rates were several orders of magnitude greater and the effect of added CuI was far less pronounced. This led the authors to suggest that the role of CuI in apolar solvents is to scavenge free triphenylphosphine and promote the transmetallation step. The optimum ratio was found to be 1:4:2 ($Pd:PPh_3$:CuI). A lower phosphine/CuI ratio leads to catalyst instability and resulted in precipitation of palladium black.

The results in the polar NMP solvent were markedly different. The rate of reaction increased as the amount of CuI was added and no plateau was reached. NMR experiments indicated that phenyltributyltin underwent transmetallation with CuI to form the presumed phenylcopper species.[140] No such reaction occurred when triphenylphosphine was used, consistent with a dual transmetallation/ligand scavenger role.

Application of transition-metal-mediated cross-coupling using fluorinated organo-metallics

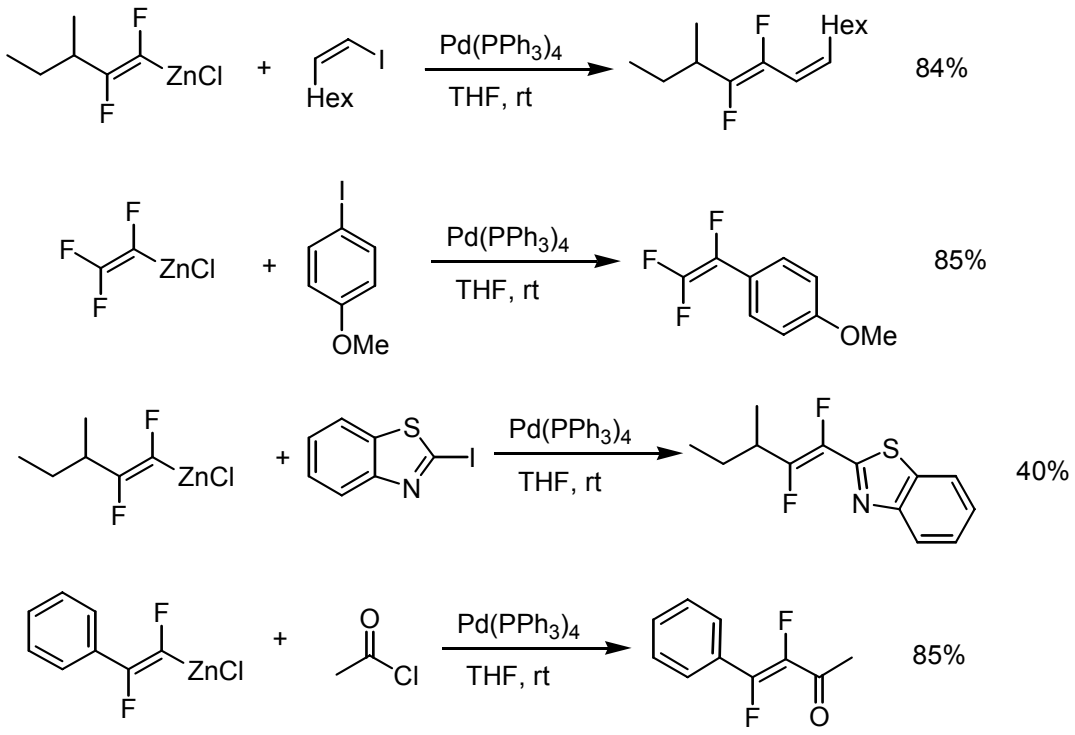
The use of fluorinated coupling agents is relatively scant in the literature, although the field is slowly expanding.

Beletskaya and co-workers provided the initial contribution to the field, who demonstrated that trifluorovinyltributyltin **89** could be coupled to a limited range of aryl iodides under relatively mild conditions.[141] Coupling to iodobenzene occurred in either HMPA or DMF at 50-70°C in a relatively short (3 hours) reaction time. Less polar solvents (DMSO, THF, benzene) were ineffective. Attempted coupling with 1,4-diiodobenzene and 1-iodo-4-nitrobenzene under these conditions proved too harsh and oligomeric products were formed. However, greatly improved results could be obtained by the addition of tetrabutylammonium halides, promoting reaction at ambient temperature, although no details were provided (**Scheme 36**).



Scheme 36: First successful coupling of a fluorinated vinylmetal component

The next major contribution was made by Normant and Sauvêtre, who described the synthesis and palladium-catalysed cross-coupling of several difluoro- and trifluorovinylzinc reagents. Coupling has been achieved under mild conditions using vinyl, aryl and heterocyclic iodides.[142] Acid chlorides have also been successfully employed as the electrophilic component.[142c] Typical examples are shown in **Scheme 37**.

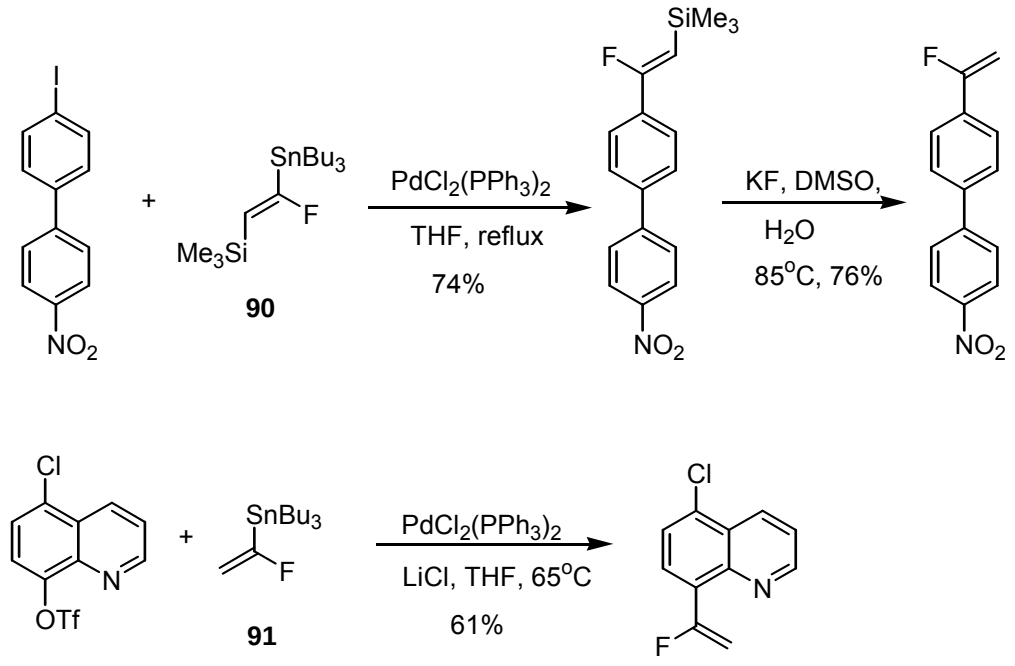


Scheme 37: Scope of couplings with fluorovinylzinc reagents

Burton has recently expanded the scope of couplings of fluorinated vinylzinc reagents with reports that (*Z*)-1,2-difluorovinylzinc iodide undergoes CuBr-catalysed cross-coupling with aryl iodides using *tetrakis*(triphenylphosphine)palladium(0) in *N*,*N*-dimethylacetamide (DMA) as solvent at RT-40°C.[143]

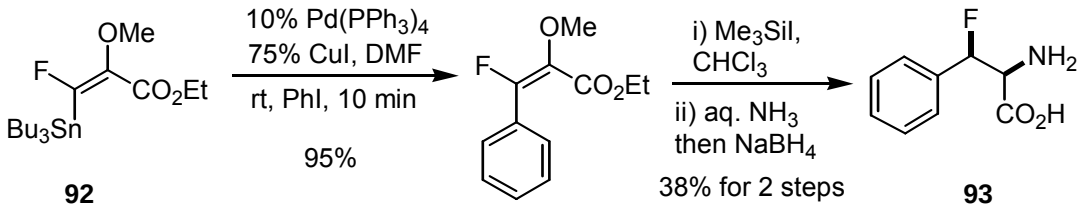
Although the above results are interesting, one drawback is the moisture-sensitive nature of the organozinc reagent, calling for an *in situ* preparation without the possibility of rigorous purification. Several other groups have therefore studied the coupling of thermally and moisture stable fluorovinyltin reagents. However, it should be appreciated that such a protocol necessitates the use and disposal of toxic tin residues.

McCarthy has described the couplings of stannane[144] **90** and stannane[145] **91**, both of which underwent coupling with a range of organic electrophiles under orthodox conditions. However, (1-fluorovinyl)tributyltin **91** was synthesised in five steps from commercially available ethyl phenyl sulfide using DAST to install the fluorine atom *via* a fluoro-Pummerer reaction of the corresponding sulfoxide. Re-oxidation, α-stannylation followed by sulfoxide elimination afforded the product stannane **91**. Although stannane **90** could be made in three steps using a Horner-Wadsworth-Emmons olefination using a fluorinated ylid, the removal of the TMS group required either forcing conditions or long reaction times at ambient temperature. However, successful coupling in the absence of CuI is of note (**Scheme 38**).



Scheme 38: Couplings of 1-fluoro-1-tributylstannylethenes

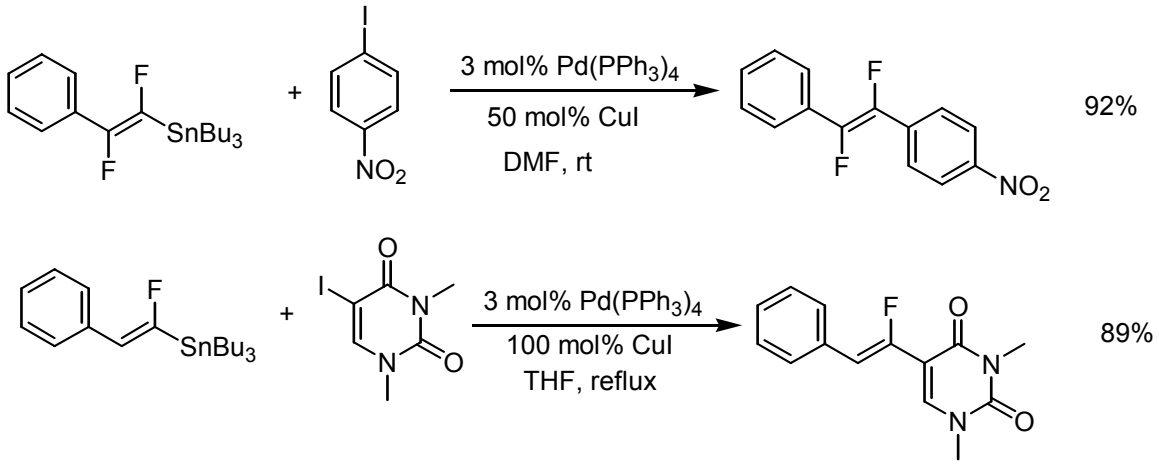
Further functionality in the fluorovinylstannanes was described by Shi and co-workers, who reacted β-fluoro-β-stannyl-α-methoxyacrylate **92** with a range of aryl iodides.[146] Reaction occurred rapidly and in good to excellent yield using 75 mol% CuI in the presence of 10 mol% *tetrakis*(triphenylphosphine)palladium(0) in DMF at ambient temperature. Poor couplings were observed in the absence of CuI and homocoupling predominated at higher reaction temperatures (no CuI). Bromobenzene failed to react effectively, even at 80°C. An example is shown, where the product was transformed into β-fluorophenylalanine **93** (**Scheme 39**).



Scheme 39: Synthesis of β-fluorophenylalanine **93** *via* a Stille coupling

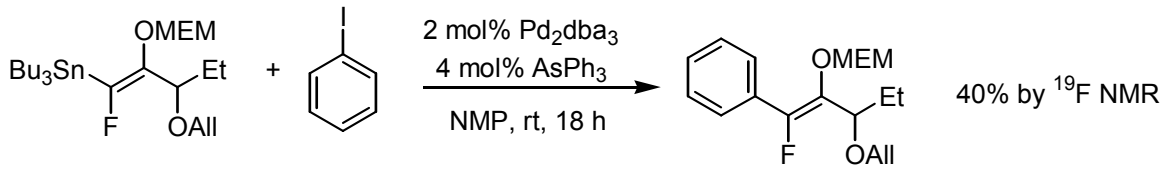
Burton and McCarthy have reported further successful couplings of fluorinated stannanes. Burton described palladium(0)/copper(I) halide-catalysed couplings of 1,2-difluorovinylstannanes with aryl and vinyl iodides.[147] No coupling was observed under orthodox conditions and decomposition occurred at higher temperatures. However, excellent yields could be obtained by using 50 mol% CuI in DMF at ambient temperature in the presence of 3-4 mol% *tetrakis*(triphenylphosphine)-palladium(0). At the same time, McCarthy described the coupling of 1-fluorovinylstannanes with aryl iodides and acyl chlorides.[148] Attempted coupling under orthodox conditions in THF resulted in very poor conversions. When DMF was used at reflux the conversion was improved but significant amounts of homocoupling

and protodestannylation were observed. When one equivalent of CuI was used in the presence of 5 mol% $Pd(PPh_3)_4$ in THF at reflux, smooth coupling occurred to afford the desired products in a short reaction time. Typical examples are depicted below (**Scheme 40**).



Scheme 40: Coupling of 1,2-difluorovinyl- and 1-fluorovinylstannanes

Our group[149] has described the attempted coupling of a functionalised 1-fluorovinylstannane with iodobenzene and benzoyl chloride. However, poor yields were obtained under standard Stille conditions although an improved conversion (ca. 40%) could be achieved by employing Farina conditions, in which triphenylarsine was used to increase the rate of transmetallation. It should be noted, however, that no attempt with CuI was tried and the catalyst system employed (2 mol% Pd_2dba_3 /4 mol% $AsPh_3$) is very prone to decomposition before full conversion could be achieved (**Scheme 41**).



Scheme 41: Inefficient coupling of a 1-fluorovinylstannane in the absence of CuI

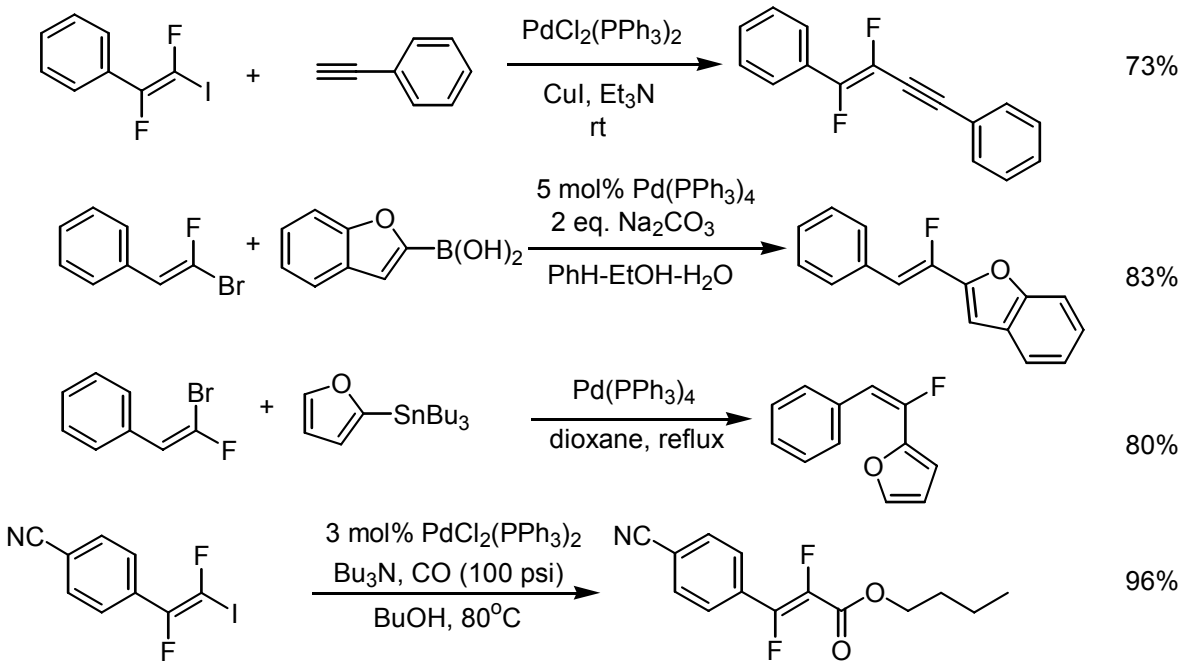
A further notable success of CuI in fluoroalkene synthesis was provided by Jeong and co-workers[150] who coupled β,β-diphenyl-α-(trifluoromethyl)tributyltin with aryl iodides using 10 mol% CuI in DMF at ambient temperature with 10 mol% *tetrakis*(triphenylphosphine)palladium(0).

As an extension, Ichikawa has also reported the successful coupling of difluorovinylcopper reagents[151] and difluorovinylzirconium halides[152] (*via* zinc transmetallation). Hanamoto has also described the application of fluorovinylsilanes as coupling components.[153] In such a way, several difluoroolefin motifs can now be accessed.

It has also been acknowledged that the use of a fluorinated electrophilic component should lead to rapid, facile couplings due to the *–I* inductive effect of the fluorine atoms. This should lead to facile palladium(0) insertion, resulting in an electron-deficient palladium complex primed for transmetallation.[154]

Indeed, Burton and McCarthy have been the main instigators of such investigations and have demonstrated the coupling of halofluoroalkenes with organoboronic acids,[154,155] organostannanes,[154,156] organozinc reagents[157] and alkynylcopper reagents[158] in Suzuki, Stille, Negishi and Sonogashira cross-coupling methodologies, respectively. Of note is the ability of chlorofluoroalkenes to undergo efficient cross-

coupling with aryl boronic acids under standard Suzuki conditions. Wilkes has also described the inefficient coupling of a functionalised 1-fluoro-1-iodoalkene with vinyl tributyltin under Farina conditions. However, Sonogashira couplings were successful and a range fluorinated enynes were synthesised.[149] Some examples of couplings of halofluoroalkenes are given below (**Scheme 42**).



Scheme 42: Selected couplings of fluorinated alkenyl halides

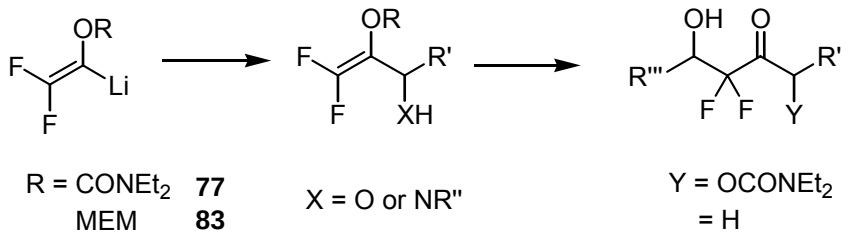
Successful couplings of β-fluoroenol triflates[159] have also been described, as well as the couplings of iodofluoro- and iododifluoroalkenes with diethyl phosphite[160] and carbon monoxide,[161] respectively.

In summary, the use of fluorovinyl organometallics in palladium-catalysed cross-coupling is increasing rapidly and the necessity of co-catalytic copper(I) iodide in order to achieve good yields is becoming more apparent. However, the range of fluorinated motifs is limited and a ubiquitous feature is the presence of a sterically

undemanding fluorine atom at the α-carbon. In addition, no couplings of 1-oxygenated-2,2-difluorovinylstannanes have been reported.

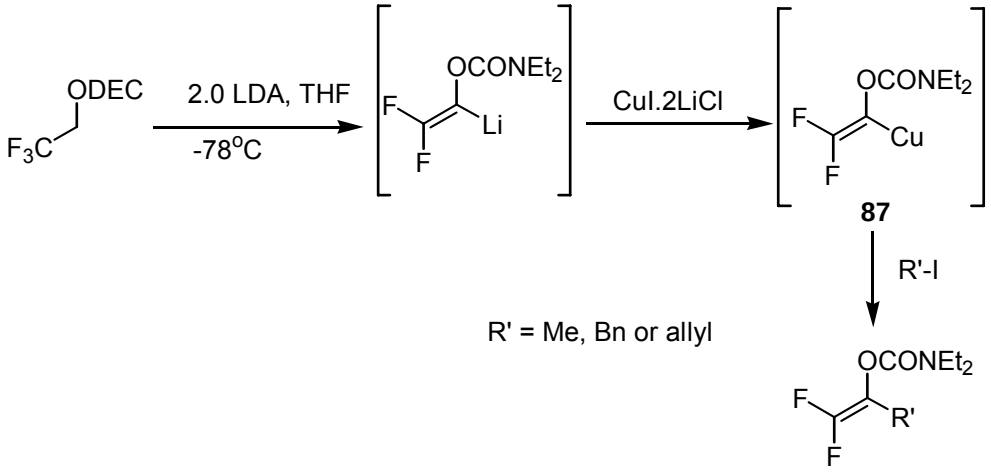
1.5 Relevant Recent Advances in the use of Trifluoroethanol as a Building-Block

Although difluoroacyl anion equivalents **77** and **83** have been extensively used in the construction of lightly-fluorinated molecules, severe limitations exist in the scope of structure around the fluorinated core. To date, within our group, carbonyl and imine electrophiles have been used and these intermediates have been shown to be a rich source of mid-chain difluoroketones (**Scheme 43**).



Scheme 43: Current use of difluoroacyl anion equivalents **77** and **83**

An attempt at trapping with the soft electrophile iodomethane failed, associated with the deactivating effect of the fluorine atoms, although the use of the more reactive methyl triflate did lead to the observation of product.[92b] In a recent advance, it was found that transmetallation of the organolithium derivative using a CuI.2LiCl mixed salt afforded a much more nucleophilic organocopper species. Carbon-carbon bond forming reactions were then possible using soft electrophiles such as methyl, benzyl and allyl halides, as well as acid chlorides, to afford unstable enones (**Scheme 44**).[104]



Scheme 44: Application of an organocopper reagent to C-C bond construction

In the course of this group's efforts to utilise Diels-Alder chemistry for constructing difluorinated cyclitol derivatives, β,β-difluorinated alkenoate **94** became a key synthetic target (**Figure 9**).

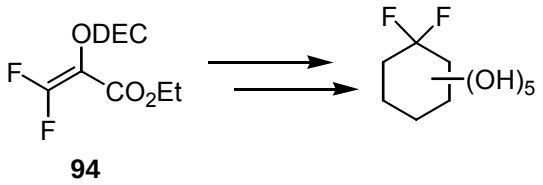
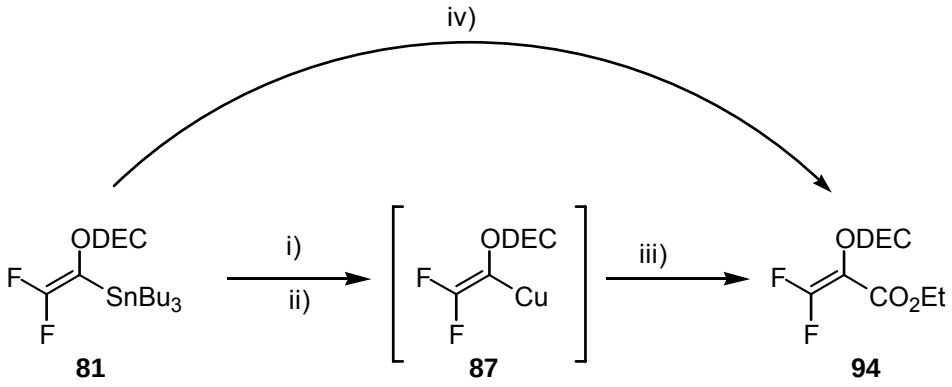


Figure 9: Application of difluoroalkenoate **94** to cyclitol synthesis

Initially, Stansfield attempted the synthesis of **94** using ethyl chloroformate as the reactive electrophile with the copper reagent; unfortunately, reduction occurred in preference to C-C bond formation. Eventually, it was found that palladium(0) mediated an efficient coupling between organocopper reagent **87** and ethyl chloroformate in THF at ambient temperature.[162] However, attempts by Moralee to repeat this work led to capricious results, with reduction being the major pathway. In

a second major advance, Moralee successfully employed a Stille coupling protocol to the synthesis of a range of alkenoate derivatives,[163] in which difluorinated vinyl stannane **81** was used as the organometal. Stannane **81** can be routinely synthesised on up to a mole scale; it is both thermally and air-stable and can be easily handled and stored.

Importantly, it was found that Farina-Liebeskind conditions, where CuI is present to activate the palladium(II) complex by phosphine complexation, was required in order to obtain good results. The requirement of this additive goes some way to explain previous failures at utilising this difluorovinyl metal species in coupling protocols. **Scheme 45** shows a comparison between the two routes to this important target.

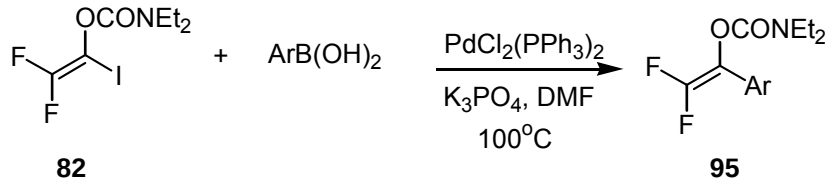


Reagents and Conditions; i) *n*-BuLi, THF, -78°C;
ii) CuI.2LiCl, THF, -78°C to rt; iii) $Pd_2dba_3.CHCl_3$, PPh_3,
EtOCOCl, THF, 50°C, 67%; iv) $Pd(OAc)_2$, PPh_3,
CuI, EtOCOCl, THF, 50°C, 70%.

Scheme 45: Synthesis of alkenoate **94** using palladium-catalysed coupling

During the course of this PhD, Thomas showed how 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene **82** can participate in Suzuki-Miyaura couplings with aryl boronic acids to afford a range of β,β-difluorostyrenes **95**.[164] The methodology was

limited, however; heteroaryl, vinyl and alkyl boronic acids or their derivatives failed to afford the desired products, producing the reduced product instead (**Scheme 46**).



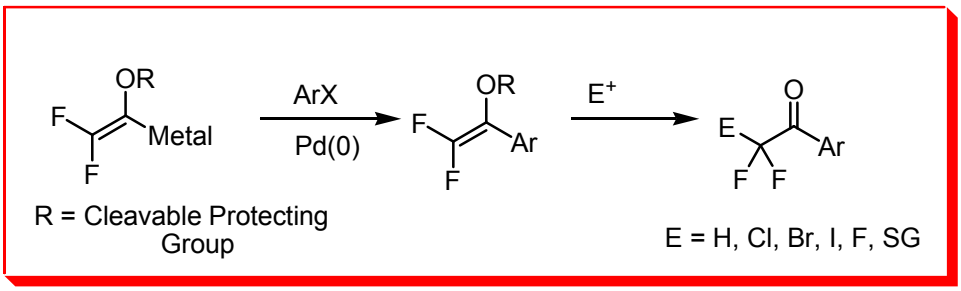
82 **95**

Scheme 46: Styrene synthesis by Suzuki-Miyaura coupling of iodoalkene **82**

1.6 Objectives

(Aryl) difluoromethyl ketones

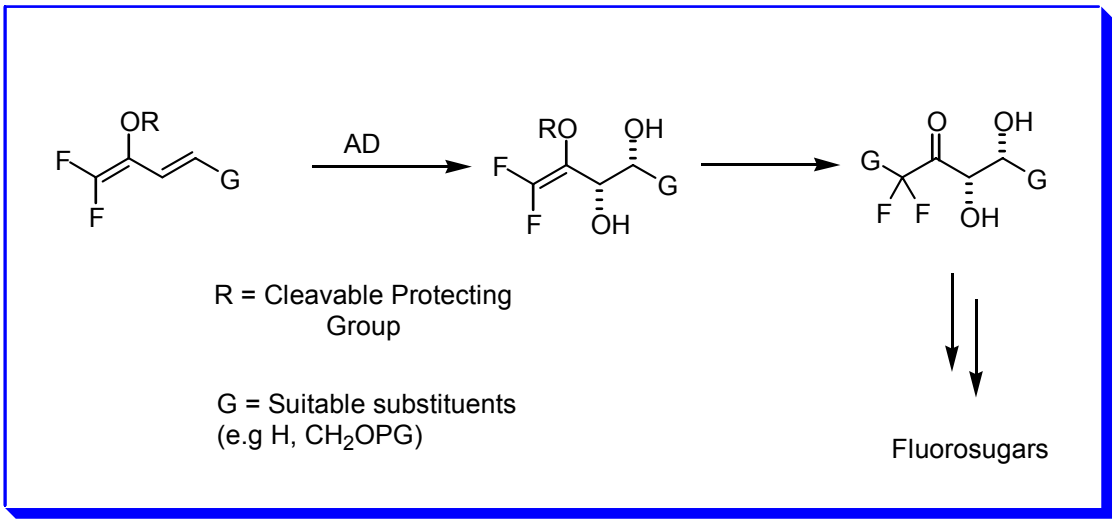
A study of the current approaches to this class of molecule shows that none are capable of generating diversity in the aromatic core or in generating a large array of materials quickly and efficiently. A novel and more succinct approach would involve pre-formation of a single difluoroenol scaffold from which aryl attachment followed by general cleavage would afford the desired materials. One such approach will be described in this thesis. **Scheme 47** outlines the idea.



Scheme 47: Outline of our approach to α,α-difluoromethyl aryl ketones

Fluorinated carbohydrates

A successful outcome to the initial study outlined above would be a method that allowed the generation of fluorinated 1,3-dienes. These materials are particularly rare in the literature and their use as building-blocks to highly oxygenated materials has not been studied. We wish to manipulate the initial diene products through asymmetric dihydroxylation reactions to afford enantiomerically enriched diols. Cleavage of the difluoroenol motif would then form a difluoroketodiol, which could serve as a building block to fluorinated carbohydrate analogues in a catalytic asymmetric fashion. **Scheme 48** outlines the approach discussed in this Thesis.

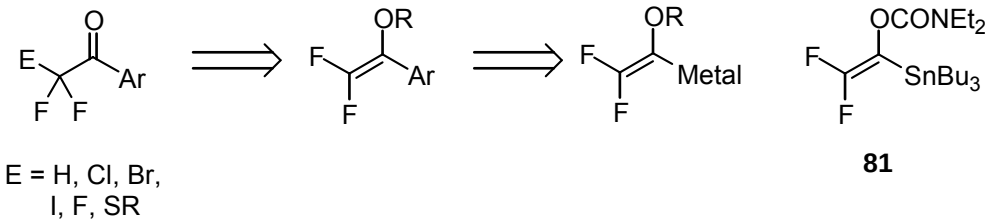


Scheme 48: Proposed catalytic asymmetric approach to oxygenated organofluorine compounds

Chapter Two

Results and Discussion

In order to expand upon the synthetic utility of difluoroacyl anion equivalent chemistry, a study was initiated in which potentially useful α,α-difluoromethyl aryl ketones were targeted using palladium-catalysed cross-coupling methodology. Retrosynthetic analysis of the target materials identified a difluorovinyl organometallic reagent as the key starting material and the known 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene **81** was chosen to develop the approach (**Scheme 49**).



Scheme 49: Retrosynthetic analysis of α,α-difluoromethyl aryl ketone synthesis using a protected metallated difluoroenol

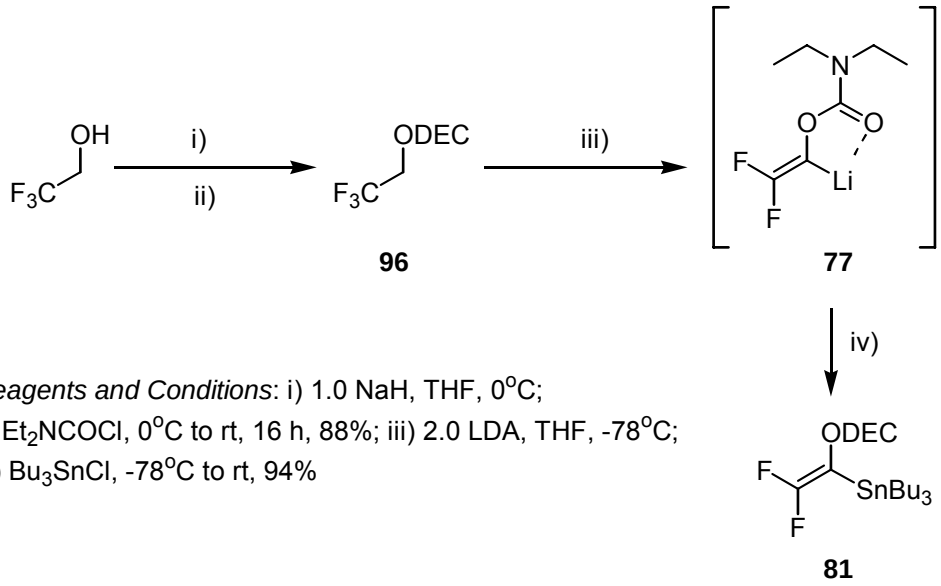
2.1 Palladium-catalysed Coupling

2.1.1 Coupling of 1-(N,N-Diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene **81**

Synthesis of stannane **81**

The requisite stannane **81** was prepared successfully according to the procedure of Haworth.[99] Deprotonation of trifluoroethanol with sodium hydride and subsequent trapping of the resultant sodium alkoxide with *N,N*-diethylcarbamoyl chloride afforded *N,N*-diethylcarbamate **96**. On treatment with two equivalents of LDA in THF at -78°C, this undergoes deprotonation with concomitant *anti*-elimination of LiF to afford an enol carbamate (an overall dehydrofluorination step). A second, more rapid metallation step[165] follows to afford thermally unstable difluorovinyllithium **77**.

Quenching of this intermediate with tributyltin chloride leads to the formation of 2,2-difluorovinylstannane **81**. Purification by column chromatography on silica gel led to **81** in excellent (94%) yield (**Scheme 50**).



Reagents and Conditions: i) 1.0 NaH, THF, 0^{o}C;
ii) Et_2NCOCl, 0^{o}C to rt, 16 h, 88%; iii) 2.0 LDA, THF, -78^{o}C;
iv) Bu_3SnCl, -78^{o}C to rt, 94%

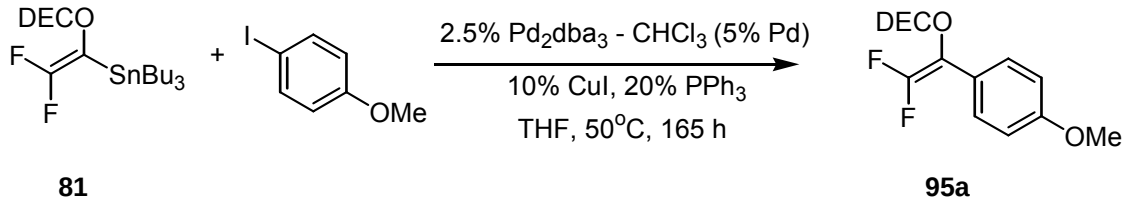
Scheme 50: Synthesis of vinyl stannane **81**

Optimisation of couplings

In order to develop an efficient coupling protocol for stannane **81**, an extensive series of experiments was conducted in which the role of solvent, temperature, catalyst, additive and ligand was studied. 4-Iodoanisole has been previously used with success in couplings to fluorinated stannanes with good efficiency and was chosen as the test substrate.[142a, 147a-b]

In order to ascertain the general reactivity of stannane **81**, conditions previously developed by Moralee to couple to chloroformates were investigated.[163a,b] When a solution of stannane **81**, 4-iodoanisole, copper(I) iodide (10 mol%),

tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct ($Pd_2dba_3.CHCl_3$, 5 mol% Pd) and triphenylphosphine (20 mol%, $Pd:PPh_3$ = 1:4) was heated at 50°C for 165 hours in THF, analysis by ^{19}F NMR indicated a 1:1 mixture of **81** and a new material exhibiting a set of doublets at -95 and -105 ppm. Isolation of this material and analysis by ^{1}H NMR and mass spectrometry identified it as the desired anisole derivative **95a** (**Scheme 51**).



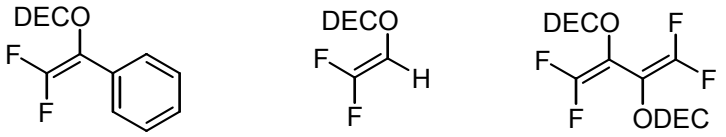
81 **95a**

Scheme 51: Initial coupling using Farina conditions

The observation of product was pleasing although the low rate of reaction was surprising, given that ethyl chloroformate, albeit a more reactive partner (*via* formation of an electron-deficient acyl palladium complex), undergoes complete reaction in 3 hours with as little as 2.5 mol% palladium(0).

Increasing the reaction temperature to reflux (65°C) allowed the complete consumption of the stannane **81** in 18 hours, but also led to the formation of three side-products with distinct sets of fluorine signals. Two such sets (at -90 and -98 ppm and -97 and -117 ppm respectively) had been previously independently identified as dimer **97** and enol carbamate **98**. These materials result from oxidative homocoupling or protodestannylation of the organostannane, respectively.[148b] A third set, at -95 and -103 ppm had not previously been observed. The similarity of the chemical shifts with the anisole **95a** suggested an aryl derivative. Indeed, upon

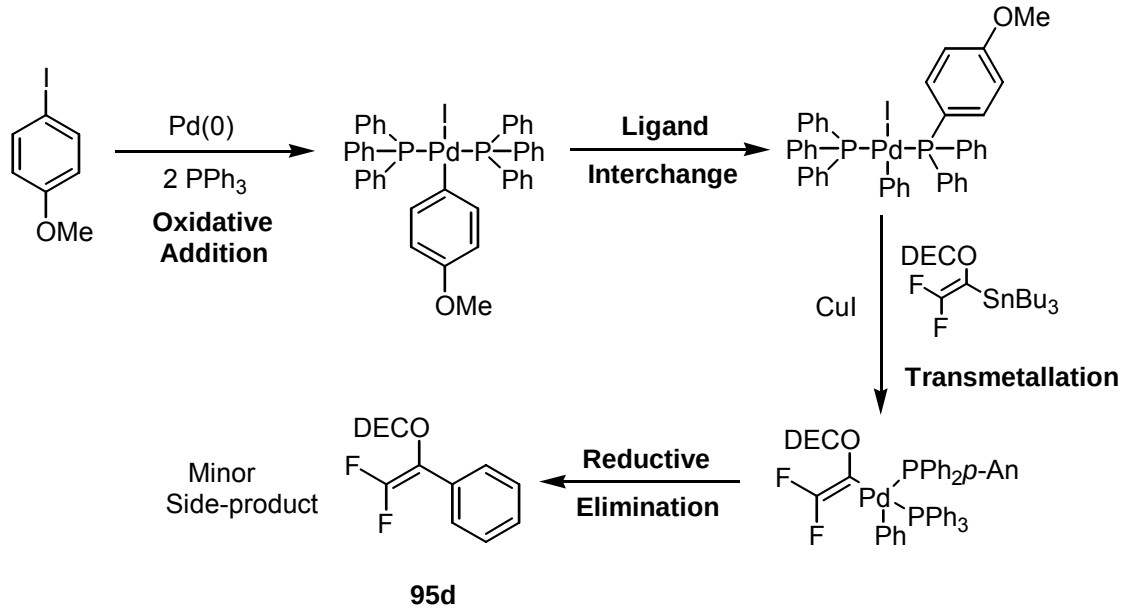
isolation of a small amount of this material and analysis by ^{1}H NMR, all signals were similar to **95a** except for the absence of the methyl singlet corresponding to the methoxy group. A mass spectrum confirmed its identity as unsubstituted styrene **95d**. This was also later corroborated by its independent synthesis (**Figure 10**).



95d **98** **97**

Figure 10: Three side-products formed by coupling in THF at reflux

The formation of **95d** is due to aryl transfer from palladium-phosphine complexes. Novak and co-workers have described the insertion of palladium(0) into a variety of aryl iodides in the presence of different phosphine ligands.[166] Aryl group interchange was found to be strongly dependent upon the identity of the phosphine ligand and the substituent on the aryl iodide. Interestingly, of those tested, the complex resulting from insertion of palladium(0) into 4-iodoanisole in the presence of triphenylphosphine gave the fastest rate of phenyl group transfer, thus explaining the presence of styrene **95d** in our case (**Scheme 52**).



Scheme 52: Proposed formation of styrene **95d**

In order to increase the rate of transmetallation, triphenylarsine was used as a soft ligand, in which the palladium(II) complex should become more electrophilic. However, no significant change was observed in product ratio although the change of ligand did suppress the formation of styrene **95d**. This proved to be a common observation in all runs with triphenylarsine, and aryl exchange only occurred with this substrate.

The persistent observation of large amounts of enol carbamate **98** and the presence of dimer **97** are both associated with a slow transmetallation step and the consequent long reaction times, resulting in decomposition of the enol stannane.[148b]

In order to attempt to increase the rate of transmetallation, a solvent change to DMF was investigated, for which precedence suggests that *in situ* transmetallation to a more reactive organocopper species should occur.[139]

When DMF (first run at 120°C, triphenylphosphine as ligand, entry 5 in **Table 1**) was used as a reaction solvent this led to a dramatic 500-fold increase in the rate with reaction complete within 20 minutes. Analysis by ^{19}F NMR indicated the presence of only the desired product **95a** and traces of styrene **95d** (*vide ante*). In order to rule out a temperature effect, a survey was undertaken in order to establish whether this result was due to the solvent medium, or the fact that the reaction was undertaken at this higher reaction temperature. Entries 5-7 in **Table 1** (runs at 120°C, 70°C and 50°C) clearly indicate that the effect is purely due to the presence of a more polar reaction medium, although the rate does indeed drop on lowering the temperature. The lower isolated yield on increasing temperature possibly indicates the progressively lower stability of the organocopper intermediate at increasing temperature. This degree of rate enhancement was unexpected and suggested that transmetallation was the rate-determining step. Comparision of entries 1 and 7 clearly indicate a positive change in the mode of action of the copper(I) salt.

The presence of the styrene impurity was duly solved by the use of triphenylarsine as the ligand. In a run at 100°C in DMF in the presence of triphenylarsine, anisole **95a** was the sole product by ^{19}F NMR, with an estimated yield of 80% using 4-fluorotoluene as an internal standard (entry 8, **Table 1**).

As a final demonstration of the effect of DMF, a run was made in which THF was used as the initial solvent at ambient temperature. After 150 hours, ^{19}F NMR indicated the slow (50%) reduction of the stannane to the enol carbamate (transmetallation is further compromised by a reduction in temperature; thermal dimerisation is presumably too slow at this temperature) with no detection of product. Addition of an equal volume of DMF with stirring for 18 hours resulted in clean

coupling of the residual stannane to afford the product (overall 1:1 **95a**:**98**) as judged by ^{19}F NMR. The ability of DMF to mediate couplings at ambient temperature *in the presence of triphenylphosphine* was remarkable, since it demonstrates that transmetallation occurs even at this temperature. This observation is in contradiction with the literature,[139] which states that, based upon NMR evidence of the reaction between phenyltributyltin and CuI in DMF (at a probe temperature of 30°C) to form phenylcopper, that triphenylphosphine completely suppressed the reaction. In a separate run, 4-iodoanisole underwent efficient coupling under arsine conditions (loading of copper(I) iodide was increased to 50 mol%) in DMF to afford **95a** as the sole product (entry 11).

In order to verify the necessity of copper(I) iodide co-catalysis, two runs were made in which both copper(I) iodide and palladium(0) were individually omitted. When a reaction was run in the absence of copper(I) iodide, a low (10%) yield was obtained with starting material being recovered, emphasising the importance of the co-catalyst (entry 9). In order to test whether copper(I) iodide could mediate the coupling alone, a run was made in the absence of palladium catalyst. In this instance, all material was converted through to enol carbamate **98** (entry 10). This is not too surprising, since aryl iodides are unreactive to S_N2 reaction, and oxidative addition into a carbon-iodine bond by copper(I) is a difficult process and usually requires activated copper(I) complexes[123a] or additives.[123c] **Table 1** summarises these results.

Table 1. Effect of temperature and solvent on the cross-coupling of stannane **81** with 4-iodoanisole using a 5% Pd(0) /20% PPh_3 /10% CuI catalytic system

Entry	Solvent	Temp/^oC	Reaction Time /h	Yield/% (NMR)
1	THF	50	165	-[a]
2	THF	65	18	27
3[b]	THF	65	24	34
4	THF/DMF[c]	23	168	- (50)
5	DMF	120	0.3	43
6	DMF	70	0.5	47
7	DMF	50	2	83
8[b]	DMF	100	1.5	63
9[d]	DMF	100	48	10
10[e]	DMF	100	2	0
11[f]	DMF	23	6	69[g]

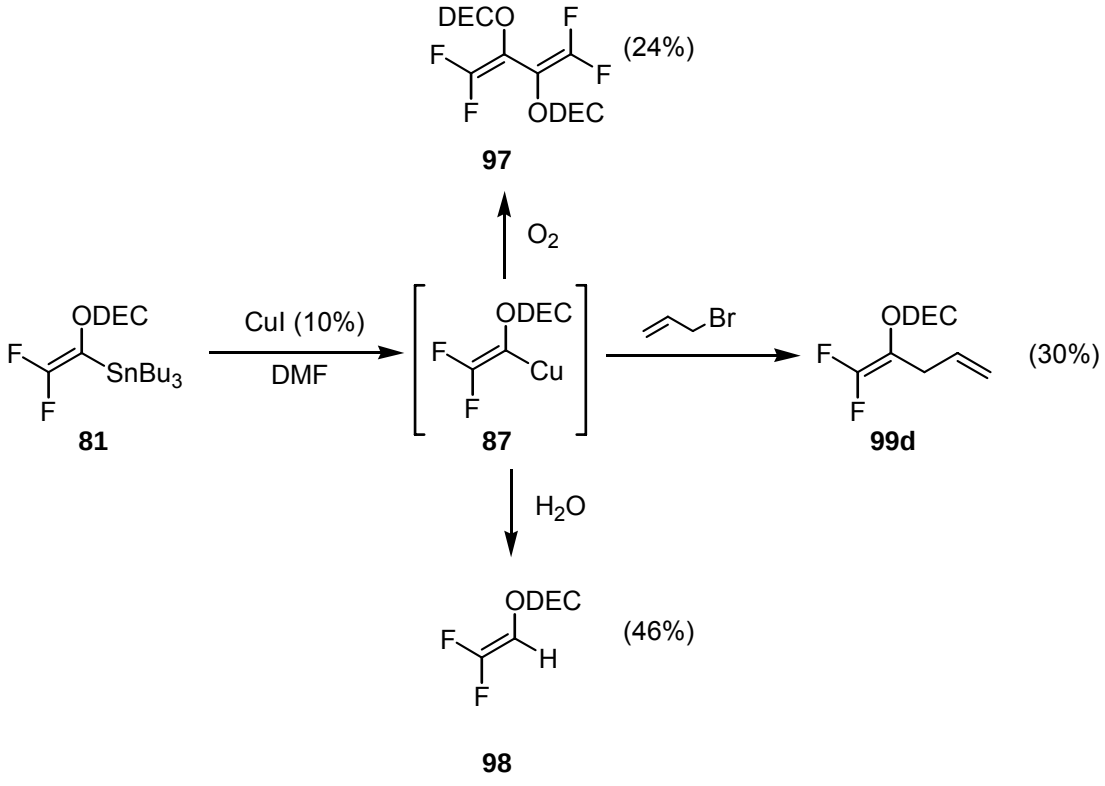
[a] Reaction was incomplete by NMR. [b] Triphenylarsine was used as ligand. [c] Reaction was run with THF for 150 hours, with NMR indicating **81** plus **98**; equal volume of DMF then added and stirred overnight, affording a 1:1 mixture of **98** and **95a** by NMR. [d] No CuI added. [e] No palladium(0) source or phosphine ligand added. [f] 50 mol% CuI used. [g] Estimate by ^{19}F NMR using 4-fluorotoluene as standard.

Role of copper(I) iodide

In order to probe the role of the copper(I) iodide further, test reactions were performed with allyl bromide, so that it would be possible to study the palladium-free cross-coupling reaction. The previously successful coupling of our organocopper reagent,[104] along with literature precedents suggest that organocopper reagents can undergo unassisted reaction with soft electrophiles[104] and only require transition-metal assistance with chloroformates[162] and aryl halides.[151a]

When stannane **81** was reacted with allyl bromide under standard palladium(0) catalysis (i.e in the absence of copper(I) iodide) at 50°C in DMF, a sluggish reaction proceeded to afford a very poor yield of diene **99d**.

When the reaction was repeated with the copper(I) salt as the sole coupling catalyst at 50°C in DMF, reaction occurred to afford a significant percentage (30%) of the desired diene by ^{19}F NMR. The large amount of reduced product and especially that of homocoupled material is characteristic of an organocopper intermediate **87** (**Scheme 53**). Though the reaction flask was pump-purged to remove oxygen and the solvent degassed, the reaction vessel may well have several leaks, leading to the presence of sufficient oxygen to facilitate dimerisation.



Scheme 53: CuI-catalysed formation of allyl product **99d** in the absence of palladium(0)

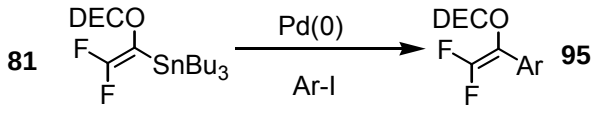
Coupling under Pd(0)/Cu(I) co-catalytic conditions successfully formed diene **99d** in high (75-87%) yield with only traces of dimer **97** and enol carbamate **98** present (see pg 64).

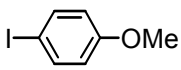
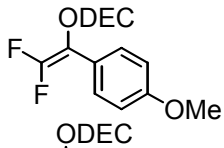
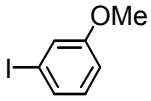
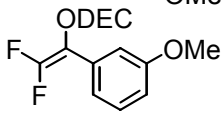
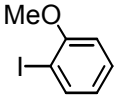
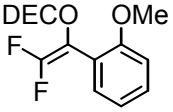
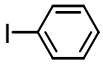
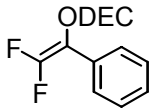
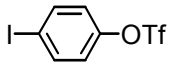
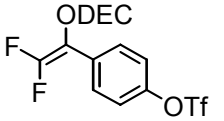
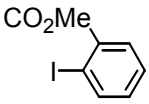
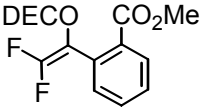
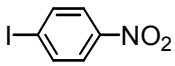
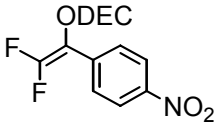
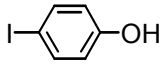
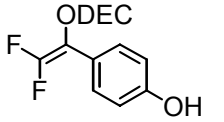
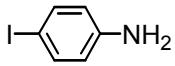
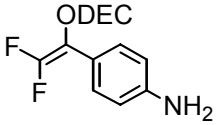
If transmetallation does indeed occur then it should be beneficial to use high loadings of copper(I) iodide in these couplings in order to increase the reaction rate. Indeed, literature methods often use 50-75 mol% for this type of coupling with fluorinated stannanes.[146,147a]

Scope of coupling process

Having developed favourable conditions (entries 7 and 8, **Table 1**), a series of couplings was then attempted to assess the reactivity of a range of aryl, heteroaryl, allyl and vinyl halides. The aryl substrates used would test the coupling system to changes in both the steric and electronic nature of the electrophilic component. **Tables 2** and **3** show the results.

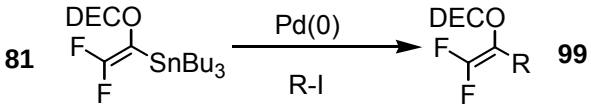
Table 2: Coupling of stannane **81** with aryl iodides

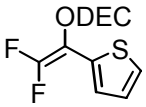
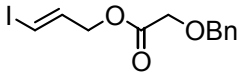
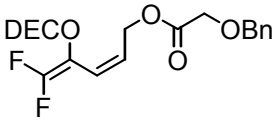
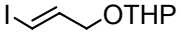
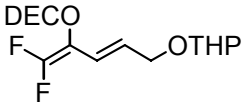
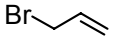
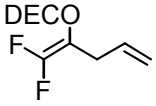


Substrate	Conditions	Product		Yield/% (NMR)
	A		**95a**	83
	C		**95b**	49
	D		**95c**	0 (0)
	A		**95d**	80
	A		**95e**	82-91[a]
	B A		**95f**	55 47
	D		**95g**	18
	B		**95h**	- (84)
	A		**95j**	- (41)

A: 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, 10% CuI, DMF, 50°C;
B: 2.5% $Pd_2dba_3.CHCl_3$, 20% $AsPh_3$, 10% CuI, DMF, 100°C;
C: 5% $Pd(OAc)_2$, 20% $AsPh_3$, 10% CuI, DMF, 100°C;
D: 5% $Pd(OAc)_2$, 20% PPh_3, 10% CuI, DMF, 50°C;
[a] Determined over 2 runs

Table 3: Coupling of stannane **81** with other organic electrophiles



Substrate	Conditions	Product		Yield/%
	A		**99a**	44
	B A		**99b**	46 62
	A		**99c**	25
	A		**99d**	64-87[b]

A: 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, 10% CuI, DMF, 50°C;
B: 2.5% $Pd_2dba_3.CHCl_3$, 20% $AsPh_3$, 10% CuI, DMF, 100°C;
[b] Determined over 4 runs

This study provides the most diverse set of examples currently known for couplings of fluorinated stannanes. It was observed that electron-deficient aryl iodides readily underwent reactions to afford crude products with clean ^{19}F NMR spectra. Therefore, under these optimised conditions which facilitate transmetallation, palladium(0) insertion into the carbon-iodine bond presumably becomes the rate-determining step. It is presumed that tin-copper transmetallation occurs readily at or just above ambient temperature (30-40°C) affording a low concentration (equal to the amount of copper(I) iodide added) of the organocopper reagent, primed to undergo reaction. If the corresponding concentration of the organopalladium(II) complex resulting from oxidative addition is low, decomposition of the organocopper reagent occurs, *via* reduction and homocoupling.

Given the fact that *tetrakis*(triphenylphosphine)palladium(0) will insert spontaneously into iodobenzene at ambient temperature,[167] aromatic rings bearing electron-withdrawing groups such as nitro (NO_2), alkoxycarbonyl (CO_2R), fluoro (F) and trifluoromethanesulfonoxy (OSO_2CF_3) should perform particularly well.

The presence of electron-donating substituents has variable effects. Though a methoxy group at the *para* position exerts a resonance (mesomeric) π-donor effect at the carbon atom bearing the iodine atom, the observed ^{19}F NMR spectrum was still clean, except for traces of **98**. This indicates that the rate of palladium(0) insertion is not greatly affected by the presence of such electron-donating groups. A *meta*-methoxy group only possesses a weak $-I$ effect and therefore performs well. A limitation was found with aryl units bearing a *para*-amino or *para*-hydroxyl group. In this case, the degree of resonance donation to the π-framework is inferred to greatly affect the ease with which palladium(0) can insert into the carbon-iodine bond.

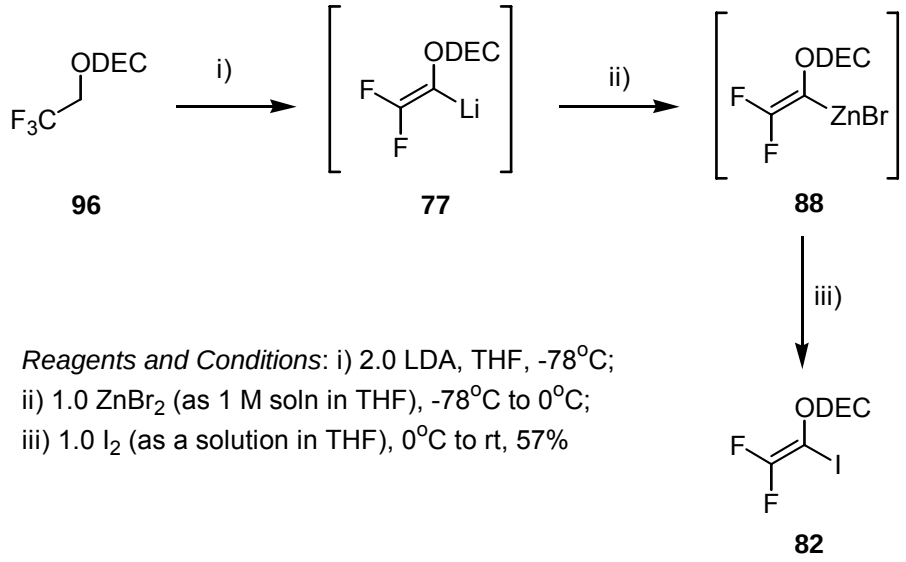
Reduction and dimerisation therefore account for the major reaction products. In addition, *ortho* sp^3 substituents were not tolerated (entry 3), although *ortho* sp^2 centres proved to react smoothly (entry 6).

2.1.2 Coupling of 1-(N,N-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene **82**

The successful coupling with the 2,2-difluorovinylstannane **81** prompted us to turn our attention to the corresponding iodoalkene **82**. One would anticipate that **82** would undergo oxidative addition rapidly to afford a reactive vinylpalladium complex; the electron-deficient fluoroalkenol group should then increase the electrophilicity of the metal centre facilitating the transmetallation reaction. The requirement of copper(I) co-catalysis should therefore be less important. In addition, this coupling is synthetically complementary to the coupling with stannane **81**, since steric effects should not affect the oxidative addition. Therefore, use of *ortho*-substituted organometals should lead to the desired products, with fewer problems, as demonstrated by the work of Thomas.[164]

Synthesis of difluoroiodoalkene **82**

The requisite difluorovinyl iodide **82** was successfully prepared according to the procedure of Howarth.[99] The lithiated intermediate **77** was generated in an identical manner to that previously described (*vide ante*) from carbamate **96**. In this instance, anhydrous zinc(II) bromide (as a solution in THF) was added presumably to afford thermally stable vinylzinc reagent **88**. Quenching with elemental iodine (as a solution in THF) at 0°C, followed by Kügelrohr distillation of the crude material afforded vinyl iodide **82** in moderate (57%) isolated yield (**Scheme 54**).



96 **77** **88** **82**

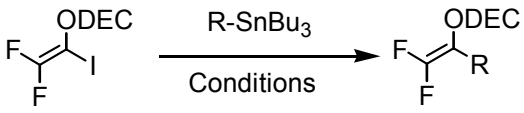
Reagents and Conditions: i) 2.0 LDA, THF, -78^{o}C;
ii) 1.0 $ZnBr_2$ (as 1 M soln in THF), -78^{o}C to 0^{o}C;
iii) 1.0 I_2 (as a solution in THF), 0^{o}C to rt, 57%

Scheme 54: Synthesis of iodoalkene **82**

Scope of coupling process

In order to test the generality of this coupling process, a range of stannanes differing in structure were reacted with vinyl iodide **82** under two sets of conditions taken from the coupling of vinyl stannane **81**. Vinyl, aryl, heteroaryl and allyl stannanes were tested. The results are shown in **Table 4**.

Table 4: Stille Couplings of iodoalkene **82**



Stannane		Conditions	Product		Yield/% (NMR)
Bu_3Sn		C	DECO, F, F	**99e**	36
		A			77
Bu_3Sn, C_5H_{11}	**100a**	A	DECO, F, F, C_5H_{11}	**99f**	72-80[a]
Bu_3Sn, OTHP	**100b**	A	DECO, F, F, OTHP	**99c**	40
Bu_3Sn, OMe	**100c**	B	ODEC, F, F, OMe	**95a**	35
Bu_3Sn, O		B	ODEC, F, F, O	**99g**	81
		A			72
Bu_3Sn, S		A	ODEC, F, F, S		31
		B		**99a**	36[b]
		B			26
Bu_3Sn, N, CHO	**100d**	A	DECO, F, F, N, CHO	**99h**	0
Bu_3Sn, N, S	**100e**	A	DECO, F, F, N, S	**99j**	0
Bu_3Sn, O, O, O	**100f**	A	DECO, F, F, O, O, O	**99k**	0 (65)
Bu_3Sn		B	DECO, F, F	**99d**	- 0[c]
		A			- 18[d]

A: 5% $Pd(OAc)_2$, 20% $AsPh_3$, 10% CuI, DMF 100°C, 16 h; B: 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, 10% CuI, DMF 50°C, 16 h; C: 2.5% $Pd_2dba_3.CHCl_3$, 20% $AsPh_3$, 10% CuI, DMF 100°C, 16 h

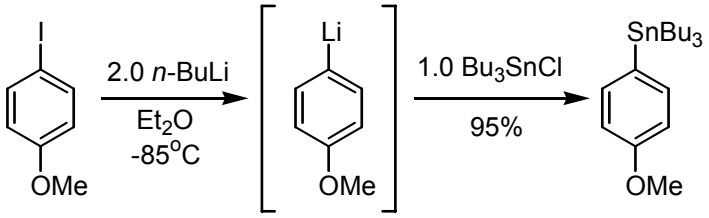
[a] Yields determined over 5 runs, 1 mmole scale. [b] Stannane was added over 1 hour. [c] Products **97** and **98** only. [d] Along with **82** (16%), **98** (34%) and **97** (32%) by NMR.

The coupling of vinyltributyltin with **82** was initially attempted using the conditions described for coupling to the corresponding stannane (conditions 8, **Table 1**). A rapid (*ca.* 10 min) and efficient reaction ensued to afford diene **99e**, but a poor isolated yield and a continuing problem of co-elution of the product with the dibenzylideneacetone (dba) ligand led to the investigation of using a palladium(II) source and generating the palladium(0) *in situ*. Repetition with palladium(II) acetate led to a cleaner reaction with 1,3-diene **99e** being isolated in up to 77% yield on a 5 mmol scale.

The use of a 5:1 isomeric mixture of *E/Z*-heptenyltributylstannanes **100a** also led to a reproducible (5 runs, 1 mmol scale), high-yielding (72-80%), clean and stereospecific reaction to afford dienes **99f** (5:1 *E*/*Z*).

In order to test the possibility of coupling protected allylic alcohol fragments (as required for sugar targets, see pg 110), stannane **100b** was synthesised according to the procedure of Corey in 71% yield.[168] However, attempted coupling led to a complex mixture of products, although the desired product **99c** could be isolated in moderate (40%) yield.

In order to establish a direct comparison between the two approaches, (4-methoxyphenyl)tributyltin was synthesised. Treatment of 4-iodoanisole with two equivalents of *n*-BuLi (in order to destroy iodobutane) at -78°C led to a yellow solution, presumably containing aryllithium **101**, which was trapped with tributyltin chloride to afford stannane **100c** in high (95%) yield. Traces of residual tributyltin chloride could not be removed, however (**Scheme 55**).



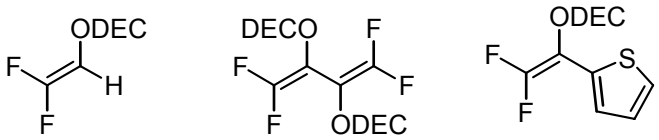
101 **100c**

Scheme 55: Synthesis of stannane **100c**

Coupling under conditions A (see **Table 4**) led to the isolation of styrene **95a** in relatively poor (35%) yield (cf. 83% for couplings with stannane **81**). This result suggests that either couplings with iodoalkene **82** are sensitive to stannane structure or that the conditions used were not optimal and that further optimisation is required.

Couplings with the commercially available heterocyclic stannanes were then pursued. 2-(Tributylstannyl)furan proved to be reactive both under conditions A and B (see **Table 4**) and furan **99g** could be isolated in good (81% and 72%) yield, respectively. The reaction also proceeded efficiently without copper(I) iodide co-catalyst, although the product was isolated in a poor yield.

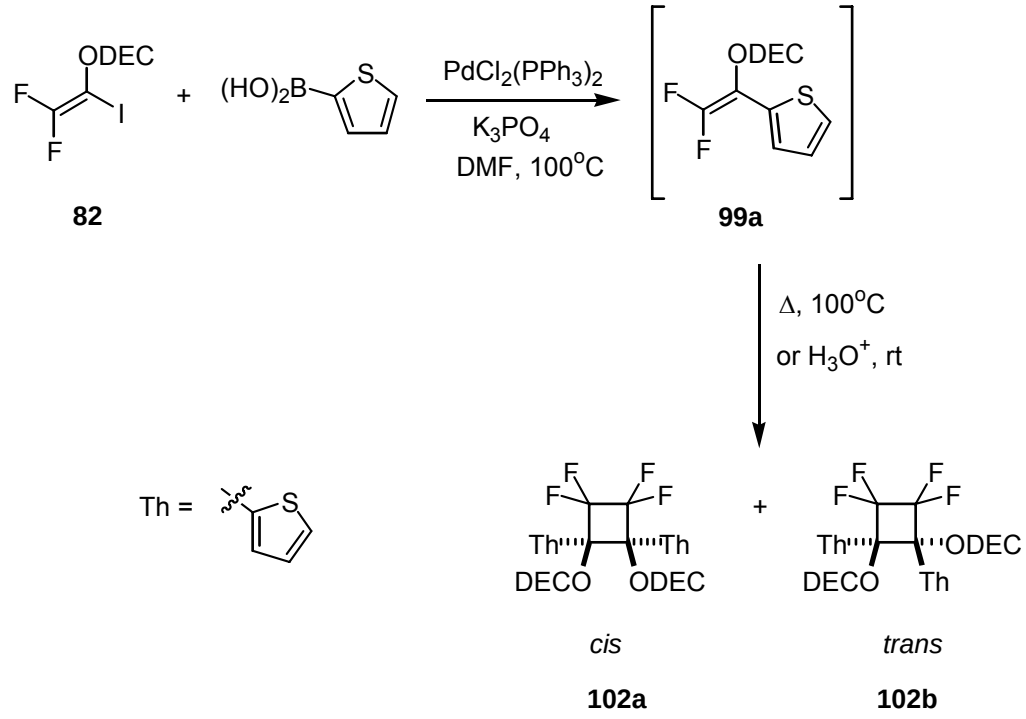
(2-Tributylstannyl)thiophene was observed to be a poorer reactant than its furyl congener, contrary to observations by McCarthy in the coupling of 1-fluoro-1-bromo-olefins.[154] Crude ^{19}F NMR were uniformly contaminated with side-products **97** and **98**, as well as the presence of signals consistent with the desired product **99a** (**Figure 11**).



98 **97** **99a**

Figure 11: Main products of coupling with 2-(tributylstannyl)thiophene

In addition, other resonances were observed which Thomas had previously assigned by NMR and mass spectrometric evidence to the dimers **102a** and **102b**, resulting from acid or thermally-promoted [2+2] cycloadditions (**Scheme 56**).[169]



Scheme 56: Decomposition of thiophene **99a** by dimerisation

Similar observations have been made by both Normant[142a] and Uneyama,[170] who have described the thermal dimerisation of difluorovinyl species to afford the corresponding tetrafluorocyclobutane derivatives.

Given the susceptibility to dimerisation described by Normant of a thienyl derivative, and that coupling of the iodide should be facile, reaction was attempted under Farina conditions (copper(I) iodide plus triphenylarsine) at ambient temperature in THF. Although the reaction was slow, an 88% conversion in 48 hours could be achieved, without the formation of any side-products.

No reaction was observed with 2-(tributylstannyl)furan at ambient temperature using a palladium(II) source, suggesting that pre-reduction of the catalyst by the stannane requires temperatures higher than *ca.* 20°C, though reduction does occur at 50°C.

Further failures were obtained with pyrrolyl stannane **100d** and thiazolyl stannane **100e**, which both preferentially underwent protodestannylation. An initial attempt using functionalised furyl stannane **100f** led to formation of furan **99k** in good yield by NMR though no product could be obtained by column chromatography. Subsequent attempts led to the recovery of starting material, possibly due to the poor quality of the stannane.

The most notable result was obtained with allyltributyltin. Under conditions A, the product mixture was extremely complex affording very low, if any, amounts of coupled product **99d**. Attempts at applying Farina conditions led to the return of starting material. The reasons for these observations are unknown, although it has been shown that the allyl group transfers from tin very slowly.[130] It is possible that this transfer is so slow that the organopalladium complex can fragment to afford decomposition products. However, Liebeskind and Farina reported near identical results in the coupling of both vinyltributyltin and allyltributyltin with iodobenzene under CuI co-catalysed conditions.[139]

These results indicate that the difluoroiodoalkene **82** can be used in palladium-catalysed couplings but that further optimisation is required. The results of Thomas suggest that palladium(0) insertion may not be as facile as expected, since high (100°C) temperatures are required, even with nucleophilic boron-*ate* species. However, conditions have appeared in the literature for coupling similar halides and should be more successful (see pages 46-47). It should be noted that CuI was not required, as predicted.

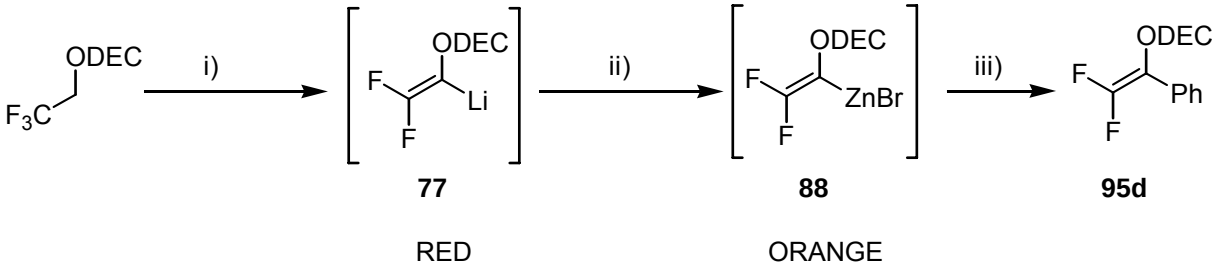
2.1.3 Potential for Negishi couplings for styrene synthesis[230]

Although Stille couplings have afforded a rich array of products, with potential for further elaboration, the inherent problems associated with the use of tin must be addressed. Tin compounds are toxic and tributyltin chloride is highly toxic and difficult to remove from reaction mixtures, so alternatives need to be sought. Zinc is a good candidate as an alternative to tin in order to avoid these problems since it is readily available, less toxic and produces water-soluble by-products.

It was decided to briefly investigate the possibility of using organozinc reagent **88** in cross-coupling with iodobenzene.

Following the usual procedure, the organolithium intermediate **77** was generated and trapped with anhydrous zinc(II) bromide. The red solution quickly changed to a pale orange solution, which persisted when the presumed zinc intermediate **88** was warmed to ambient temperature, with no indication of decomposition. A solution of iodobenzene in THF was added, followed by triphenylphosphine and [$Pd_2dba_3.CHCl_3$] adduct. After stirring for 48 hours at ambient temperature, work-up

and ^{19}F NMR analysis indicated a 66:34 ratio of styrene **95d** and reduced product **98**. Purification was facile affording pure **95d** in 55%, isolated yield (**Scheme 57**).



Reagents and Conditions: i) 2.0 LDA, THF, -78°C; ii) $ZnBr_2$, -78°C to rt; iii) 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, iodobenzene, THF, rt, 48 h, 55%

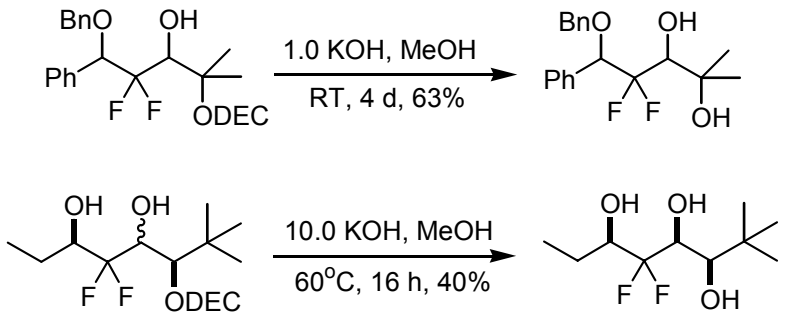
Scheme 57: Successful Negishi coupling of vinylzinc reagent **88** with iodobenzene

The large amount of reduced product was seen as possibly being associated with the high hygroscopicity of the zinc bromide, so the reaction was repeated using a commercial solution of zinc chloride in THF. Unfortunately, the system appears prone to opportunistic hydrolysis, since large amounts of reduced product were again observed, along with a small amount of coupled product **95d**. $ZnCl_2$(TMEDA) represents a non-hygroscopic source of zinc(II) chloride[171] and could be used in future studies. Nevertheless, these initial results represent a promising move forward away from a tin protocol.

2.1.4 Cleavage of the N,N-diethylcarbamoyl protecting group

Balnaves has demonstrated that treatment of tertiary and some secondary *N,N*-diethylcarbamoyloxy aldol products with methanolic KOH resulted in the required deprotection of the carbamate moiety.[172] Reaction occurred in a considerably cleaner fashion with tertiary aldols. Secondary alcohols were much less reactive and often

led to complex mixtures, although the desired products could be isolated by column chromatography. In addition, only those with 1,3-*syn* relationships underwent reaction (**Scheme 58**).

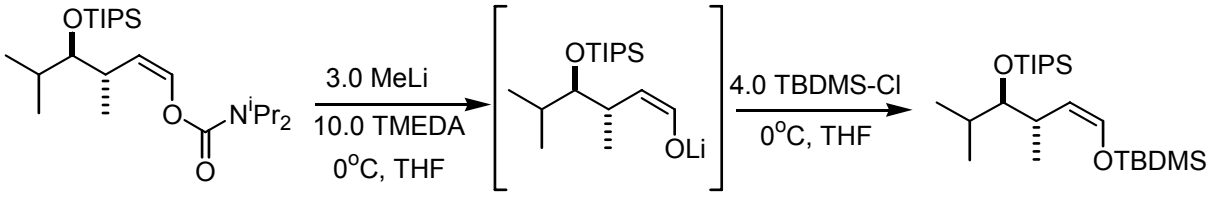


Scheme 58: Cleavage of a *N*,*N*-diethylcarbamoyloxy group from tertiary and secondary centres

In styrene derivatives, the latent ketone must be revealed by cleaving the *N*,*N*-diethylcarbamoyl group with an external nucleophile or electrophile.

Cleavage with nucleophiles

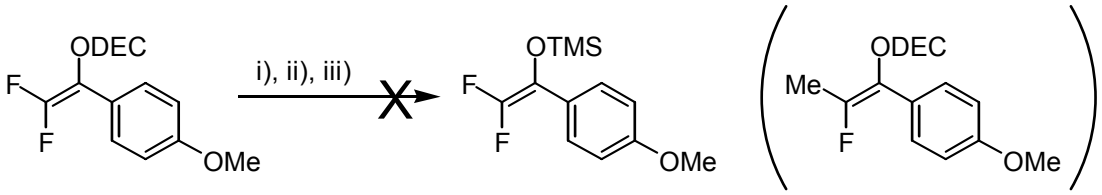
Férézou and co-workers have described the use of methyllithium as a nucleophilic species capable of deprotecting vinyl *N,N*-di*iso*propylcarbamates.[173]The reaction is facilitated by the addition of TMEDA to activate the methyllithium by forming a monomeric species and three equivalents are used in order to produce simple by-products (**Scheme 59**).



Scheme 59: Deprotection of *N,N*-di*iso*propylcarbamates

Given the known reactivity of silyl difluoroenol ethers to cleavage, it was decided to attempt a reaction with methyllithium, using chlorotrimethylsilane to trap the potential lithium enolate.

Following the literature procedure, anisole derivative **95a** was treated with three equivalents of MeLi at 0°C for 1 hour, followed by the addition of ten equivalents of TMEDA. The reaction was then allowed to stir for 15 minutes. Quenching with chlorotrimethylsilane followed by analysis by ^{19}F NMR after work-up indicated the consumption of starting material, though no fluorinated components survived the reaction. Inspection of the ^{1}H NMR indicated the absence of any carbamate signals, suggesting that successful cleavage of the DEC group had indeed occurred. Repetition of the reaction with quenching at -78°C led to the observation of a clean conversion to a single monofluorinated compound rather than silyl difluoroenol ether **103**. Column chromatography allowed the isolation and characterisation of (*E*)-fluorovinylstyrene **104**, formed by single stereoselective fluoride replacement by a methyl group (**Scheme 60**).



95a **103** **104**

Reagents and Conditions: i) 3.0 MeLi, THF, -78^{o}C, 1h;
ii) TMEDA, 15 min; iii) Me_3SiCl, -78^{o}C to rt, 64%

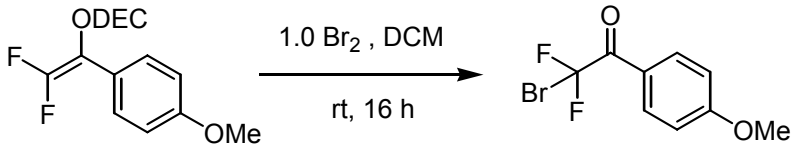
Scheme 60: Monodefluorination by MeLi at -78°C

This result shows that the difluoromethylene centre is more electrophilic than the carbamate carbonyl group. This reactivity precludes the use of nucleophilic reagents to cleave the enol *N*,*N*-diethylcarbamate.

Cleavage with electrophiles

It was hoped that the carbonyl group could be activated to attack by a nucleophile by reacting the olefin with an electrophile to form a carbocation that should fragment to release the ketone.

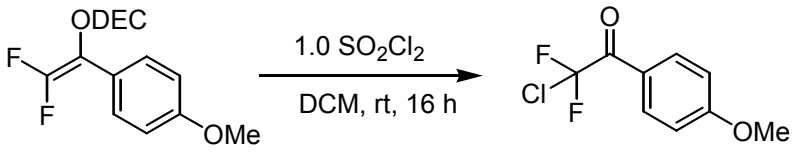
Indeed, treatment of anisole **95a** with one equivalent of bromine in dichloromethane for 16 hours led to the disappearance of starting material and the formation of a new material by TLC. Analysis by ^{19}F NMR revealed a singlet at -60 ppm, consistent with the formation of bromodifluoromethyl ketone **105** (**Scheme 61**).



95a **105**

Scheme 61: Cleavage of the DEC group with bromine

A similar outcome was observed when sulfuryl chloride was used as a source of electrophilic chlorine. After 3 h, starting material was absent by TLC, although the initial violet colour of the reaction had not cleared. Water was added to quench the reaction and the violet colour disappeared. After an extractive work-up, analysis by ^{19}F-NMR revealed chlorodifluoromethyl ketone **106** as the major component (δ_F -60.2) in addition to a minor by-product (**Scheme 62**).



95a **106**

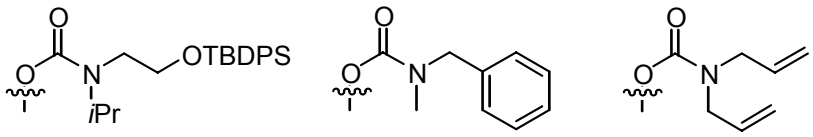
Scheme 62: Cleavage of the DEC group with electrophilic chlorine

The cleavage of the DEC group with halogen electrophiles shows that this approach to α,α-difluoromethyl aryl ketones is feasible. However, although the DEC group can be cleaved, it was hoped that a more diverse cleavage strategy could be achieved.

2.1.5 Generalising the coupling protocol to variable enol protection

With successful coupling results, it was decided to briefly study the α-steric effect of the enol protecting group, since it was thought that the DEC group might well be superceded by others at a later date.

The cleavage of the enol-protecting group is the key step in the approach to aryl ketones and the mode of cleavage should be compatible with other functional groups present in the substrate. Balnaves has studied the installation and cleavage modes of several carbamate derivatives, [172] including those shown in **Figure 12**.

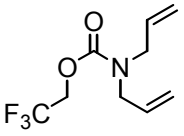
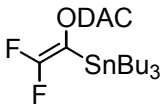
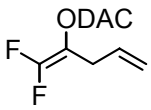
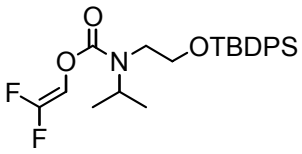
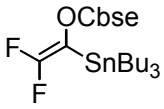
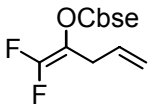
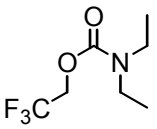
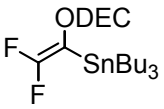
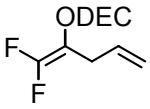


Cbse MBC DAC

Figure 12: Carbamate protecting groups investigated to date for use in difluoroketone synthesis

In order to study the α-steric effect in coupling efficacy, two difluoroenol *C*-stannane derivatives were synthesised using our standard procedures and the coupling reaction examined with allyl bromide. ^{19}F NMR of crude reaction mixtures was used to determine the efficiency of the reaction. **Table 5** shows the results.

Table 5: Effect of enol protecting group upon efficiency of coupling

Carbamate	Stannane	Yield/%	Product		Yield/% by ^{19}F NMR
		94%		**107**	63%
		86%[163b]		**108**	60%
		94%		**99d**	87%

Generation of the lithio derivatives occurred without any problems and electrophilic trapping with tributyltin chloride led to the stannane derivatives in good yield after simple purification.

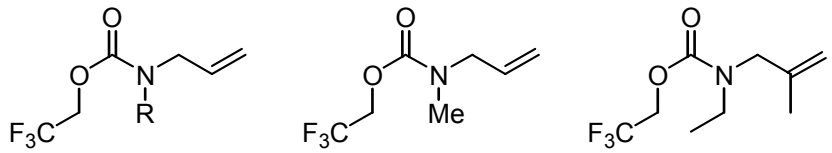
Coupling of each derivative occurred with reasonable efficiency under the previously optimised conditions and the 1,4-dienes were the major products by ^{19}F NMR with the corresponding enol carbamates present as the by-products.

HPLC of the Hoppe-derived product allowed the separation of the two materials, resulting in 60% yield for the allyl product **108**, in addition to 13% for the proto-destannylation product. The high proportion of coupled material is important, as it

indicates that the steric demands around the carbamate has minimal effect on the efficiency of the coupling. The large protecting group could potentially sweep a large volume around the reaction centre.

An N-ethyl-N-(2-methylallyl)carbamato protecting group

Although the Hoppe carbamate has been successfully used in difluoropolyol synthesis,[103,172] the high cost detracts from its use in the possible large-scale synthesis of aryl difluoromethyl ketones. It was hoped that it would be possible to mimic the mode of cleavage of this protecting group through the formation of an *N*-alkylated allylcarbamate derivative **109**, such as those shown in **Figure 13**.



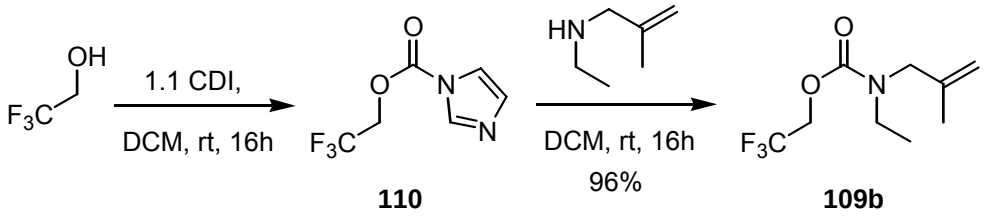
109 **109a** **109b**

Figure 13: Possible *N*-allyl carbamates in synthesis

Early attempts at synthesising carbamate **109a** (designated MAC) resulted in limited success. The corresponding secondary carbamate could be synthesised in good (86%) yield by treating trifluoroethanol with allyl isocyanate in the presence of copper(II) chloride according to the method of Duggan.[174] However, many attempts to *N*-methylate with iodomethane and various bases resulted in isocyanate expulsion followed by multiple addition to form the carbamate, allophanate and isocyanurate.[175] Carbamate **109b** (designated Emac) was a more attractive target since it could be

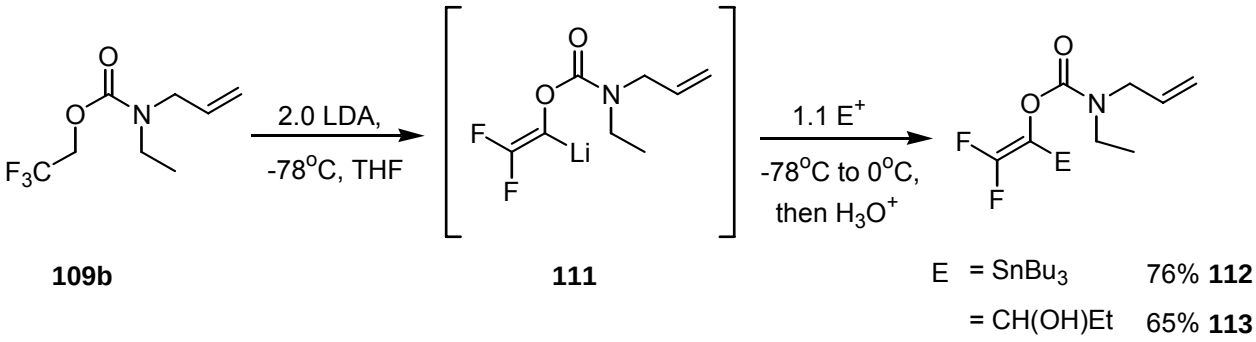
potentially formed in one step and from the cheap and commercially available secondary amine.

Treatment of trifluoroethanol with 1,1'-carbonyldiimidazole presumably afforded an intermediate imidazolide[172,176] **110** which underwent reaction with *N*-ethyl-*N*-(2-methylallyl)amine in the presence of imidazole to form carbamate **109b** in excellent 96% yield on a 100 mmol scale (**Scheme 63**).



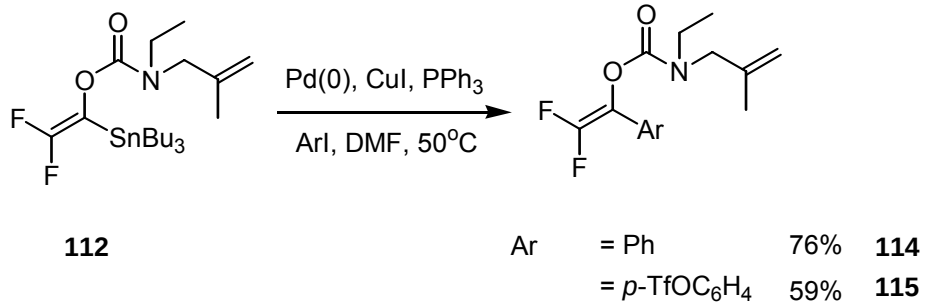
Scheme 63: Formation of carbamate **109b**

Exposure to LDA at -78°C resulted presumably in the formation of vinyllithium **111** which could be intercepted with both tributyltin chloride and propionaldehyde to form the stannane **112** and allylic alcohol **113** respectively (**Scheme 64**). The isolated yields indicated that the vinyllithium **111** was a "well-behaved" nucleophile.



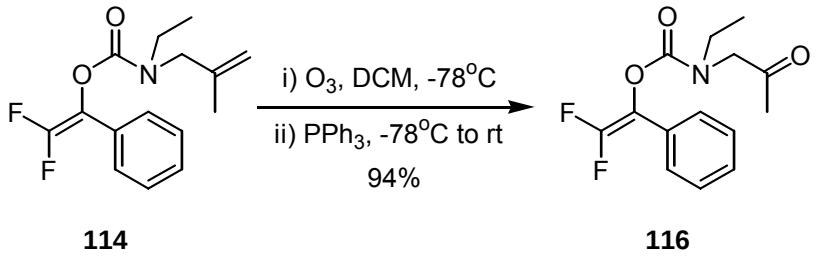
Scheme 64: Electrophilic trapping of vinyllithium **111**

Stille coupling of stannane **112** with iodobenzene under the optimised conditions afforded styrene **114** in good (76%) yield after distillation. Coupling with 4-iodophenyl triflate was also successful and aryl triflate **115** could be isolated in good (59%) yield (**Scheme 65**).



Scheme 65: Coupling of stannane **112** with aryl iodides

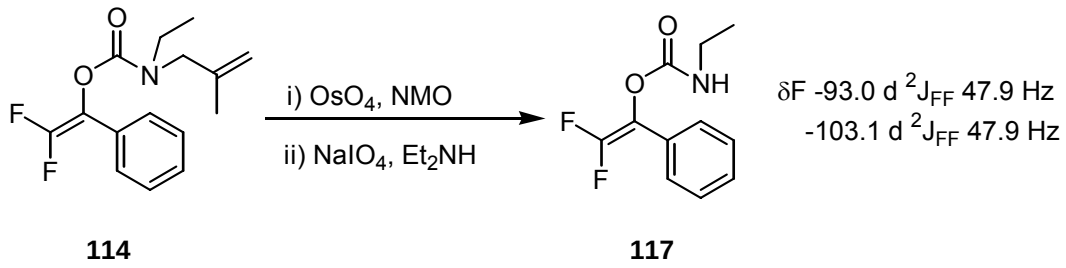
Initial attempts at cleavage have provided some encouraging results. Exposure of a dichloromethane solution of styrene **114** to ozone led to molozonide formation as judged by the appearance of the characteristic blue colour of ozone along with the disappearance of starting material by TLC. Work-up with triphenylphosphine, followed by purification by column chromatography afforded ketone **116** as a colourless oil in excellent (94%) yield (**Scheme 66**).



Scheme 66: Ozonolysis of styrene **114** to afford ketone **116**

Treatment with sodium borohydride presumably formed the corresponding sodium alkoxyborohydride, which underwent partial cleavage, in a similar manner to levulinate esters,[177] to form traces of the acetophenone derivative. It may be possible to isolate the alcohol and generate a more nucleophilic sodium alkoxide by treating the alcohol with an appropriate sodium base, such as NaH.

In an alternative approach, treatment with catalytic osmium tetroxide in the presence of NMO presumably afforded the diol, which underwent cleavage with sodium periodate in the presence of diethylamine to form traces of the deallylated carbamate **117** (**Scheme 67**).[178] Treatment with alkyllithium reagents should then release the desired enolate after elimination of ethyl isocyanate.



114 **117**

Scheme 67: Formation of carbamate **117** from carbamate **114**

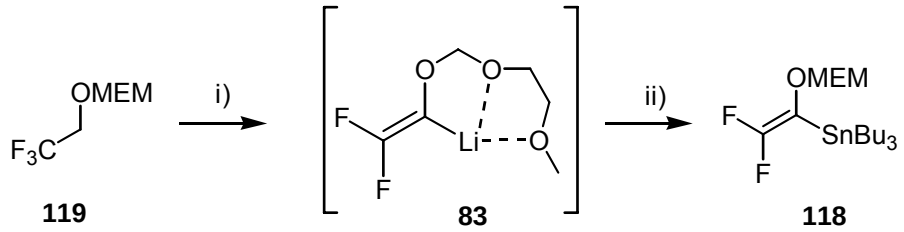
Further development of this protecting group to aryl difluoroketone synthesis was cut short due to a lack of time. The development of a suitable carbamate to difluoroketone synthesis is therefore ongoing.

2.1.6 Use of a 2-methoxyethoxymethyl (MEM) protecting group strategy

The inherent problem with DEC deprotection and the successful cleavage of enol MEM acetals[102c] suggested that a much more straightforward route to functionally diverse difluoromethyl aryl ketones was feasible.

Synthesis of 2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-1-(tributylstannyl)-ethene

The requisite stannane **118** was prepared according to the procedure of Patel.[101] Exposure of the MEM acetal of trifluoroethanol **119** to 2.0 equivalents of LDA at -78°C in THF led presumably to vinyllithium **83** which was trapped with tributyltin chloride to afford enol stannane **118** (**Scheme 68**).



Reagents and Conditions: i) 2.0 LDA, THF, -78°C;
ii) Bu_3SnCl, -78°C to rt, 89%

Scheme 68: Synthesis of MEM stannane **118**

Dilution with diethyl ether and treatment with potassium fluoride could remove trace amounts of residual tributyltin chloride. It was also found that *n*-butyllithium could be used directly, although the reaction had to be run under more dilute (0.3 M) conditions in order to avoid decomposition.

Stille coupling of stannane **118**

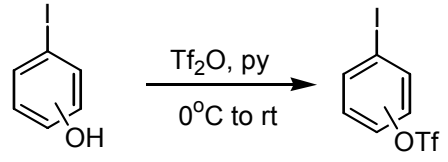
Optimisation of coupling process

Initial coupling conditions were based upon those found for the DEC derivatives (2.5% $Pd_2dba_3{\cdot}CHCl_3$, 10% CuI, 20% PPh_3) using 4-iodophenyl triflate **120a** as the electrophile. In an attempt to reduce the cost, a reaction with 2.5 mol% palladium(0) was undertaken by using 1.25 mol% of the Pd_2dba_3-$CHCl_3$ catalyst. It was found that

no significant change was observed in the crude reaction. However, the persistent problem with co-elution of the dba ligand with products led to the successful application of palladium(II) acetate as the palladium(0) source instead. In two final optimisation steps, the amount of CuI was increased to 20% in order to increase the rate of reaction and reactions were run at 0.3-0.5 M rather than 0.1-0.2 M. This led to the eradication of the reduced material.

Scope of couplings

The use of MEM stannane **118** under our optimised conditions (*vide supra*) with 4-iodophenyl triflate proceeded efficiently and aryl triflate **121a** could be isolated in excellent (96%) yield. The *meta* (**121b**) and *ortho* (**121c**) isomers were subsequently synthesised in an identical manner using 3-iodophenyl triflate and 2-iodophenyl triflate, respectively. The requisite aryl triflates were synthesised by treating the appropriate iodophenol with trifluoromethanesulfonic anhydride in pyridine.[179] The three isomeric aryl triflates **120a**, **120b** and **120c** could be isolated in 93%, 95% and 94% yield, respectively (**Scheme 69**).



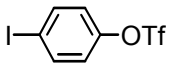
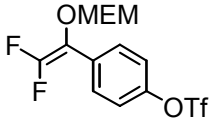
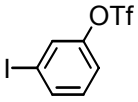
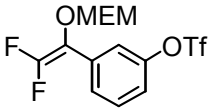
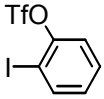
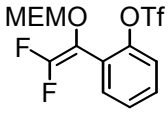
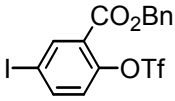
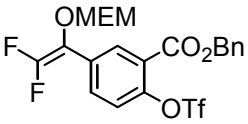
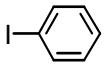
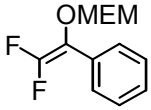
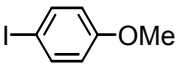
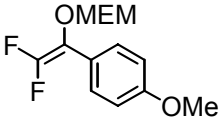
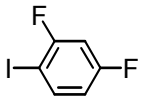
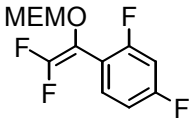
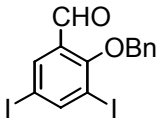
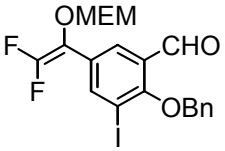
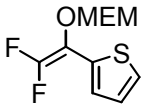
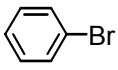
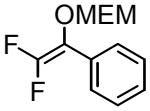
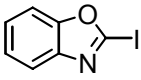
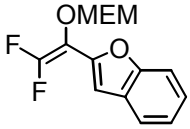
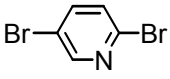
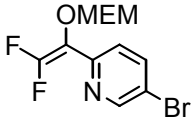
2-OTf	94%	**120c**
3-OTf	95%	**120b**
4-OTf	93%	**120a**

Scheme 69: Synthesis of regioisomeric aryl triflates **120a**-**c**

Although the *meta*- triflate **121b** could be isolated in high (86%) yield, the more sterically demanding *ortho*- triflate **121c** was formed in only low (21%) yield (33% by NMR), with large amounts of reduced and dimerised material present.[180]

Coupling also proceeded with varying efficiency with a range of other electrophiles (**Table 6**).

Table 6: Couplings of MEM stannane **118**

Electrophile		Product		Yield/%
	**120a**		**121a**	96
	**120b**		**121b**	86
	**120c**		**121c**	21
	**122**		**121d**	70
			**121e**	81
			**121f**	71
			**121g**	55
	**123**		**121h**	25
			**121j**	45
			**121e**	0
	**124**		**121k**	0
			**121m**	30

Coupling with functionalised triflate **122** also worked satisfactorily and functionalised triflate **121d** could be isolated in good (70%) yield.

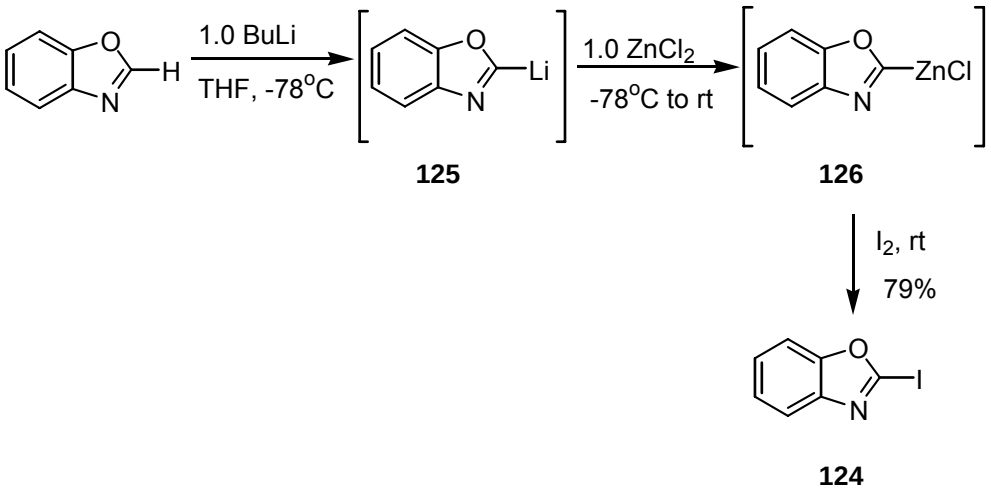
Coupling with iodobenzene afforded styrene derivative **121e** in good (81%) yield after kügelrohr distillation. Use of an electron-rich aryl iodide such as 4-iodoanisole also led to a clean conversion and anisole **121f** could be isolated in good (71%) yield.

Interestingly, the use of 2,4-difluoro-1-iodobenzene as the electrophile led to a slower reaction and large amounts of the enol carbamate and dimer were observed. The desired product **121g** could be isolated in moderate (55%) yield. This observation indicates that even a relatively small fluorine atom at the *ortho* position is sufficient to significantly affect the rate of insertion of Pd(0) into the carbon-iodine bond, although electronic factors may also be relevant.

In order to test the steric requirements and given the slow insertion with 2-iodophenyl triflate, *bis*-iodide **123** was used, in which selective coupling to the less hindered carbon-iodine bond should predominate. Indeed, analysis of the crude reaction mixture suggested selective coupling to afford **121h**, although some *bis*-coupled material and traces of the presumed regioisomeric styrene were visible. Functionalised iodide **121h** could be isolated in low (25%) yield.

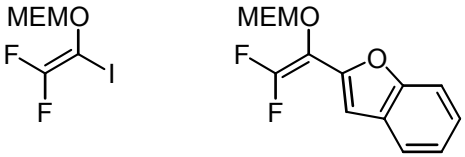
Coupling with a heteroaryl iodide, namely 2-iodothiophene, also proceeded smoothly and unstable thiophene **121j** could be isolated in moderate (45%) yield. In addition, it was hoped that 2-iodobenzoxazole **124** could be used in order to access benzoxazole **121k**, since certain difluoroketones potentially accessible from this material could possess interesting properties.[56, 63a]

2-Iodobenzoxazole **124** was synthesised by trapping the corresponding organozinc reagent[181] **126** (derived from organolithium **125**)[182] with elemental iodine (**Scheme 70**).



Scheme 70: Synthesis of 2-iodobenzoxazole **124**

Unfortunately, attempted coupling with this substrate failed to afford any of the desired benzoxazole **121k**. Instead, isolation of the major product and analysis by ^{19}F and ^{1}H NMR identified the reaction product as the iodide **127** (**Figure 14**).



127 **121k**

Figure 14

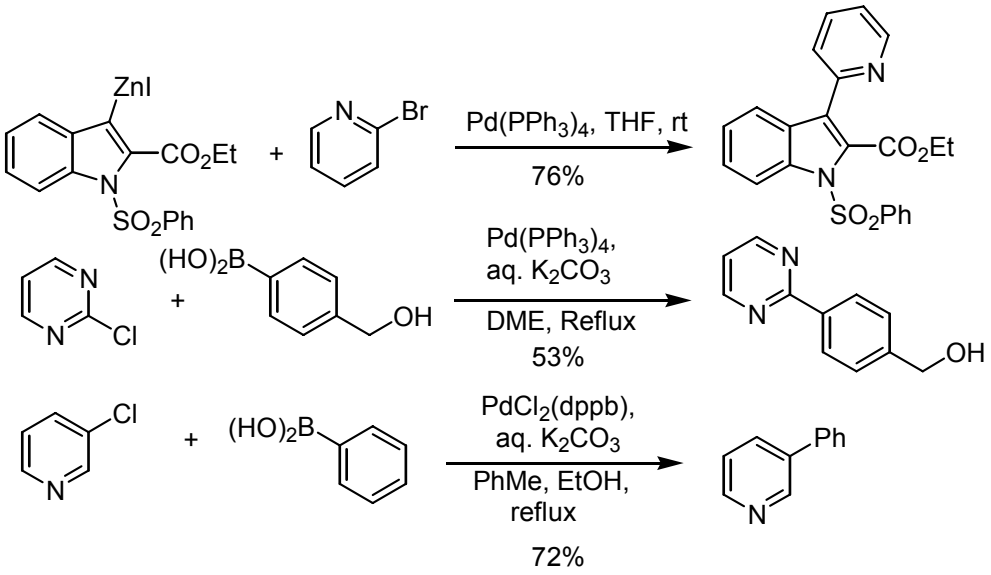
This is a strange result that may result from decomposition of 2-iodobenzoxazole under the reaction conditions with the liberation of iodine. Reaction with the stannane

118 could then potentially form iodide **127**. Further avenues to benzoxazole **121k** were not attempted due to a lack of time.[183]

Although successful coupling reactions have been achieved with aryl iodides, the most interesting compounds with pharmaceutical appeal are those containing heterocycles. Unfortunately, the vast majority of commercially available heterocyclic compounds with coupling potential consist of aryl bromides or aryl chlorides, which do not participate well in the current coupling reaction and is thus a severe limitation to generalisation.

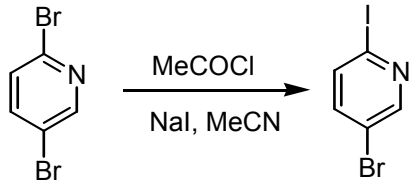
When coupling was attempted with bromobenzene, analysis of the reaction mixture indicated complete conversion to either the reduced product or to the dimer. This has been observed several times in the literature.[146,150] This result reiterates that the rate of insertion into the carbon-halogen bond must be of a rate comparable to that of tin-copper transmetallation, otherwise decomposition of the organocopper intermediate can occur. Indeed, the absence of starting material means that the difluorovinyl stannane itself undergoes both oxidative dimerisation and reduction.

It is known, however, that heterocycles are activated towards nucleophilic attack due to the *–I* inductive effect of the ring heteroatoms.[184] The insertion of palladium(0) also follows a similar pattern and $Pd(PPh_3)_4$ can insert into 2-bromopyridine at ambient temperature,[185] whilst 2-chloropyrimidine[186] and even 3-chloropyridine[187] react at reflux in THF and DME respectively, though a more reactive catalyst is required in the latter case (**Scheme 71**).



Scheme 71: Pd-catalysed coupling reactions involving heteroaryl bromides/chlorides

The coupling ability of 2,5-dibromopyridine **128** and 5-bromo-2-iodopyridine **129** were compared to test the ability of heteroatoms to increase the lability of α- and γ- carbon-bromine bonds, and to a lesser degree β- carbon-bromine bonds. The latter compound was prepared from **128** according to the procedure of Song (**Scheme 72**).[188]

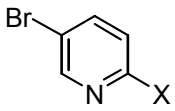


128 **129**

Scheme 72: Synthesis of 5-bromo-2-iodopyridine

Several sets of reaction conditions were tried, in which the CuI:Pd(0) ratio was changed from 8:1 through to 1:2. The results are depicted in **Table 7**.

Table 7: Coupling of 2-iodo- or 2-bromo-5-bromopyridine



Entry	X	Conditions	NMR Yield/%	CuI:Pd(0)
1	Br	A	20	8:1
2	I	A	39	8:1
3	Br	B	51	2:1
4	I	B	30	2:1
5	Br	C	55	1:1
6	Br	D	57	1:2

A: 2.5% $Pd(OAc)_2$, 10% PPh_3, 20% CuI, DMF, 50°C; B: 2.5% $Pd(OAc)_2$, 10% PPh_3, 5% CuI, DMF, 50°C; C: 5% $Pd(OAc)_2$, 20% PPh_3, 5% CuI, DMF, 50°C; D: 5% $Pd(OAc)_2$, 20% PPh_3, 2.5% CuI, DMF, 50°C

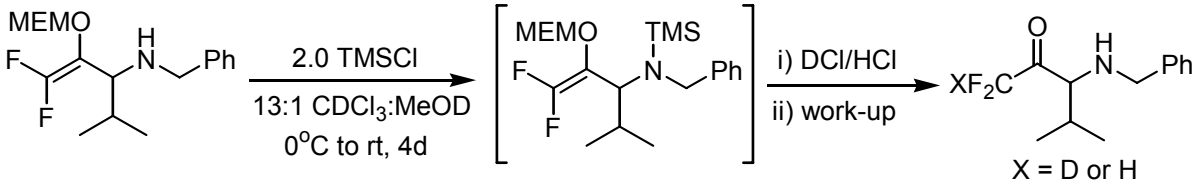
Entry 1 shows that the rate of insertion is too slow at 50°C to prevent the organocopper intermediate from undergoing decomposition. In entry 2, clearly the rate of insertion into the carbon-iodine bond is higher than that of the corresponding carbon-bromine bond, as expected (entry 2 *vs* 1). Upon reducing the concentration of the copper intermediate, the rates of the decomposition pathways were lowered, allowing a greater proportion of cross-coupling (entry 3 *vs* 1). The corresponding reaction with the iodopyridine (entry 4) gave an anomalous amount of the reduced product, probably due to poor quality DMF. Upon reducing the Pd(0):Cu(I) ratio two fold (entry 5), a slight increase in coupling efficiency was observed. Under the best set of conditions, in which the ratio was reversed, coupling occurred in 57% efficiency. These conditions give rise to the swamping of the organocopper intermediate with the organopalladium complex, promoting the cross-coupling reaction. Isolation of the product from the reaction mixture gave unstable bromopyridine **121m** in moderate (30%) yield.

Electrophilic cleavage of styrene derivatives

In order to confirm that the MEM enol ether could be cleaved under mild conditions, styrene **121a** was treated with a range of electrophiles and analysed by ^{19}F NMR for product formation.

Protiolysis

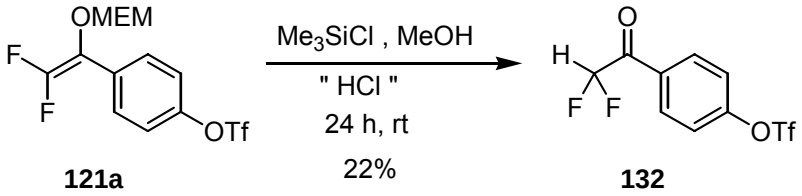
Prime showed how vinyl MEM ethers could be cleaved by the treatment with thionyl chloride in dry methanol (forming dry HCl *in situ*).[102c] Treatment of chlorotrimethylsilane with methanol also generates the desired acid. In a single example, Thomas showed how allylic amine **130** underwent deprotection using the above method to form difluoromethyl ketone **131** as a mixture of isotopomers (**Scheme 72**).[169]



130 **131**

Scheme 72: Protiolysis of a difluoroenol MEM ether with DCl

In order to test the ability of these latter conditions to generally cleave *difluoro*vinyl MEM ethers, triflate **121a** was added to a solution of chlorotrimethylsilane at 0°C in methanol. After stirring overnight, analysis by NMR indicated complete consumption of the starting material with the production of the desired difluoroketone **132**, after azeotropic distillation with toluene in order to remove traces of the hemiacetal and hydrate (**Scheme 73**).

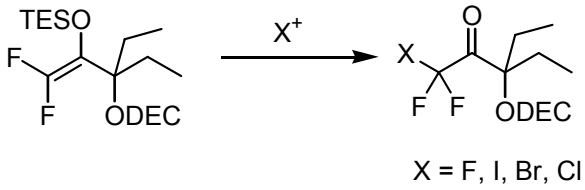


Scheme 73: Protiolysis of aryl triflate **121a**

The difluoromethyl ketone **132** could be isolated, albeit in low (22%) yield, possibly due to methanolysis of the O-S bond. This material possessed a doublet at -122 ppm for the difluoromethylene group.

Halogenolysis

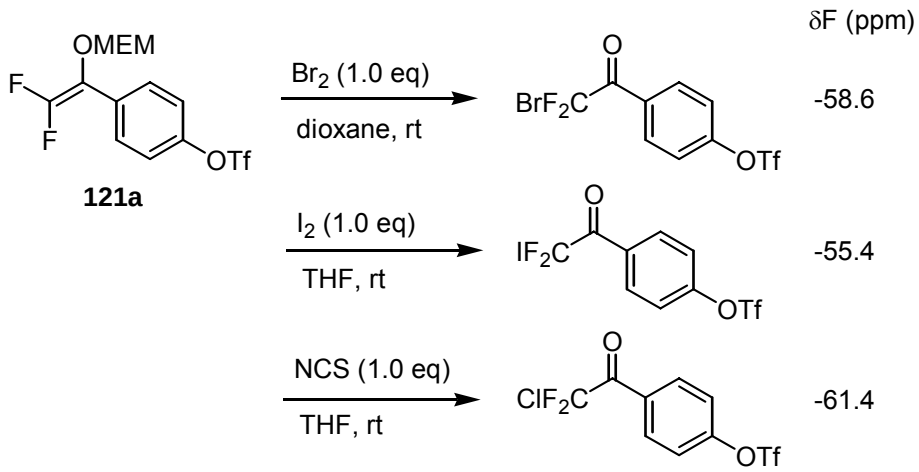
Silyl difluoroenol ethers have been previously shown to be labile to a range of halogen electrophiles. Howarth and Laily showed how fluorine, bromine, iodine and chlorine electrophiles could be used to cleave triethylsilyl ethers to the corresponding halodifluoromethyl ketones (**Scheme 74**).[189]



Scheme 74: Installation of halodifluoromethyl ketones from a silyl difluoroenol ether

In a series of NMR experiments, different electrophiles were tested against triflate **121a**. Addition of bromine, chlorine and iodine electrophiles successfully converted the difluoroenol MEM ethers to the corresponding halodifluoromethyl ketones.

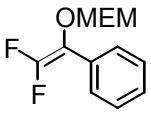
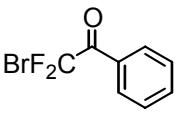
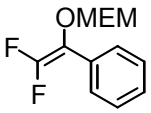
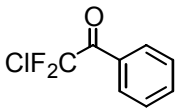
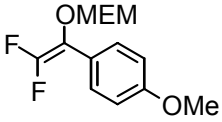
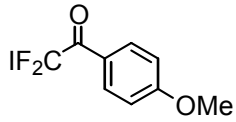
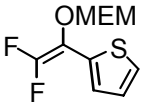
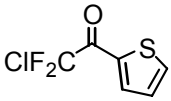
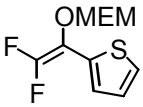
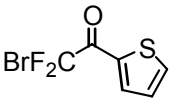
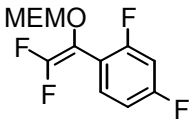
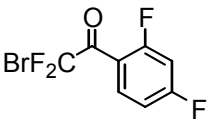
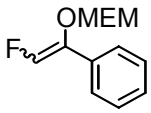
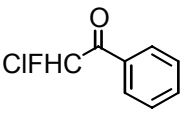
Scheme 75 shows the conditions used. The shifts of the difluoromethylene centre in the ^{19}F NMR are also shown.



Scheme 75: Observation of ketone formation with halogen electrophiles in NMR experiments

Several coupling products were then treated with various halogen electrophiles to provide the range of materials shown in **Table 8**.

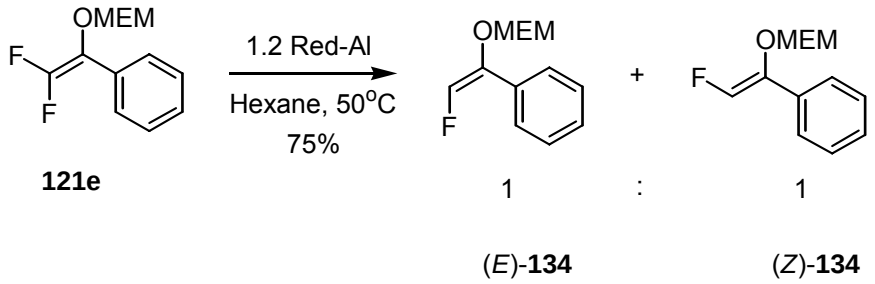
Table 8: Cleavage of difluoroenol MEM ethers with halogen electrophiles

Substrate		Conditions	Product		Yield/%
	**121e**	A		**133a**	71
	**121e**	B		**133b**	60
	**121f**	C		**133c**	65
	**121j**	B		**133d**	36
	**121j**	A		**133e**	29
	**121g**	A		**133f**	36
	**134**	B		**133g**	76

A: 1.0 Br_2, DCM, rt,16 h
B: 1.0 SO_2Cl_2, DCM, rt, 16 h
C: 1.0 I_2, DCM, rt, 16 h

All cleavages occurred smoothly at ambient temperature to afford a diverse array of halodifluoromethyl ketones. It was found that particularly fast and clean chlorinations could be achieved by the use of sulfuryl chloride, SO_2Cl_2 (see pg 99). This therefore represents a good method for accessing such species.

Styrene **134** (1:1 *E*/*Z*) was synthesised by reducing difluorostyrene **121e** with sodium *bis*(2-methoxyethoxy)aluminium hydride (Red-Al®)[102a] (**Scheme 76**).

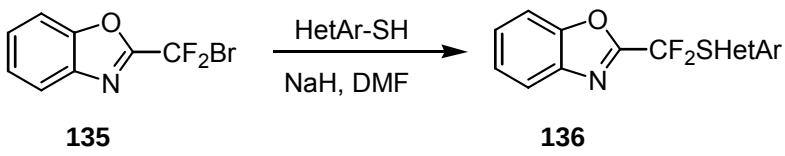


Scheme 76: Formation of monofluorostyrenes **134**

Chlorination with sulfuryl chloride was observed to occur very rapidly. In a competition reaction between styrene **121e** and monofluorostyrenes **134**, highly selective cleavage of the monofluorostyrenes was observed. This can be related to the increased stability of the initial carbocation due to the reduction in the number of inductively destabilising fluorine atoms.

α-(Heteroarylthio)-α,α-difluoroacetophenones

Recently, Dolbier and co-workers described the synthesis of a range of α-(heteroarylthio)-α,α-difluoromethyl benzoxazole derivatives **136** *via* $S_{RN}1$ methodology using (bromodifluoromethyl)-benzoxazole **135** and a range of aryl thiols (**Scheme 77**).[63a,190]



Scheme 77: Synthesis of a range of benzoxazole derivatives **136** using $S_{RN}1$ methodology

Following these initial results, the group successfully extended the methodology to difluoroacetophenone derivatives, using chlorodifluoromethyl ketones as starting materials (**Figure 15**).

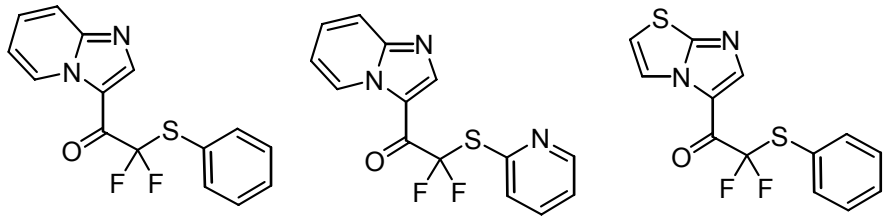
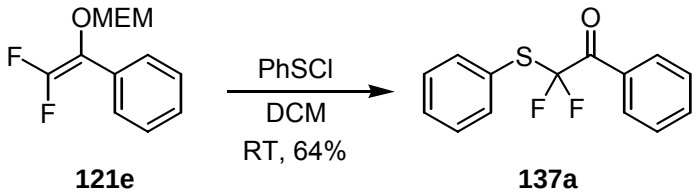


Figure 15: Difluoroketones synthesised by Médebielle

Therefore, electrophilic cleavage of the MEM enol ether with a sulfur electrophile would represent a valuable extension of the methodology. The key step is the addition of a sulfenyl halide to the enol ether.

Treatment of styrene **121e** with phenylsulfenyl chloride led to the clean formation of ketone **137a**, which could be isolated in good (64%) yield (**Scheme 78**).



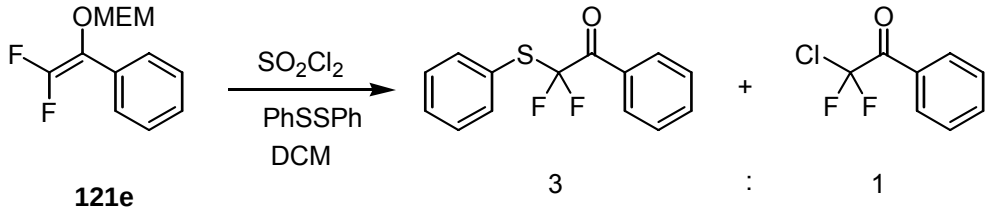
121e **137a**

Scheme 78: Synthesis of (phenylthio)difluoromethyl ketone **137a**

However, in order to avoid repetitious isolation of several heteroaryl sulfenyl chlorides, a separate method of *in situ* generation was investigated. The literature contains several methods for the synthesis of aryl sulfenyl halides, so a survey as to their simplicity and reliability was undertaken. All attempts to generate[191] phenylsulfenyl halides using NCS/PhSH,[192] Br_2/PhSH[193] or Br_2/PhSSPh[194] failed in

my hands. Two of the aforementioned procedures still require the use of an aryl thiol each time a cleavage reaction is attempted. In a much more attractive method, Suzuki *et al.* described the use of disulfides[195] and sulfuryl chloride (SO_2Cl_2) as a facile and rapid method for sulfenyl chloride production at room temperature.[196] Tsanaktsidis has also used this method for the synthesis of more complex heteroaryl sulfenyl chlorides.[197] Tsanaktsidis also described the addition of catalytic amounts of pyridine in order to increase the rate of formation of the sulfenyl halide.[197]

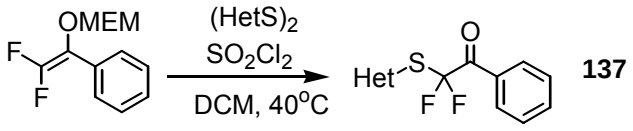
On addition of sulfuryl chloride to diphenyl disulfide at ambient temperature, an immediate red solution was produced. Addition of styrene **121e** after 30 min afforded a 75:25 ratio of (phenylthio)difluoro- and chlorodifluoromethyl ketones by NMR after stirring overnight. The presence of the chlorinated material indicated that sulfenyl chloride formation was incomplete under these conditions (**Scheme 79**).



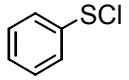
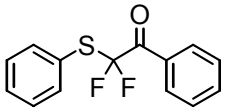
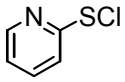
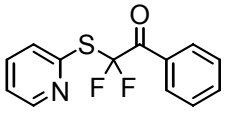
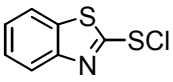
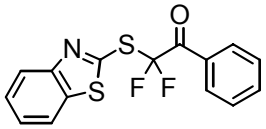
Scheme 79: Sulfenylation using sulfuryl chloride and diphenyl disulfide

Extending the initial stirring time to 1.5 hours led to the near complete conversion to phenylsulfenyl chloride, as indicated by a crude NMR of the reaction mixture after addition of styrene **121e**. Purification afforded α-(phenylthio)-α,α-difluoro-acetophenone **137a** in good (76%) yield. The procedure was repeated using dipyridyl disulfide and dibenzothiazolyl disulfide to produce the ketones shown in **Table 9**.

Table 9: Synthesis of some (α-heteroarylthio)difluoromethyl ketones



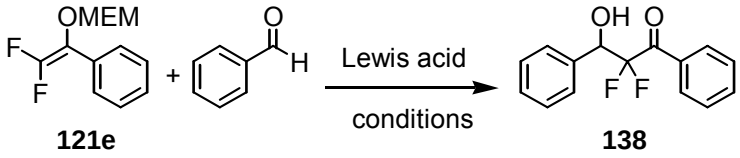
137

HetS-Cl	Product		Yield/%
		**137a**	76
		**137b**	48
		**137c**	60

Possibility of Mukaiyama-type aldol condensations

A valuable extension to the above methodology would be the possibility of direct aldol condensation reactions of the MEM enol ether linkage with aldehydes. This is a particularly important option for fluorinated carbohydrate synthesis (see Section 2.2.4). In order to investigate briefly the possibility of such a transformation, styrene **121e** was treated with benzaldehyde in the presence of Lewis acids at varying temperature. **Table 10** shows the results.

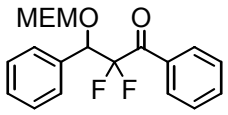
Table 10: Attempted aldol condensation of styrene **121e** with benzaldehyde



121e **138**

Lewis Acid	Solvent	Temp./^{o}C	Products
$ZnCl_2$	THF	-20	**121e**
$TiCl_4$	DCM	-78	**121e**
$TiCl_4$	DCM	-40	**138, 139**[a]
$TiCl_4$	DCM	-20	**138**, **139**[a]

[a] An unknown aldol product was also present but could not be identified by NMR or MS



139

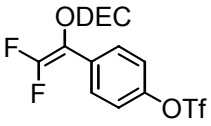
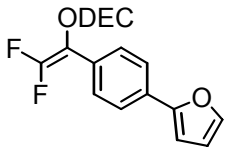
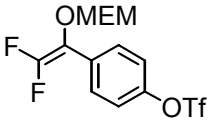
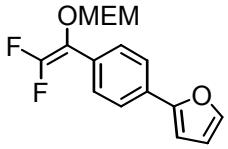
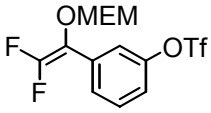
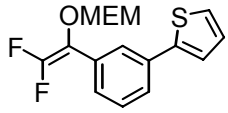
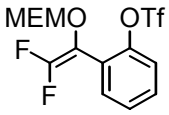
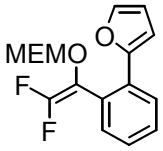
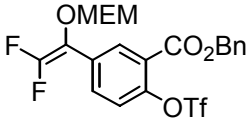
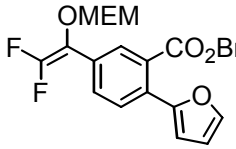
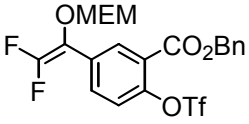
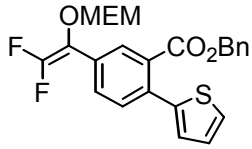
These initial results indicate that the MEM enol linkage can be used for aldol reactions with benzaldehyde. Zinc(II) chloride was found to be insufficiently Lewis acidic to promote the reaction. On the other hand, titanium(IV) chloride successfully promoted the reaction, as long as the reaction temperature was controlled. The recovery of starting material at -78°C suggests that the difluoroenol or difluoroenolate has reduced nucleophilicity, as previously observed.[99,198]

Generation of biaryl scaffolds using a second coupling protocol[199]

With the aryl triflates **121a-d** in hand, attempts were made to utilise the C-O bond of the triflate as a second coupling site.

Initial coupling of aryl triflate **95e** with 2-(tributylstannyl)furan was attempted using a catalytic amount of lithium chloride (30 mol%) to assist in the transmetallation step,[111d] but work-up and analysis of the mixture after 24 hours indicated a modest 65% conversion to the product. Separation of the furan **139** from the starting triflate proved to be difficult, so an attempt was made to drive the reaction to completion. Repetition of the reaction with a three-fold excess of lithium chloride and extending the reaction time to 72 hours, failed to improve the relative progress of reaction, with only an 89% conversion being achieved. These initial results indicated that the use of lithium chloride was detrimental to the reaction rate. In accordance with this observation, reaction with 1.5 equivalents of 2-(tributylstannyl)furan in the presence of *tetrakis*(triphenylphosphine)palladium(0) in THF resulted in the fast, clean reaction to give furan **139**. Purification afforded furan **139** in good (60%) yield (**Table 11**). **Table 11** shows the results with coupling of other triflate derivatives.

Table 11: Stille couplings of aryl triflates

Aryl Triflate	Conditions	Product	Yield/% (NMR)
	**95e** A		**138** 60
	**121a** B		**139a** 86
	**121b** B		**139b** 71 (89)
	**121c** B		**139c** 0 (0)
	**121d** C D E B B[a] F		**139d** - - - 96 82 62 (<5) (10) (20)
	**121d** B		**139e** 85 (98)

A: 5% $Pd(PPh_3)_4$, 1.5 eq. stannane, DMF, 80°C; B: 5% $PdCl_2(PPh_3)_2$, DMF, 85°C; C: 5% $PdCl_2(PPh_3)_2$, dioxane, 85°C; D: 5% Pd(0), 20% PPh_3, 10% CuI, DMF, 60°C; E: 5% Pd(0), 20% PPh_3, toluene, 85°C; F: 5% $Pd(OAc)_2$, 10% PPh_3, DMF, 85°C; [a] As for B except that 3.0 eq. LiCl was added.

Aryl triflate **121a** was coupled with 2-(tributylstannyl)furan under standard Stille conditions. Reaction at 90°C in DMF, followed by flash column chromatography allowed the isolation of furyl adduct **139a** in good (86%) isolated yield, with complete consumption being achieved to a single fluorinated material by ^{19}F NMR. Coupling of

triflate **121b** with 2-(tributylstannyl)thiophene was also successful affording thiophene **139b** in good (71%) yield. However, attempted coupling with triflate **121c** using 2-(tributylstannyl)furan resulted in the recovery of starting material; no furan **139c** was observed.

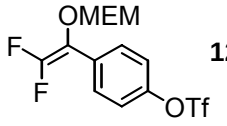
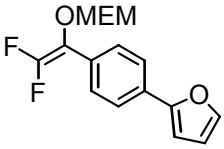
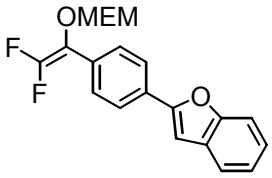
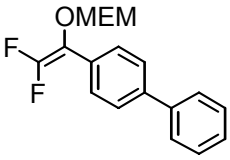
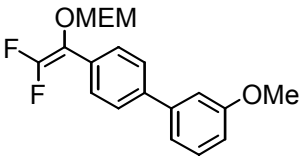
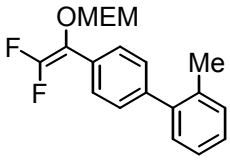
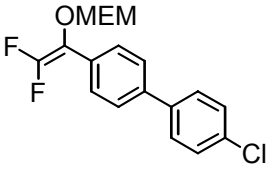
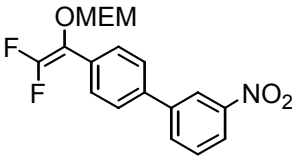
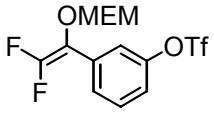
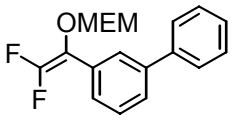
Of particular note was the reaction of triflate **121d** with 2-(tributylstannyl)furan to afford highly UV active furan **139d**. Use of a palladium(0) catalyst with triphenylphosphine (1:4 ratio) led to the clean coupling in 18 hours. Upon changing to dichloro*bis*(triphenylphosphine)palladium(II), an even more rapid (3 minutes) reaction was observed. A similar observation was made in the presence of lithium chloride. In addition, palladium(II) acetate with triphenylphosphine (ratio 1:2) could also be used as the catalyst system.

It was also noted that no appreciable reaction was observed when DMF was replaced with dioxane or toluene; instead, palladium black was precipitated due to catalyst decomposition. Jutand and co-workers have indicated that such a solvent medium effect is possibly due to the formation of intermediate complexes with differing reactivity and stability profiles.[200] Similar reactivity was shown with 2-(tributylstannyl)thiophene and thiophene **139e** could be isolated in 85% yield after a short (10 minutes) reaction time.

Although Stille couplings are prominent in the literature, the availability, and moreover, the toxicity of both the reagents and by-products has led to the use of boronic acids as alternative nucleophiles.[201]

Several literature sets of conditions were used in order to optimise the reaction.[202] **Table 12** shows the results with a range of boronic acids.

Table 12: Coupling of aryl triflates with aryl boronic acids

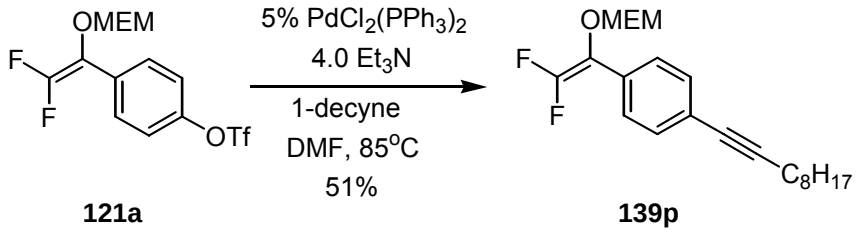
Aryl Triflate	Conditions	Product	Yield/% (conv)
 **121a**	A		**139a** 49
121a	A B		**139f** 51 80
121a	C		**139g** 67
121a	A B C		- (15) **139h** 73 40
121a	A B		**139j** 84 65
121a	A		**139k** - (50)
121a	A C		**139m** - (0) - (0)
 **121b**	A B		**139n** 48 (87) 67

A: 5% $PdCl_2(PPh_3)_2$, 4.0 Et_3N, 2.0 $ArB(OH)_2$, DMF, 90°C
B: 8% $Pd(PPh_3)_4$, 1.5 K_3PO_4, 1.5 $ArB(OH)_2$, DMF, 85°C
C: 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, 1.5 K_3PO_4, 1.1 $ArB(OH)_2$, 1,4-dioxane, 85°C

Attempts to employ the conditions described by Chen (conditions A) were found to be only moderately successful over the range of boronic acids tested. Reaction with electron-rich aryl units led to full conversions to a single product by ^{19}F NMR (see **139a**, **139f**, **139j**). Electron-deficient aryl units gave uniformly poor conversions (see **139h**, **139k**, **139m**). 3-Nitrophenylboronic acid represented the lowest level of reactivity and starting material was recovered in all trials.

The second set of conditions (B) was far more successful; much more rapid couplings were observed to afford the products in good (65-80%) isolated yields. The conditions described by Oh-e *et al.* (conditions C) also proved successful in converting triflate **121a** into biphenyl **139h** bearing a *meta*-methoxy substituent. Once again, 3-nitrophenylboronic acid failed to react.

In an extension to the substrates able to undergo coupling to aryl triflate **121a**, a Sonogashira procedure was attempted with 1-decyne. Although no reaction occurred under standard conditions, decyne **139p** could be isolated in moderate (51%) yield under the conditions described by Chen (**Scheme 80**).[202]



121a **139p**

Scheme 80: Successful Sonogashira coupling

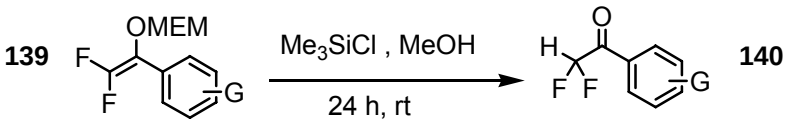
Electrophilic cleavage of biphenyl derivatives

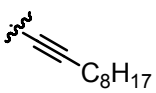
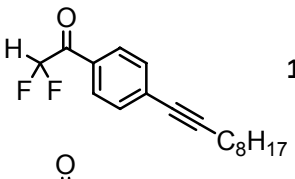
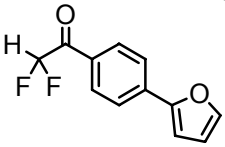
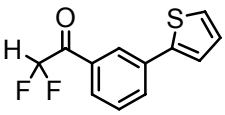
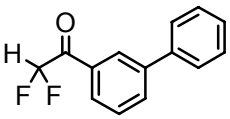
Having accomplished a second coupling to afford several biphenyl derivatives, the MEM enol ether linkage was cleaved with both protic, halogen and sulfur electrophiles to afford a range of biphenyl-ethanones.

Protiolysis

Cleavage of a range of enol ethers occurred cleanly in methanol in the presence of chlorotrimethylsilane and pure α,α-difluoroketones **140a**-**d** could be isolated after filtration through a short plug of silica (**Table 13**).

Table 13: Protiolysis of difluorovinyl MEM enol ethers



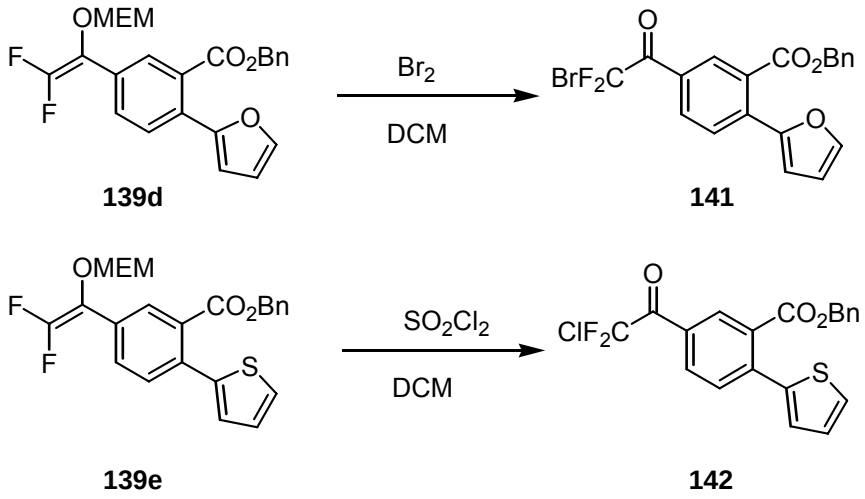
G	Product	Yield/%
		**140a** 78
		**140b** 60
		**140c** 62
		**140d** 53

Other cleavage reactions

Cleavage of some biphenyl derivatives was also attempted with chlorine, bromine and sulfur electrophiles.

Addition of one equivalent of bromine to a solution of furan **139d** in DCM led to a major product presumed to be bromoketone **141**. However, several side products were present and these could not be removed by column chromatography.

A similar observation was made when one equivalent of sulfuryl chloride was added to a solution of thiophene **139e** in DCM. A major product was observed by ^{19}F NMR, presumed to be chloroketone **142**, but trace impurities could not be removed (**Scheme 81**).

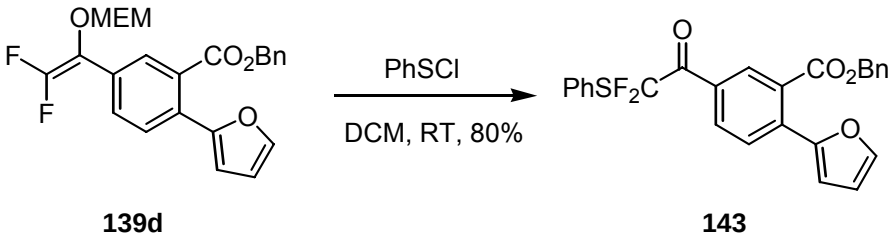


Scheme 81: Formation of functionalised halodifluoromethyl ketones

The complexity of the reaction mixtures is probably due to the high reactivity of furan and thiophene to halogen electrophiles at ambient temperatures.[203]

It should also be noted that these halodifluoromethyl ketones are difficult to purify due to their tendency to streak badly on stationary phases.

Treatment of furan **139d** with phenylsulfenyl chloride led to ketone **143** as the major product. Purification by chromatography afforded **143** in good (80%) yield, although several minor side-products could not be removed (**Scheme 82**).



139d **143**

Scheme 82: Synthesis of functionalised ketone **143**

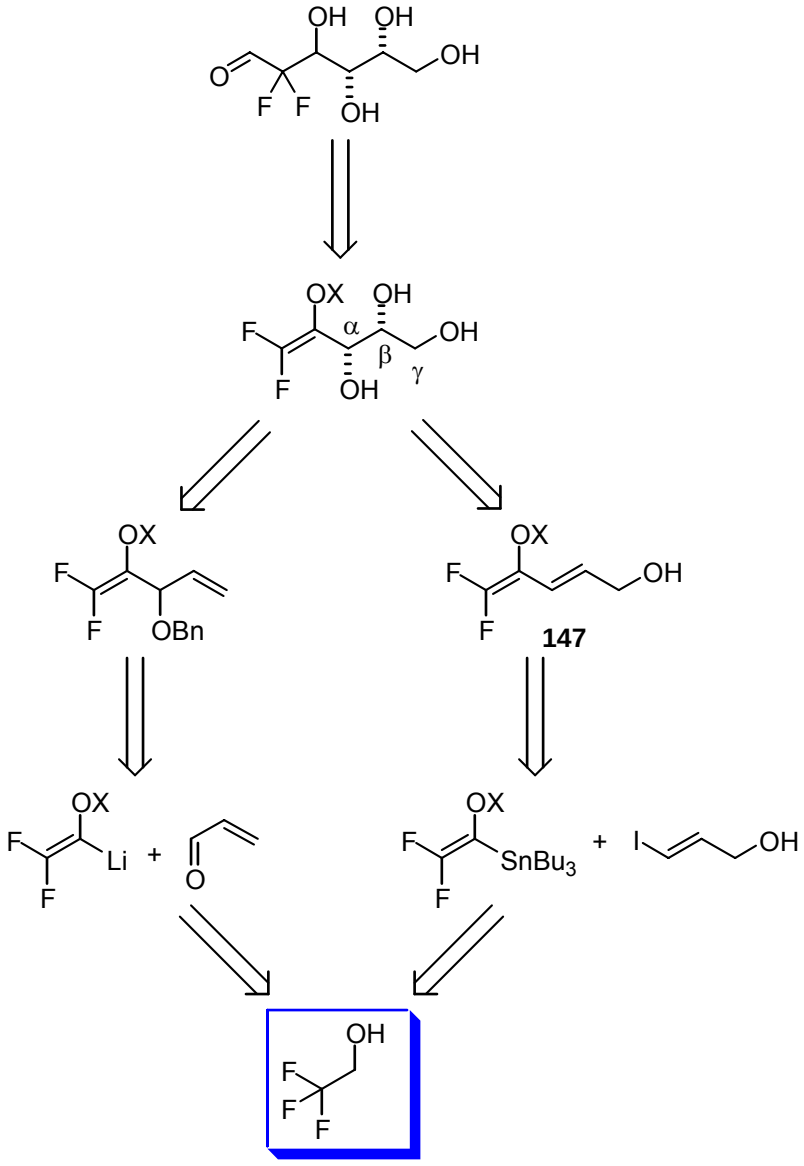
2.1.7 Summary of this approach

This research has demonstrated that a stable difluoroenol stannane can be taken through two consecutive coupling reactions followed by cleavage with a range of electrophiles to afford a range of aryl difluoromethyl ketones.

2.2 Building-block Approach to Fluorinated Carbohydrates

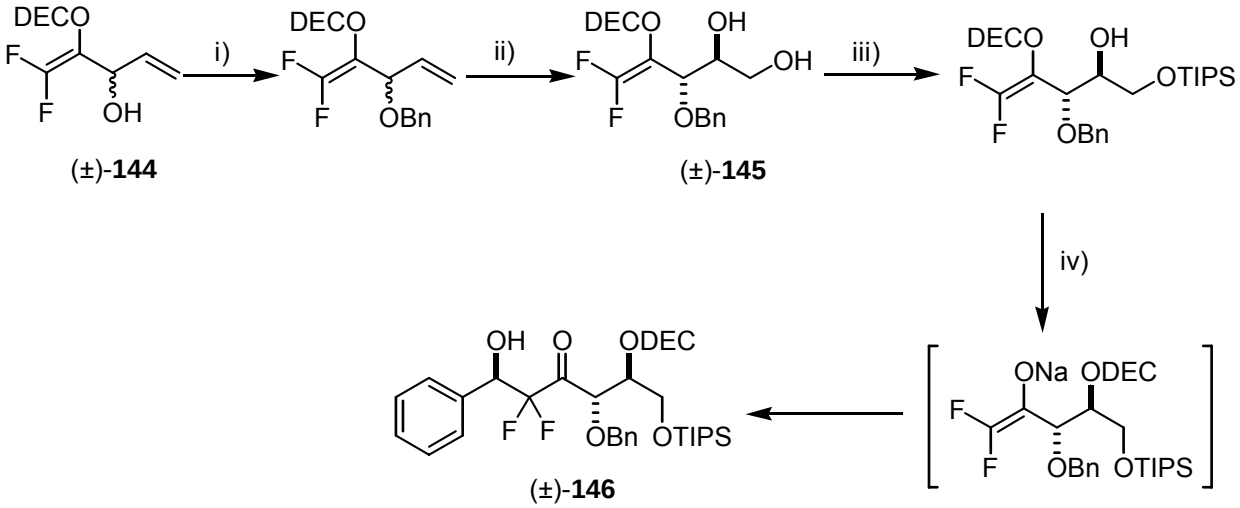
Regioselective and enantioselective dihydroxylation of a suitably functionalised fluorinated diene unit would represent a valuable methodology to highly oxygenated fluorinated molecules. Fluorinated carbohydrates represent possible targets.

Retrosynthetic analysis of 2-deoxy-2,2-difluorohexose analogues indicates two possible strategies (**Scheme 83**).



Scheme 83: Aldohexose synthesis from trifluoroethanol

Balnaves has studied the left-hand approach in which disconnection of the β- and γ-hydroxyl groups affords known allylic alcohol **144**.[98b] Benzylation and dihydroxylation of the non-fluorinated double bond affords diol **145** which can be orthogonally protected and taken through a transacylation/aldol reaction sequence affording a protected sugar analogue precursor **146** (**Scheme 84**).[172]

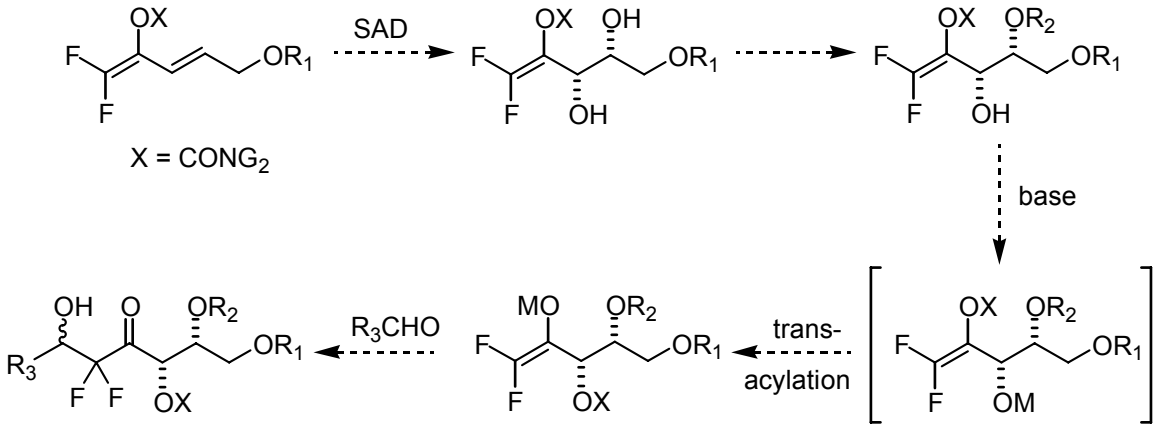


(±)-**144** (±)-**145** (±)-**146**

Reagents and Conditions: i) NaH, BnBr, DMF; ii) 0.05 mol% OsO_4, 2.5 eq. NMO, *t*-BuOH, RT, 16 h, 78%; iii) 1.1 eq. TIPS-Cl, 2.5 eq. imidazole, DCM, 3 d, 76%; iv) 1.0 eq. NaH, -10^{o}C, THF, 4 h then benzaldehyde, 16 h

Scheme 84: Balnaves's synthesis of aldol **146**

Unfortunately the route suffers from lack of control of absolute stereochemistry given the racemic nature of the allylic alcohol **144**. An alternative route is to perform a regio-[231] and enantioselective Sharpless Asymmetric Dihydroxylation[204] on a 5,5-difluoropenta-2,4-dienol fragment **147** (see the right-hand approach in **Scheme 83**). With suitable hydroxyl group protection, a transacylation reaction (in the case of a carbamate-protected enol) would release a metal enolate capable of condensation with suitable aldehyde electrophiles (**Scheme 85**).

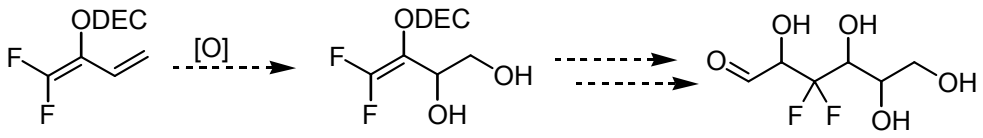


Scheme 85: Approach to hexoses using carbamate protection

Furthermore, dienol **147** can also potentially undergo asymmetric epoxidation[232] and aminohydroxylation,[233] which would deliver products with potential for transformation into sugars[232a] or aminosugars.

2.2.1 Asymmetric dihydroxylation of conjugated fluorinated dienes

Diene **99e** was chosen as the initial substrate for testing the reactivity towards osmylation. The potential diol **148** had been targeted for hexose synthesis (**Scheme 86**).



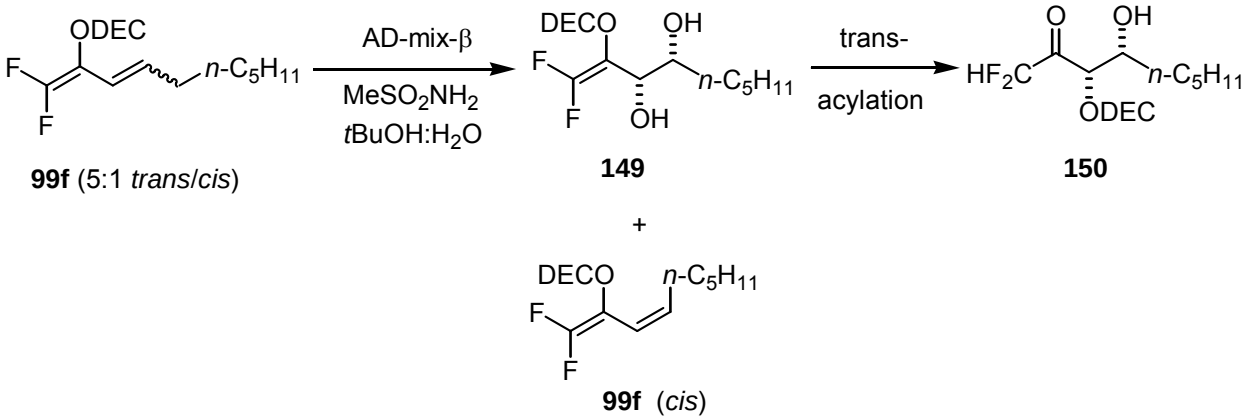
99e **148**

Scheme 86: Potential formation and use of diol **148**

When diene **99e** was subjected to racemic dihydroxylation conditions (0.4 mol% Os, 3 mol% quinuclidine, 3 eq. K_2CO_3, 3 eq. $K_3Fe(CN)_6$, 1:1 v/v ^tBuOH-H_2O), ^{19}F NMR

indicated a slow conversion (27% after 3 hours) to a material consistent with diol **148** (δ_F -93.62, d, ^2J 50.1 Hz; -105.44, dd, ^2J 50.1, $^4J_{HF}$ 4.0 Hz). However, repetition led to an inconsistent, low (6%) conversion after 21 hours. Attempts to increase the rate of turnover, by addition of methanesulfonamide to possibly aid osmate ester hydrolysis[204] were unsuccessful. Attempts at Sharpless Asymmetric Dihydroxylation using AD-mix-β resulted in recovery of the starting material, even after extended (75 hours) reaction times.

Upon changing to alkyl-substituted diene **99f** (using AD-mix-β), an immediate change was observed, with the characteristic change from orange to yellow, as the ferricyanide is reduced to ferrocyanide. TLC after 19 hours indicated the near complete consumption of starting material. However, column chromatography afforded a poor (19%) yield of the diol **149** (**Scheme 87**). Traces of *cis* **99f** were also observed in the crude ^{19}F NMR spectrum, confirming the lower reactivity of *cis* dienes with the $(DHQD)_2PHAL$ ligand.[204] Facial selectivity is represented consistent with the model proposed by Sharpless.[204]

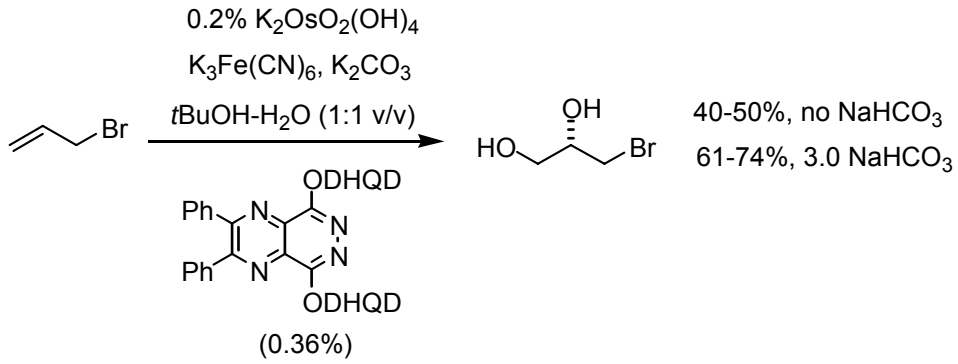


99f (5:1 *trans*/*cis*) **149** **150** **99f** (*cis*)

Scheme 87: Dihydroxylation of isomeric 1,1-difluorononona-1,3-dienes **99f**

Repetition of the reaction with crude ^{19}F NMR analysis indicated that *in situ* transacylation to several ketones (presumably *via* **150**) had occurred under the basic (pH 12.2) reaction conditions.

Sharpless has described the formation of epoxides upon attempted dihydroxylation of allylic halides. The use of a sodium bicarbonate buffer, to reduce the pH to *ca.* 10.3 allowed the shutdown of this undesired pathway (**Scheme 88**).[204]

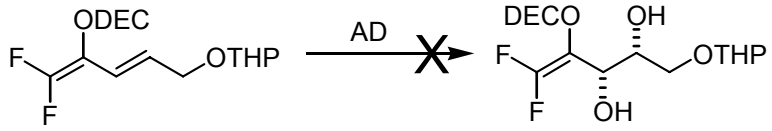


Scheme 88: Buffering of an AD reaction with $NaHCO_3$

In accordance with these observations, the addition of three molar equivalents of sodium bicarbonate (1:1 with potassium carbonate) led to the complete shutdown of ketone formation, although the desired diol was only obtained in a low (23%) isolated yield, presumably due to problems of extraction from the aqueous phase. Attempts to increase the amount of bicarbonate to greater than six equivalents led to an extremely slow reaction, indicative of a low hydroxide concentration and consequent problems in osmium recycling.

The positive effect of the hyperconjugative π-donor effect of the alkyl group is of particular note, and indicated that electron donation to the alkene π-system, however small, results in a positive change in the reactivity profile.

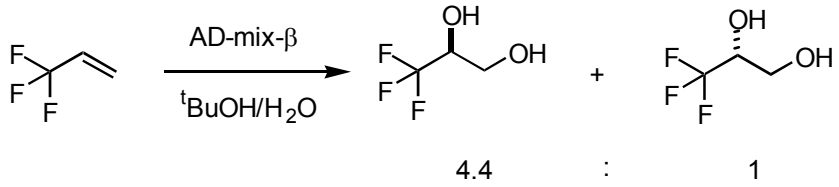
When an attempt was made to asymmetrically dihydroxylate the THP-protected allylic alcohol **99c**, none of the desired diol **151** was formed even after extended reaction times and after increasing the osmium loading to 3 mol% (**Scheme 89**).



99c **151**

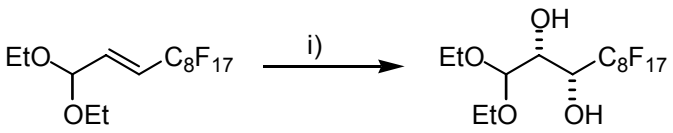
Scheme 89: Unreactivity of allylic alcohol **99c** to AD reagents

Overall, the extreme lack of reactivity of certain substrates, especially of the parent diene **99e**, suggests that subtle effects are in operation. Presumably, the reactivity of the system is in balance between the *–I* inductive effects of the two fluorine atoms and the carbamoyloxy substituent as well as polarisation effects caused by the presence of the vinylic fluorine atoms.[205] The ability of a π-donor to restore the reactivity is not in itself enough evidence to suggest simple fluorine atom inductive deactivation. Sharpless[206] has described the efficient AD of 1,1,1-trifluoropropene in 63% *ee*, a substrate in which *three* fluorine atoms reside *alpha* to the reactive olefin (rather than *two* residing *beta*) (**Scheme 90**).



Scheme 90: Reactivity of 1,1,1-trifluoropropene

Furthermore, Zhu and Li[207] have described a successful AD reaction (albeit at a slow rate) of an octafluoroalkyl acrolein diethyl acetal (**Scheme 91**).



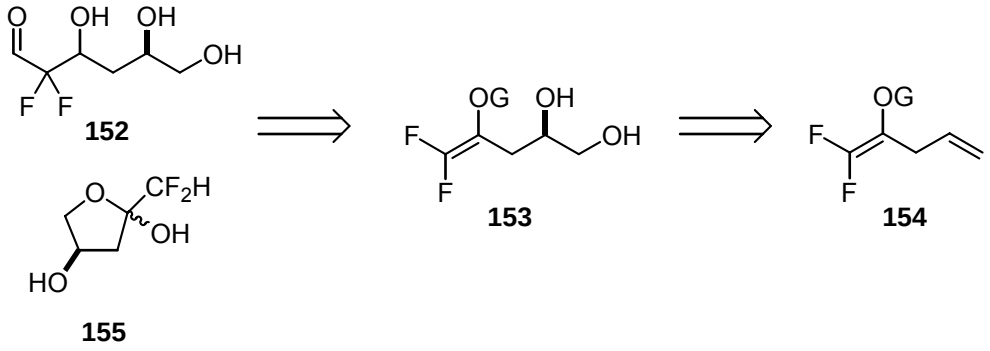
Reagents and Conditions: i) 0.5% $K_2OsO_2(OH)_4$, 1.3% $(DHQ)_2PHAL$, 6.1 eq. $K_3Fe(CN)_6$, 7.3 eq. K_2CO_3, 1.05 eq. $MeSO_2NH_2$, *t*BuOH-H_2O (1:1 v/v), 4°C

Scheme 91: Successful AD of a highly electron-deficient olefin

The general lack of reactivity of difluorinated 1,3-dienes was disappointing, since we require an enantiomerically enriched triol unit in order to pursue sugar synthesis.

2.2.2 *Synthesis of 1,3-dideoxy-1,1-difluoro-D-glyceropent-2-ulofuranose*

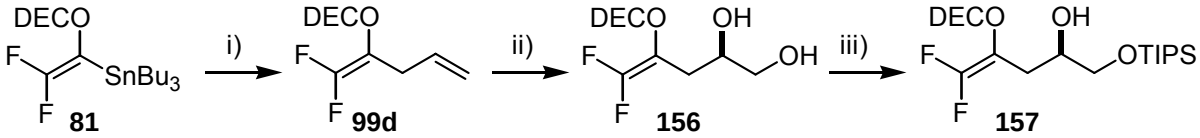
Retrosynthetic analysis of 2,4-dideoxy-2,2-difluorohexose analogues **152** is shown in **Scheme 92** and relies upon an intermediate enediol **153** which should be available from 1,1-difluoro-1,4-pentadiene **154**. Pentulose **155** was seen as an initial target to test the synthetic methodology (**Scheme 92**).



Scheme 92: Retrosynthetic analysis of target dideoxy sugars

In the first approach, the *N*,*N*-diethylcarbamoyl protecting group (G = DEC) was chosen with a transacylation step *via* a six-membered ring being the key step.

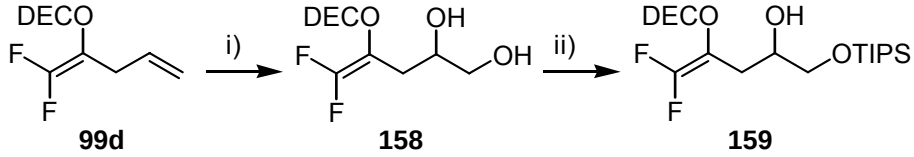
Coupling of stannane **81** with allyl bromide afforded 1,1-difluoro-1,4-pentadiene **99d**, which underwent smooth dihydroxylation with AD-mix-β to afford diol **156** in good (88%) yield on a 10 mmol scale. Regioselective protection of the primary alcohol as a silyl ether afforded alcohol **157** in quantitative yield (**Scheme 93**). The assignment of absolute stereochemistry is based upon the Sharpless model.



Reagents and Conditions: i) 2.5% $Pd_2dba_3.CHCl_3$, 20% PPh_3, 10% CuI, DMF, 50°C, 75%; ii) AD-mix-β, 3.0 $NaHCO_3$, *t*BuOH-H_2O (1:1 v/v), rt, 88%; iii) 1.0 TIPS-Cl, 1.1 imidazole, DMAP (cat.), DCM, rt, 100%.

Scheme 93: Synthesis of alcohol **157** from stannane **81**

In order to determine the extent of asymmetric induction, the diene **99d** was taken through a racemic dihydroxylation process using quinuclidine as an achiral donor nitrogen ligand. Racemic diol **158** was formed in moderate (49%) yield. Protection of the primary alcohol as a TIPS ether afforded racemic alcohol **159** (**Scheme 94**).



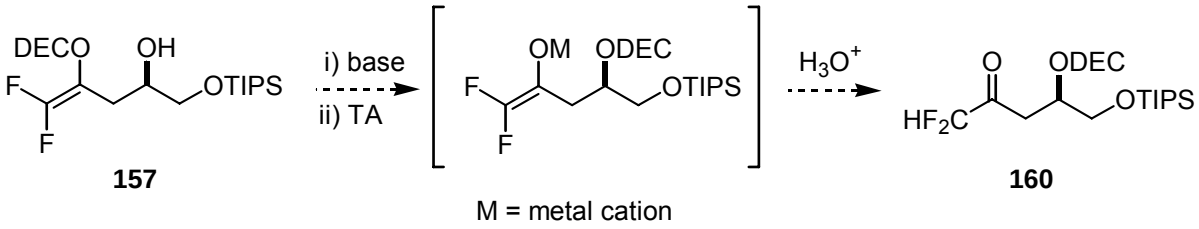
Reagents and Conditions: i) 0.8% $K_2OsO_2(OH)_4$, 3.0 eq. $K_3Fe(CN)_6$, 3.2 eq. K_2CO_3, 1.0 eq. $NaHCO_3$, 3.8% quinuclidine, *t*BuOH-H_2O (1:1 v/v), rt, 49%; ii) 1.0 eq. TIPS-Cl, 1.1 eq. imidazole, DMAP (cat.), DCM, rt, 95%.

Scheme 94: Preparation of racemic alcohol **159**

Alcohols **157** and **159** were analysed by chiral HPLC using a Chiralcell OD column. The racemic mixture was found to be a 50:50 mixture of two enantiomeric alcohols, as expected (**Appendix I**). Chiral alcohol **157** was analysed and found to consist of a 95:5 mixture of two alcohols (**Appendix II**). The two HPLC traces had a perfect overlay with each other (**Appendix III**). These data therefore represented a very pleasing 95:5 *er* (90% *ee*) for the AD reaction with AD-mix-β.

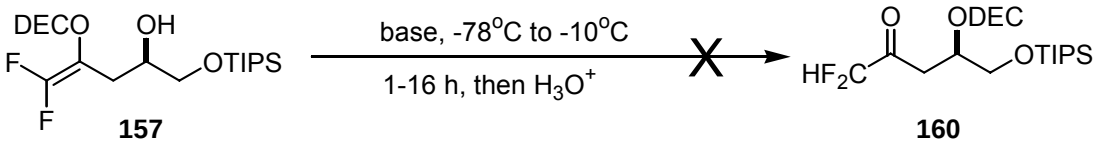
Attempted transacylation of enantiomerically enriched alcohols

With enantiomerically enriched alcohol **157** in hand, attempts were made to employ the key transacylation (TA) reaction to afford ketone **160** (**Scheme 95**). Control of this step could also allow the extension of the carbon backbone *via* aldol chemistry.



Scheme 95: Proposed transacylation from a chiral centre to afford difluoroketone **160**

Addition of *n*-butyllithium to a solution of alcohol **157** in THF at -78°C presumably led to the intermediate alkoxide, but warming to -10°C and stirring for 1 hour, followed by a protic quench, returned starting material. In order to increase the nucleophilicity of the alkoxide oxygen atom, the counterion was changed to sodium (using NaH or NaHMDS as base) or potassium (using KH, KHMDS or KO*t*Bu as base). However, in all cases, the only products observed were those resulting from protonation of the intermediate alkoxide or those resulting from decomposition (**Scheme 96**). The use of crown ethers to increase the reactivity of the resultant alkoxide was not studied.



Scheme 96: Failure to initiate enolate formation using lithium, sodium or potassium bases

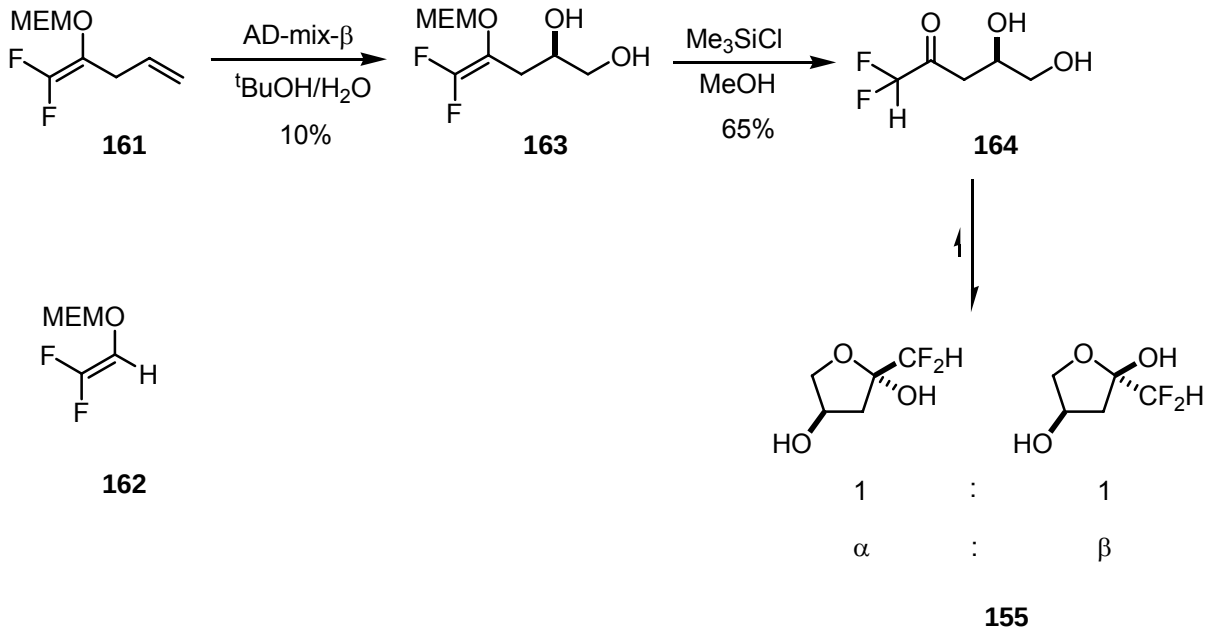
This lack of reactivity is presumably due to the requirement of transacylation through a six-membered ring, which occurs very slowly at these reaction temperatures. It should be noted that the difluoroenolates are believed to be unstable above -10°C, so higher temperatures were not investigated. Balnaves has reported a transacylation reaction of this nature, in which a benzyloxy group was present at the allylic centre (see pg 111).[172] The presence of a group at this position appears to be critical in determining the ease of the transacylation step.

Due to this disappointing result, this line of research using the carbamate (DEC) group was abandoned. A more direct approach employing a MEM protecting group strategy was therefore pursued.

Application of a MEM group protection strategy

Use of a cleavable enol derivative, such as the MEM acetal, could allow a facile synthesis of the simple dideoxydifluoropentulose **155**.

Stille coupling of the stannane **118** derived from MEM acetal **119** with allyl bromide proceeded uneventfully to afford diene **161**, along with a minor amount of the inseparable reduced product **162**. Sharpless Asymmetric Dihydroxylation proceeded surprisingly slowly (*vide ante*), although diol **163** could be isolated in 10% yield. Deprotection with chlorotrimethylsilane in methanol presumably afforded ketodiol **164**, which spontaneously cyclised to afford the target dideoxy sugar **155** as a slowly equilibrating 1.3:1 mixture of α:β anomers in 65% isolated yield (**Scheme 97**).



Scheme 97: Synthesis of pentulose **155** from penta-1,4-diene **161**

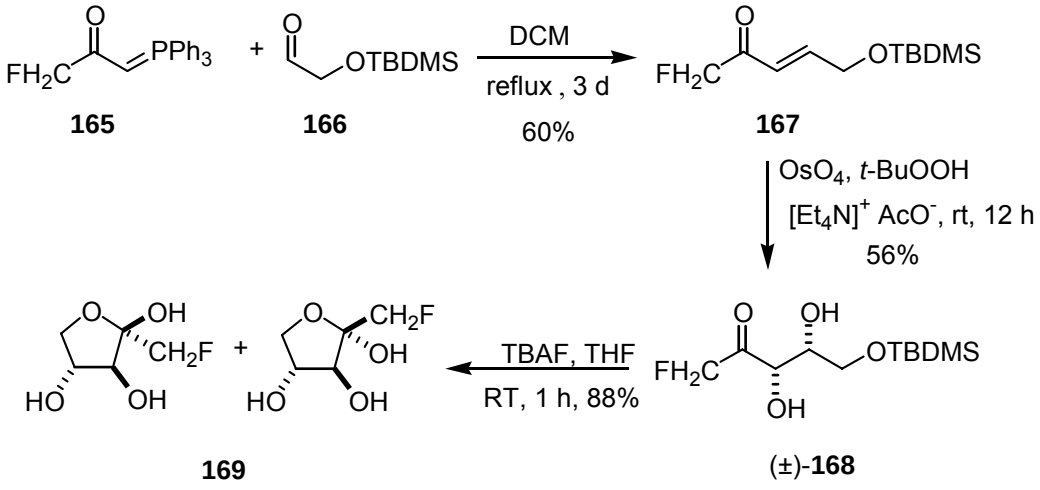
Analysis by 2D NMR techniques allowed the identification of the two anomers and the anomer stereochemistry was successfully elucidated using 1-D GOESY techniques (**Appendices IV-XII**).

This line of work successfully concluded in the synthesis of a difluorinated dideoxy-D-xylulose analogue and demonstrates the possible application of geminally difluorinated 1,4-pentadienes[208] in target synthesis. On the success of this work, a similar approach using difluorinated 1,3-pentadienes was investigated.

2.2.3 Synthesis of 1-deoxy-1,1-difluoro-D-xylulose

Introduction

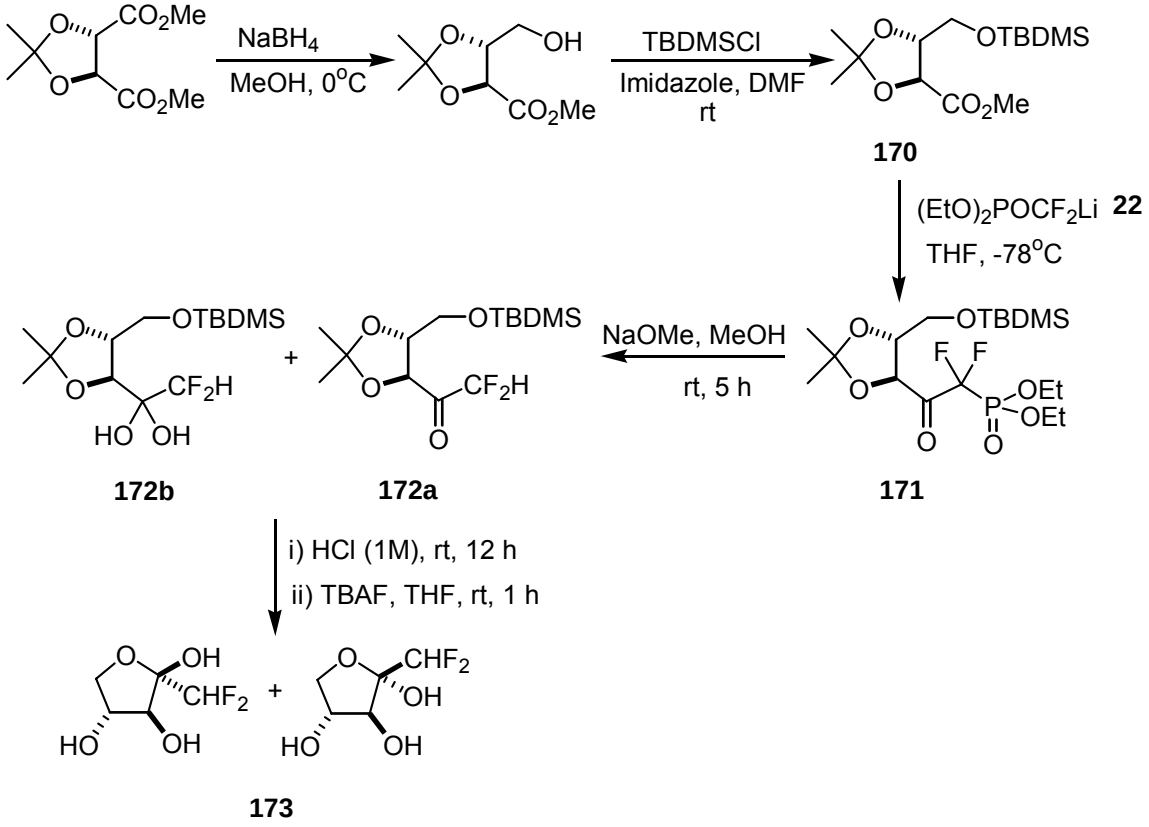
In recent years, the profile of 1-deoxy-D-*threo*-pent-2-ulose (1-deoxy-D-xylulose, 1-DX) and its phosphate (1-DXP) has risen dramatically.[209] Recent reports have shown that 1-DX/1-DXP are pivotal metabolites in the biosynthesis (catabolism) of the bacterial co-factors (vitamins) pyridoxal phosphate (PLP), thiamine pyrophosphate (TPP, vitamin B_1) and the phytyl chain of ubiquinone (co-enzyme Q) in *E.coli*.[210,211] O'Hagan and co-workers became interested in the synthesis of fluorinated analogues of 1-deoxy-D-xylulose, in the hope that they may act as anti-metabolites and hence show antibiotic behaviour against *E.coli*.[211] Both 1-deoxy-1-fluoro- and 1-deoxy-1,1-difluoro-D-xylulose were prepared (**Schemes 98** and **99**).



Scheme 98: Synthesis of racemic 1-deoxy-1-fluoro-D-xylulose (1-F-DX)

The route to 1-F-DX starts with a Wittig condensation reaction between fluorinated ylid **165** and silyl-protected hydroxyacetaldehyde **166** to afford α,β-unsaturated ketone **167**. Dihydroxylation under racemic conditions afforded racemic ketodiol **168**

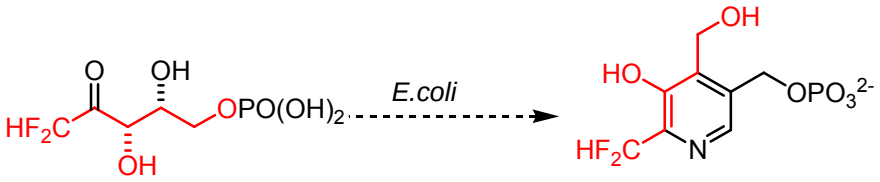
which underwent fluoride-promoted desilylation to afford pentuloses **169** as a mixture of anomers.



Scheme 99: Synthesis of 1-deoxy-1,1-difluoro-D-xylulose (1,1-F_2-DX) **173**

The route to 1,1-F_2-DX relies upon the condensation of a lithiated difluorophosphonate **22** with tartrate derivative **170** to afford phosphonate **171**. Cleavage of the C-P bond occurs under basic conditions to afford ketone **172a** (hydrate **172b** was also present). Deprotection then affords the desired xylulose **173**. The fluoroketones should have a higher reactivity in the initial imine formation step and hence an ability to decrease the amount of natural vitamin B_6 in the bacterium (thereby acting as anti-metabolites). However, the observation that the sugar existed exclusively in the cyclic furanose form inhibited the requisite phosphorylation step.

Therefore, the complete failure to inhibit the growth of *E.coli* was not surprising. However, 1-deoxy-1,1-difluoro-D-xylulose-5-phosphate (1-F_2-1-DXP, **174**) may very well show some interesting behaviour. Any identification of the biosynthesis of fluorinated vitamin B_6 would also confirm the incorporation of the entire xylulose backbone into the metabolite (**Scheme 100**).

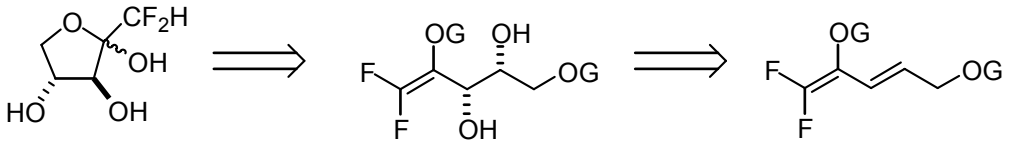


174

Scheme 100: Possible incorporation of 1-F_2-1-DXP into unnatural PNP

Retrosynthetic analysis

Disconnection of the target xylulose **173** reveals enetriol **175** as a key intermediate. This material should be available from coupling product **176** (**Scheme 101**).



173 **175** **176**

Scheme 101: Retrosynthetic analysis of target sugar **173**

Initial work (see Section 2.2.1) has shown that dienes of type **176** exhibit very low reactivities to dihydroxylation. In order to make progress, it was necessary to find a means to increase the reactivity of the olefin to the AD reagents.

Enhanced AD reactivity of para-methoxybenzoate (pMBz) esters of allylic alcohols[212]

The work of Corey has demonstrated that the use of certain hydroxyl protecting groups for allylic alcohols can dramatically improve their reaction with the AD-mixes. After examining several protecting groups, the *para*-methoxybenzoyl (*p*MBz, *p*-$MeOC_6H_4$) group was found to give the highest *ee*'s and the lowest degree of acyl transfer during the reaction. Corey postulated that the ligand forms a binding pocket in which the osmium reagent docks preferentially onto one of the nitrogen centres, affording a catalyst within a well-defined chiral environment (**Figure 16**).

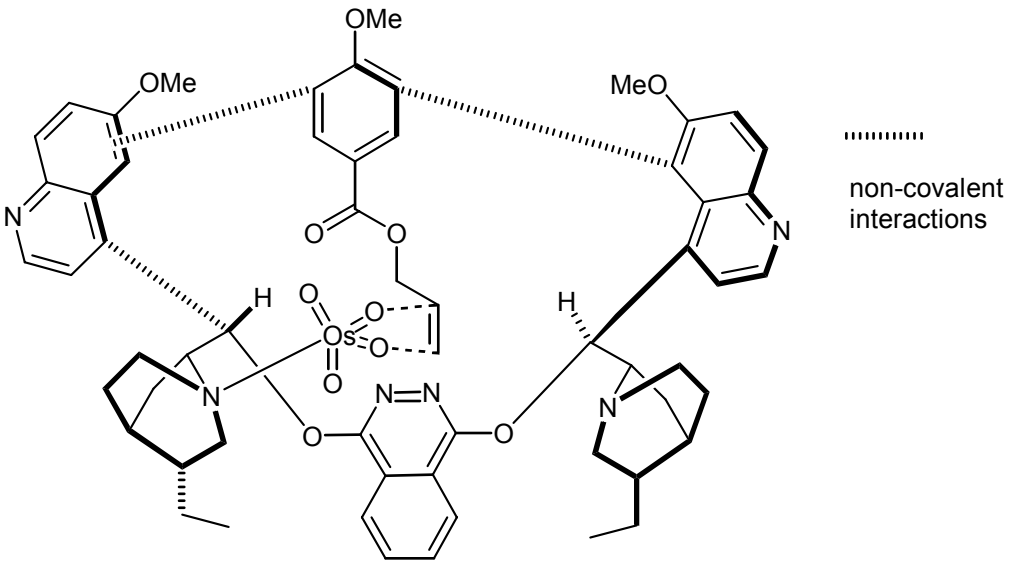


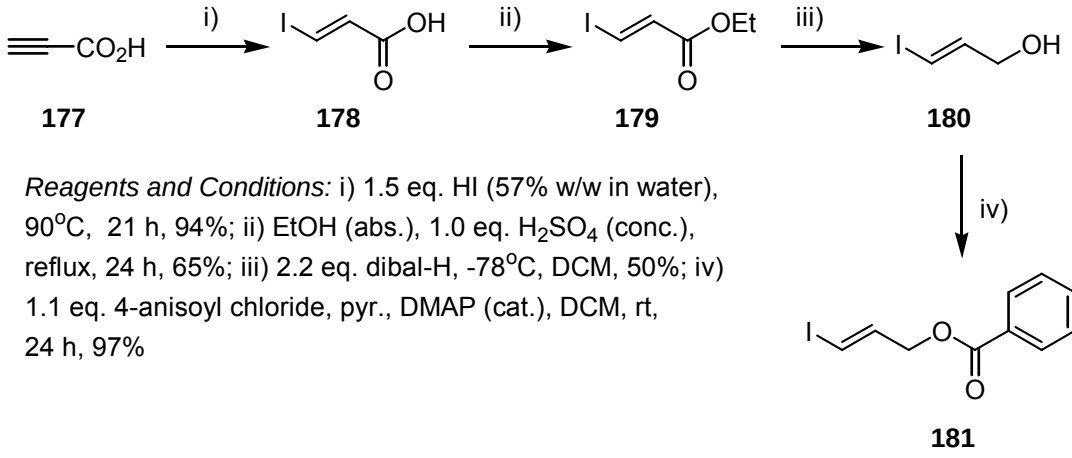
Figure 16: Binding model explaining enhanced reactivity of *para*-methoxybenzoate esters of allylic alcohols to AD reagents

One can perceive that the substrate enters the cavity, reacts with the complexed osmium reagent to form the osmate ester, which undergoes either intra- or extracavity hydrolysis (assisted by methanesulfonamide) to the diol. The recycled osmium reagent then re-enters the cavity and re-forms the activated osmium catalyst. It is therefore important that the ratio of ligand to osmium catalyst is greater than one

(2-3 fold in general) in order to guarantee a complexed osmium catalyst. Of course, the whole idea relies on the premise that the substrate can enter the cavity and that the olefin reacts immediately, before having an opportunity to diffuse. If the second case is false, then the reactivity will be extremely low requiring a higher catalyst concentration and/or longer reaction times.

Corey suggested that if one could attach a group to the substrate with the ability to participate in π-π stacking with the 4-methoxyquinoline "walls" of the ligand, one would increase its reactivity, presumably by increasing the longevity of the olefin within the vicinity of the osmium catalyst.

In order to test this theory, iodoester **181** was synthesised in four steps from propiolic acid **177** (**Scheme 102**).



177 **178** **179** **180** **181**

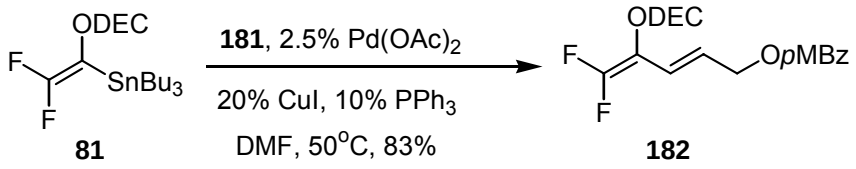
Reagents and Conditions: i) 1.5 eq. HI (57% w/w in water), 90°C, 21 h, 94%; ii) EtOH (abs.), 1.0 eq. H_2SO_4 (conc.), reflux, 24 h, 65%; iii) 2.2 eq. dibal-H, -78°C, DCM, 50%; iv) 1.1 eq. 4-anisoyl chloride, pyr., DMAP (cat.), DCM, rt, 24 h, 97%

Scheme 102: Synthesis of iodoester **181**

Addition of aqueous hydriodic acid across the acetylene unit occurred smoothly upon heating in an Ace® tube at 90-95°C for 21 hours. Washing with water and then with light petroleum afforded the corresponding (*E*)-3-iodopropenoic acid **178** as white

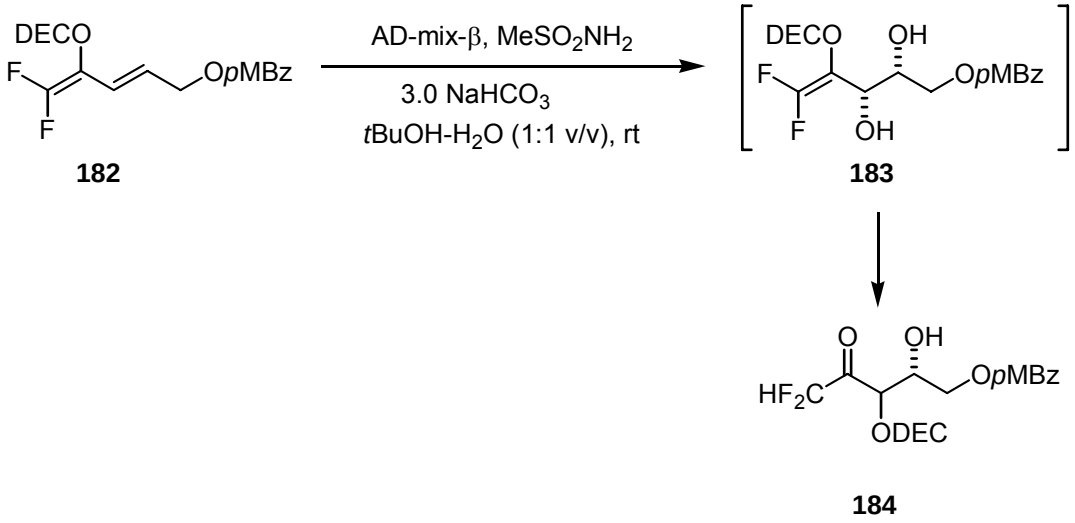
needles in 94% yield.[213] Fischer esterification using ethanol and concentrated sulfuric acid afforded the corresponding ethyl ester **179**,[213a] which underwent a double reduction to the alcohol **180** using di*iso*butylaluminium hydride.[214] Esterification to the target vinyl iodide **181** was achieved using 4-anisoyl chloride with pyridine or 2,6-lutidine as a base in the presence of 4-(dimethylamino)pyridine as a nucleophilic catalyst.

Coupling with stannane **81** was attempted using the previously optimised conditions, and gratifyingly ester **182** could be isolated in good (83%) yield (**Scheme 103**).



Scheme 103: Synthesis of AD substrate bearing a *p*MBz group

Subjecting **182** to the usual buffered AD conditions led to an immediate difference in colour of the AD mix, as previously observed with the pentyl derivative. After stirring for 5 days, TLC indicated near complete consumption of the starting material and the production of a more polar compound. ^{19}F NMR indicated that most of the starting material had been consumed, but no signals corresponding to the expected diol **183** were present. Instead, several sets of AB signals were observed indicating that any diol intermediate formed had undergone transacylation under the basic (pH 10.3) conditions to afford a mixture of difluoromethyl ketones **184** (**Scheme 104**).



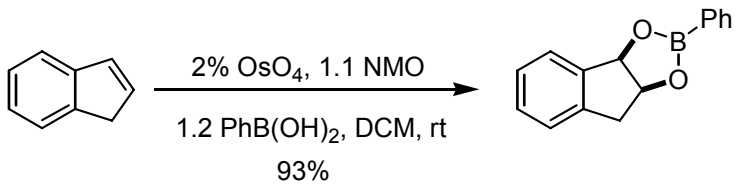
Scheme 104: Attempted AD of dienyl ester **182** using AD-mix-β

It was deduced that the *p*MBz group had indeed increased the reactivity of the olefin, though it is still extremely unreactive.[215] The presence of several ketones indicates that the resultant enantiomerically enriched ketone also underwent partial epimerisation at the α-carbon, and scrambling of the *N,N*-diethylcarbamoyl group had also occurred, leading to at least four ketones.

Unfortunately, all attempts to curtail the side-reaction failed; an increase in sodium bicarbonate buffer had no effect while an increase in osmium loading led to a slightly faster reaction, though ketones still predominated. The use of 3 mol% catalyst (in conjunction with 1 mol% chiral ligand), with interruption of the reaction allowed the observation of diol, though ketone contamination was still significant. It was apparent that the diol underwent transacylation at a much faster rate than it underwent dihydroxylation, meaning that the desired diol would never be isolated in good yield by this method.

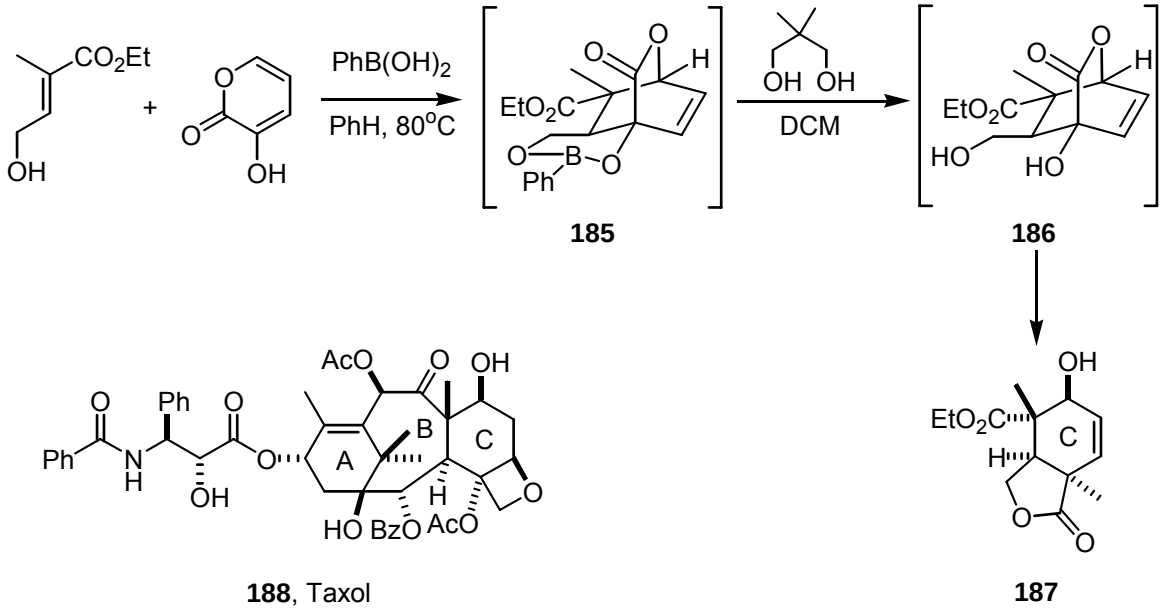
Attempts to trap the diol intermediate

In order to be able to secure the diol intermediate, a method was required that could trap the diol *in situ*. Narasaka has described the use of boronic acids as trapping reagents during dihydroxylation reactions. The method uses Upjohn conditions (NMO as re-oxidant) with phenylboronic acid in slight excess (**Scheme 105**).[216]



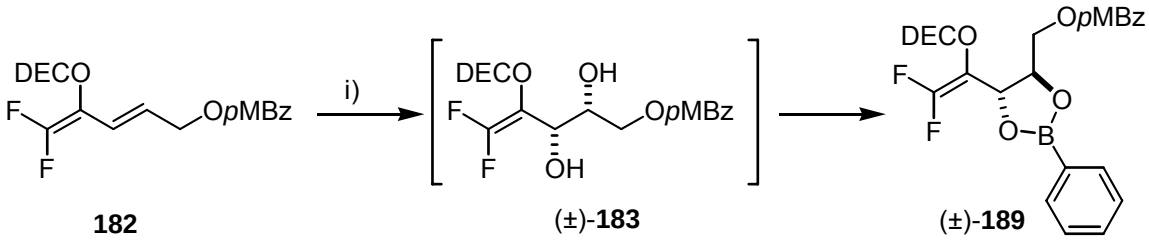
Scheme 105: Formation of a boronate ester *in situ* from indene

Crystalline boronate ester products of this type are able to undergo deborylation using sodium peroxide or more interestingly glycol exchange using neopentyl glycol in DCM under neutral conditions. Nicolaou and co-workers described the synthesis of boronate ester **185** which underwent glycol exchange with neopentyl glycol to form diol **186** *in situ*, which rearranged to bicyclic lactone **187**.[217] This was used to construct the C ring of Taxol **188** (**Scheme 106**).



Scheme 106: Glycol exchange of a boronate ester

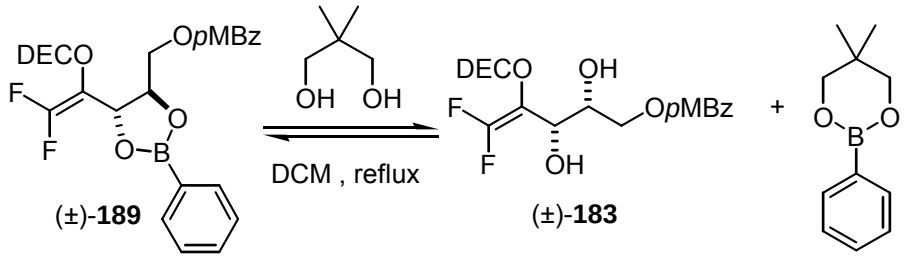
Subjecting ester **182** to Narasaka's modified dihydroxylation conditions (1.5 eq. phenylboronic acid present) cleanly transformed the intermediate racemic diol **183** to a product consistent with the boronate ester **189** by ^{19}F NMR and ^{1}H NMR (**Appendix XIII**). This material, however, could not be purified by chromatographic methods (**Scheme 107**).



Reagents and Conditions: i) 3.0% $K_2OSO_2(OH)_4$,
2.0 eq. NMO, 1.5 eq. $PhB(OH)_2$, acetone-water (4:1), rt

Scheme 107: Trapping of the diol unit as a boronate ester

When the presumed boronate ester **189** was treated with one equivalent of neopentyl glycol (2,2-dimethylpropane-1,3-diol) in DCM at ambient temperature for one hour, NMR indicated only the presence of the boronate ester **189**. Upon turning to more forcing conditions (at reflux overnight), NMR indicated the successful conversion through to diol **183** (^{19}F NMR signals agreed with those observed earlier), without any trace of ketone by-products (**Scheme 108**).

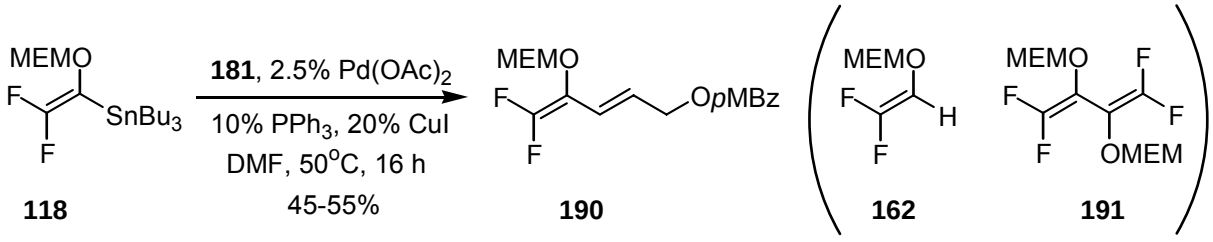


Scheme 108: Glycol exchange with neopentyl glycol to afford diol **183**

Although diol can be accessed, this line of work appeared unpromising, so it was abandoned, in favour of pursuing the use of MEM as a protecting group.

Application of a MEM protecting group strategy

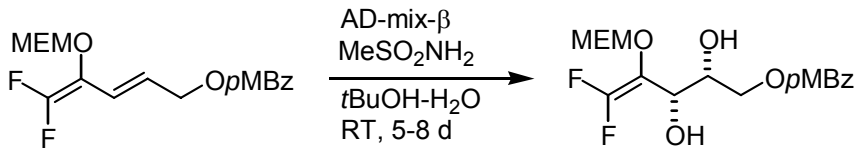
Coupling of iodoalkene **181** with stannane **118** with a Pd(II)/CuI/PPh_3 catalyst system led to the formation of diene **190** by ^{19}F and ^{1}H NMR. Trace amounts of alkene **162** and dimer **191** were also usually observed (**Scheme 109**).



Scheme 109: Stille coupling of MEM-derived difluorovinyl-stannane **118** with iodoester **181**

Dimer **191** results from reduction of the Pd(II) complex by the stannane to Pd(0). Diene **190** proved to be difficult to purify and unstable to storage. However, purification by column chromatography through a short plug of alumina afforded diene **190** in moderate (45-55%) yield. A highly coloured impurity was observed by ^{1}H and ^{13}C NMR, and isolation by fortuitous crystallisation from a chloroform solution identified the red material as the known palladium(II) complex, $Pd(PPh_3)_2I_2$.

With diene **190** in hand, exposure to AD mix-β (0.4% Os) using methanesulfonamide in a ^{t}BuOH-water mixed solvent led to the very slow conversion to diol **192** (**Scheme 110**). Several minor unidentified impurities were also observed in the crude ^{19}F NMR.



190 **192**

Scheme 110: AD of MEM-derived dienyl ester **190**

Analysis by NMR indicated that the conversion reached its maximum at *ca.* 85% after 4 days, with no change after a further 4 days. It has been noted that long reactions using the $K_3Fe(CN)_6$-K_2CO_3 oxidant can often stop due to 'deactivation', and that re-addition is required.

In order to reduce the reaction time, increases in the loading of osmium catalyst were investigated. Use of 1 mol% Os (by addition of 0.6 mol% $K_2OsO_2(OH)_4$) led to no significant increase in rate. Attempts with higher loadings were carried out by addition of the individual reagents, so as to allow an addition of extra chiral ligand and because it has also been noted that the individual reagents can out-perform the pre-

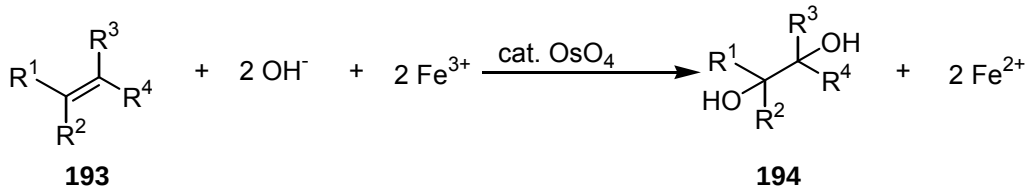
mixes. Use of 5 mol% catalyst (with 8 mol% ligand) led to high (86%) conversion after only 48 hours.

It was also noted that the presence of tributyltin halides (impurities in substrate) totally deactivated the osmium and led to the precipitation of the osmium catalyst, affording black reaction mixtures. Purification of the diol product is reasonably facile due to the polarity of this material, though methanesulfonamide must be removed prior to chromatography. Washing of the crude material with ice-cold 2M KOH removes this material as the water-soluble potassium salt. The sulfonamide can otherwise be removed by cooling the purified diol, whereby the sulfonamide crystallises out and can be removed by filtration.

Although diol **192** could be isolated, the requirement for large amounts of catalyst was undesirable due to its high cost and toxicity. Furthermore, the rate of reaction is still low (*ca.* 3 days for near complete reaction) which could possibly lead to slow decomposition of the substrate and/or product.

In order to optimise the reaction further, the first goal was to attain complete conversion of the starting material. As described above, it was found that the reaction stopped at *ca.* 90% conversion in all circumstances. However, readdition of the reoxidant combination successfully promoted the complete conversion of the remaining diene to the diol product.

At this stage, Beller and co-workers reported a paper describing a pH effect.[218] Under the present conditions, the overall reaction of a diene can be described using the following redox equation (**Scheme 111**).



193 **194**

Scheme 111: Overall equation for dihydroxylation

The desired diene **193** undergoes an overall double addition of hydroxide, mediated by osmium tetroxide, to afford the desired diol **194**. Ferricyanide (Fe^{3+}) is used as the oxidant.

As written, two hydroxide ions are consumed per turnover during the reaction. The consequence of this is that the pH drops during the reaction causing a reduction in the rate of recycling of the osmium. The authors showed how the pH dropped rapidly from 12.2 to *ca.* 11.0 with a concomitant 40% conversion within one hour (using *trans*-5-decene), before the rate of change of pH lowered significantly, requiring a further 33 hours to reach 100% conversion. The same reaction was complete within 1.7 hours when the pH was maintained at 12.0 throughout.

In order to study this dramatic effect more closely for our system, the pH was monitored during an attempted racemic dihydroxylation. Aqueous sodium hydroxide (1M) was added at such time that the pH had dropped below *ca.* 11.0. A representation of the data obtained is shown below and qualitatively confirms Beller's quantitative observations (**Figure 17**).

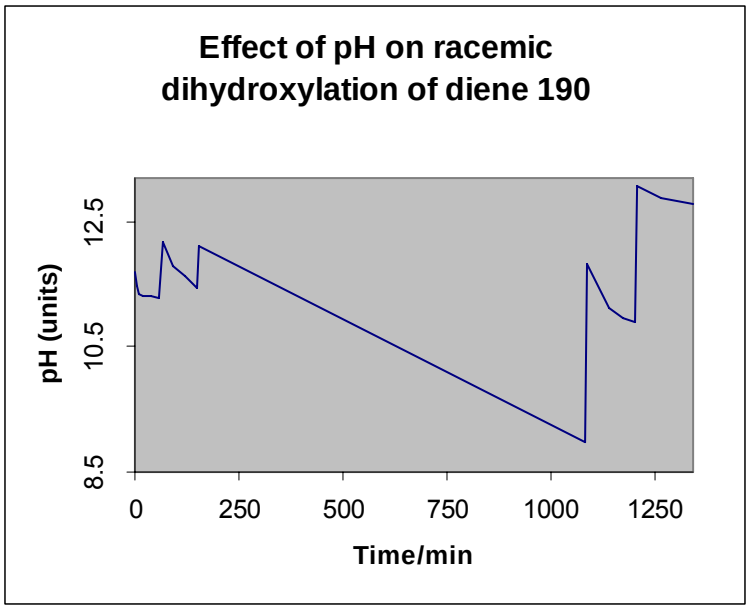
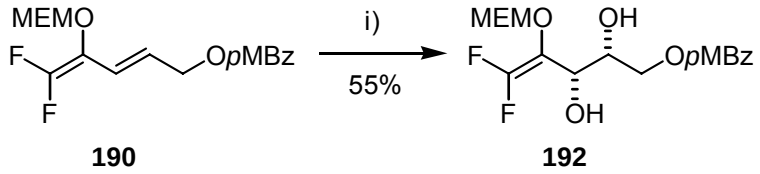


Figure 17: Change of pH during racemic dihydroxylation

Clearly, the pH begins to drop immediately, but at a shallower gradient than usual due to the lower reactivity of the diene. At *ca.* pH 11.0, the reaction begins to slow considerably. On the addition of aqueous NaOH, the required pH level is re-established and the pH begins to drop at a similar rate as previously observed. If left for a long period, the pH slowly reduces down to pH 9.0, at which point the reaction rate would be deemed to be very slow. This crude experiment therefore clearly demonstrates that pH indeed plays a vital role in determining the overall rate of reaction.

When this method was used under asymmetric conditions, complete consumption of the starting diene could be achieved in several hours if the pH was maintained in the range 11.0-12.0. Maintaining the pH at near 12.0 at all times allowed complete reaction in 30 minutes, with confirmation coming from TLC and ^{19}F NMR (**Scheme 112**).

It was noted that the pH should not be taken above 12.0 since decomposition of the starting material began to occur, presumably due to either ester cleavage or attack of hydroxide at the difluoromethylene centre.



190 **192**

Reagents and Conditions: i) $K_2OsO_4.2H_2O$ (2 mol%), $(DHQD)_2PHAL$ (5 mol%), K_2CO_3 (300 mol%), $K_3Fe(CN)_6$ (300 mol%), *t*BuOH-H_2O (1:1 v/v), pH 12.0, rt, 30 min

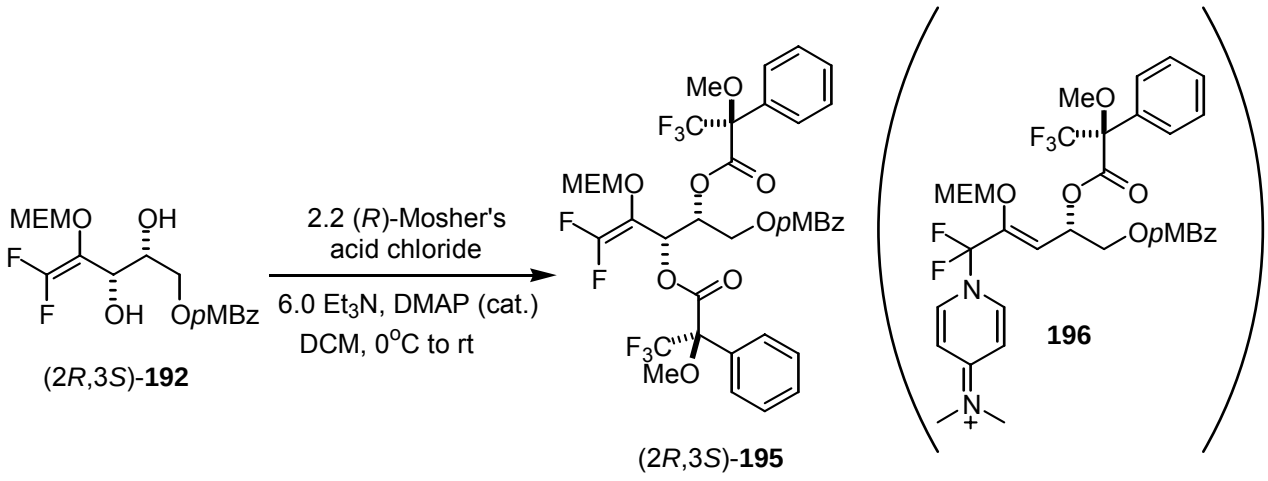
Scheme 112: pH-controlled synthesis of diol **192**

In order to determine the degree of asymmetric induction, samples of diol obtained from AD-mix-β (not pH-controlled) and racemic dihydroxylation (pH-controlled) were both obtained by preparative HPLC. Both samples were then subjected to chiral HPLC on a Chiralcell OD column using a 10% *iso*propanol/hexane mobile phase. Unfortunately, no separation of the enantiomeric diols was observed under these conditions, with both samples affording a single peak.

This was a disappointing result since this column has been successfully used to determine the *ee*'s of diols. Two other column types commonly used (Chiralpak AS and Welkmann (*S,S*)-0.1) were unavailable, so an NMR method was pursued.

NMR can be used to resolve enantiomers by employing a chiral derivatising agent, thus forming diastereoisomers with different physical properties. A common method for analysing alcohols is to generate Mosher (MTPA) esters. It was decided to synthesise a *bis*-Mosher ester **195** and to analyse the product by ^{19}F NMR, in which the difluoromethylene unit can be used as a second reporter centre. Reaction of pure

chiral diol with (*R*)-Mosher's acid chloride under typical esterification conditions afforded a crude material **195** showing a single set of fluorine signals (**Scheme 113**). Close monitoring of the reaction was essential in order to prevent the attack of DMAP on the difluoromethylene centre with carboxylate expulsion, affording **196** (identified by ^{19}F NMR[219] and MS).

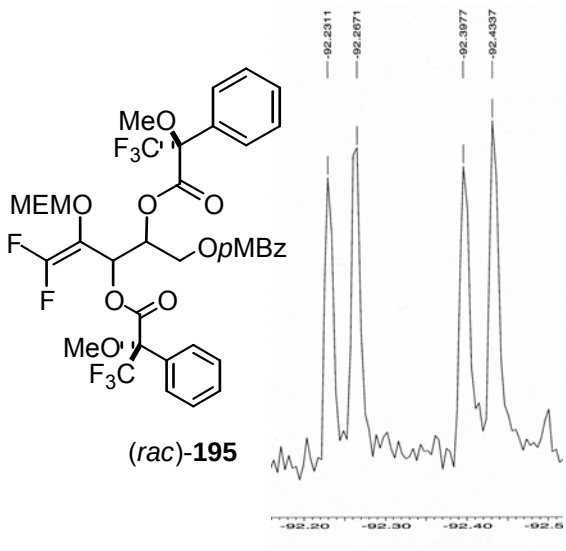


Scheme 113: Formation of *bis*-Mosher ester **195**

The reaction was then repeated using pure racemic diol **192**. In the first trial, there was insufficient acid chloride to drive the second esterification. However, the result clearly indicated the reactivity difference between the two hydroxyl groups (the allylic hydroxyl being less reactive) and that the diastereoisomers had different ^{19}F NMR shifts for the difluoromethylene centre. Repetition of the reaction using fresh acid chloride allowed the clean conversion to the racemic *bis*-Mosher ester **195** as judged by TLC. Analysis by ^{19}F NMR clearly indicated the presence of two diastereoisomers in both fluorine environments (CF_3 and $=CF_2$) in a 1:1 ratio, as expected.

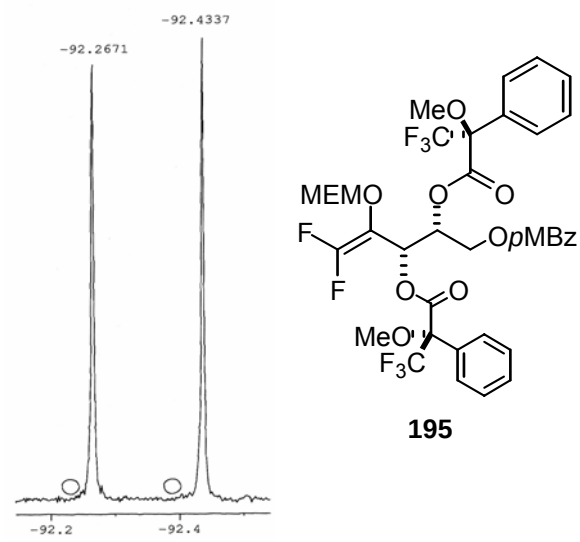
This result, in conjuction with that obtained with the chiral diol, indicated an excellent *ee*, greater than 95%. The reaction with the chiral diol was repeated and subjected to

high resolution ^{19}F NMR at 300 MHz (4096 scans and 512K data points) allowing an estimation of the *ee* to be greater than 99.5%. The partial ^{19}F NMR spectra are depicted below (**Figure 18**).



(*rac*)-**195**

Partial ^{19}F NMR of *bis*-Mosher ester of racemic diol

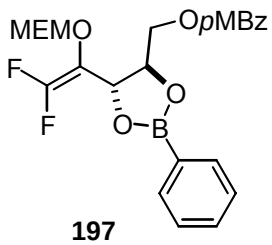


195

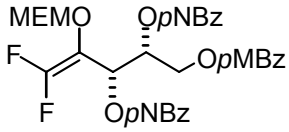
Partial ^{19}F NMR of *bis*-Mosher ester of chiral diol

Figure 18: Partial NMR of *bis*-Mosher esters of diol **192**

Attempts to make crystalline derivatives, which could be analysed by X-ray crystallography to confirm the connectivity and relative stereochemistry were unsuccessful. Though boronate ester **197** could be prepared cleanly by ^{19}F NMR (**Appendix XIV**), the material proved difficult to purify. On the other hand, triester **198** was successfully prepared but existed as an oil.

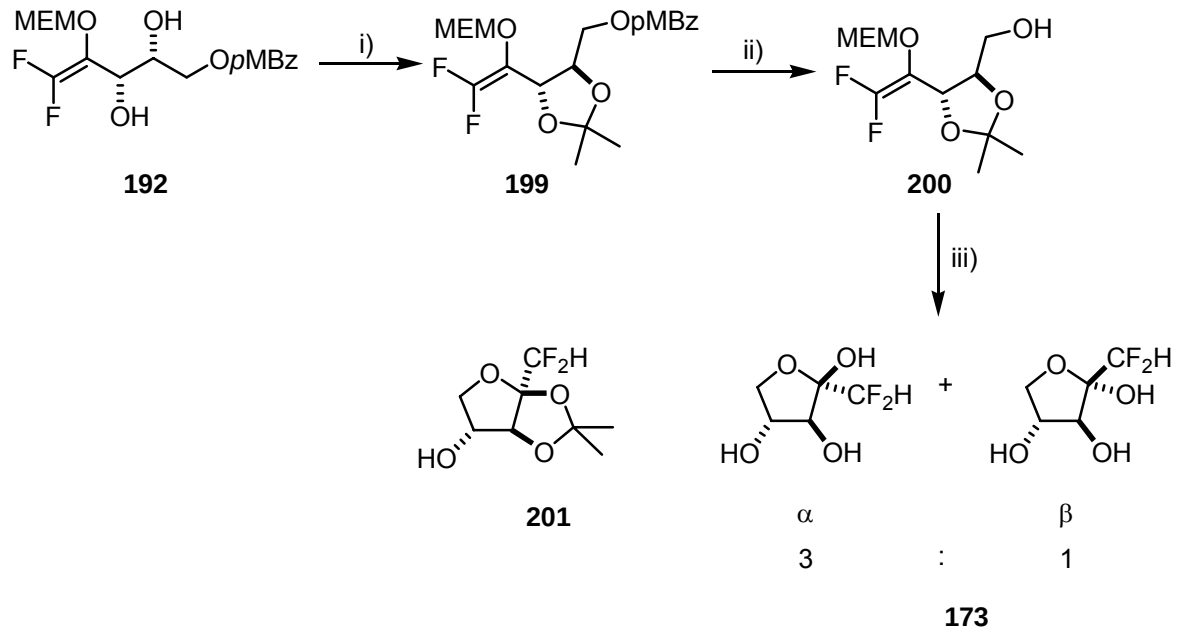


197



198

Completion of the synthesis of the target xylulose **173** is shown in **Scheme 114**.



Reagents and Conditions: i) 2.0 eq. $CuSO_4$, *p*TSA (cat.), acetone, rt, 48 h, 68%; ii) 4.0 eq. H_2O_2 (30% w/w in water), 2.1 eq. $LiOH.H_2O$, THF-H_2O (3:1 v/v), rt, 140 h, 61%; iii) 1.1 eq. Me_3SiCl, MeOH, rt, 88%

Scheme 114: Synthesis of target sugar **173** from diol **192**

Protection of the diol[234] **192** as the acetonide **199** was accomplished using acetone and an acid catalyst, using anhydrous copper(II) sulfate as a dehydrating agent. Attempts to use Amberlyst-15 and 2,2-dimethoxypropane resulted in the desired product on a 0.5 mmol scale, but returned starting material on scaling up. The acetonide was unstable on silica gel and purification was achieved by chromatography on basic alumina.

Saponification of the ester to alcohol **200** was successful using lithium hydroperoxide, prepared *in situ* from hydrogen peroxide and lithium hydroxide.[220]

Dual cleavage of the MEM enol ether and acetal linkages occurred in methanol containing chlorotrimethylsilane and the target sugar **173** could be isolated in

excellent (88%) yield as a 3:1 mixture of α and β anomers. Both anomers could be converged into a single acetonide derivative **201** by treatment with acetone and an acid catalyst.[221]

The D-xylulose **173** was characterised by 2D NMR techniques, in order to distinguish the two anomers. The connectivity was confirmed by COSY, HSQC and HMBC experiments (**Appendices XV-XXVI**). The relative configuration at the anomeric centre was confirmed by a 1D-GOESY experiment, in which the major (α) anomer showed a positive NOE between the H-3, H-5b and H-1 protons (**Figure 19**).

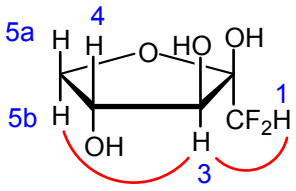
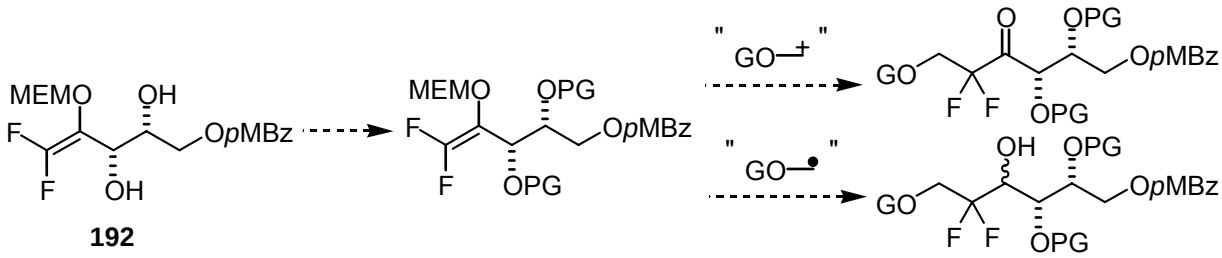


Figure 19: Assignment of anomeric configuration by 1D-GOESY

Accurate measurement of the optical rotation gave a value comparable with that reported by O'Hagan, thereby confirming the absolute stereochemistry of the α-anomer as that shown. The observed sense of enantioselection is also consistent with that predicted using the Sharpless model.

2.2.4 Evaluation of one carbon extension strategies

The successful completion of a synthesis of a 2-deoxy-2,2-difluorohexose requires the addition of a hydroxymethyl equivalent to the difluoromethylene centre (**Scheme 115**).



Scheme 115: Two generic strategies to formylation of diol **192**

Analysis of the desired target indicated that several methods could potentially install the key formyl component (or equivalent) to the difluoromethylene centre. Several possible methods have been studied only briefly due to a lack of laboratory time.

Radical additions

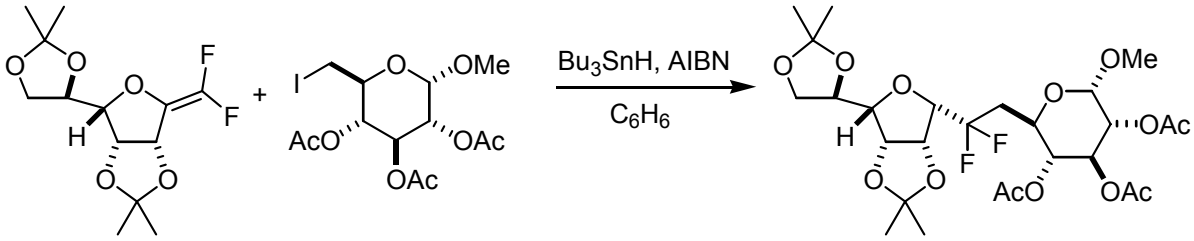
At the outset it was realised that although $=CF_2$ centres are electrophilic, the most common pathway was *via* addition-elimination, leading to monofluorinated materials.[222] Therefore, if such a process is to be used, a good leaving group at the allylic centre is required. Disconnection readily shows that this requires the loss of a chiral centre, painstakingly installed through a dihydroxylation reaction. This option was therefore ruled out.

A more profitable solution was deemed to be the addition of a nucleophilic radical, since the loss of a highly energetic fluorine atom is very unfavourable. In addition, the

neighbouring chiral centre may control the facial reduction of the intermediate radical, leading to control of the relative stereochemistry between C-3 and C-4.

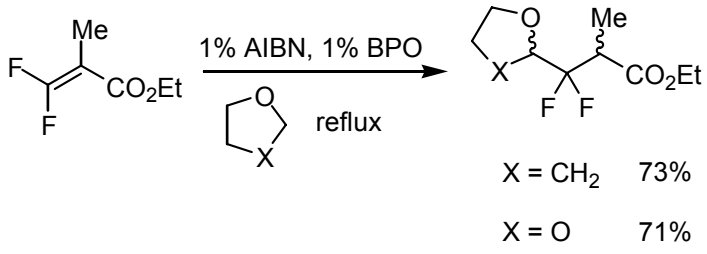
Motherwell and Bumgardner have both described the addition of nucleophilic and electrophilic radicals to vinylic CF_2 centres.

Motherwell[223] showed how difluoroenol ethers, derived from sugar lactones, showed significant reactivity towards nucleophilic radicals, such as those derived from cycloalkanes and sugars (**Scheme 116**).



Scheme 116: Addition of a nucleophilic radical to a difluoroenol ether

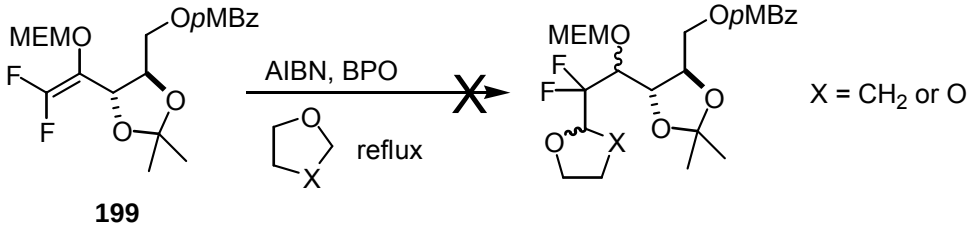
Bumgardner[224] also showed how β,β-difluoroacrylates are susceptible to the addition of nucleophilic radicals, derived from cyclic ethers or aldehydes (**Scheme 117**).



Scheme 117: Addition of cyclic ether radicals to a difluoroalkenoate

Initial attempts in this research concerned the attempted addition of carbon-centred radicals derived from cyclic ethers, namely tetrahydrofuran and 1,3-dioxolane to

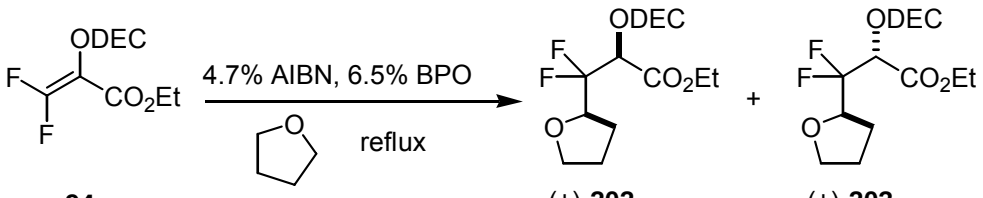
acetonide **199**. Based upon the above protocol, azo*bisiso*butyronitrile (AIBN) and benzoyl peroxide (BPO) were used as a combined radical initiator system. Runs employing THF and 1,3-dioxolane with acetonide **199** uniformly gave discouraging results. Starting material was present in all cases (**Scheme 118**).



199

Scheme 118: Failure to add a cyclic acetal radical to acetonide **199**

In order to test the initiator system, difluoroalkenoate **94** was used in direct analogy to the work of Bumgardner, which strongly suggested that reaction should be feasible. Indeed, heating a solution of **94** in refluxing THF in the presence of AIBN (4.7 mol%) and BPO (6.5 mol%) successfully promoted the addition of a THF radical with the formation of diastereoisomeric esters **202** and **203** in good (82%) isolated yield after column chromatography (**Scheme 119**).

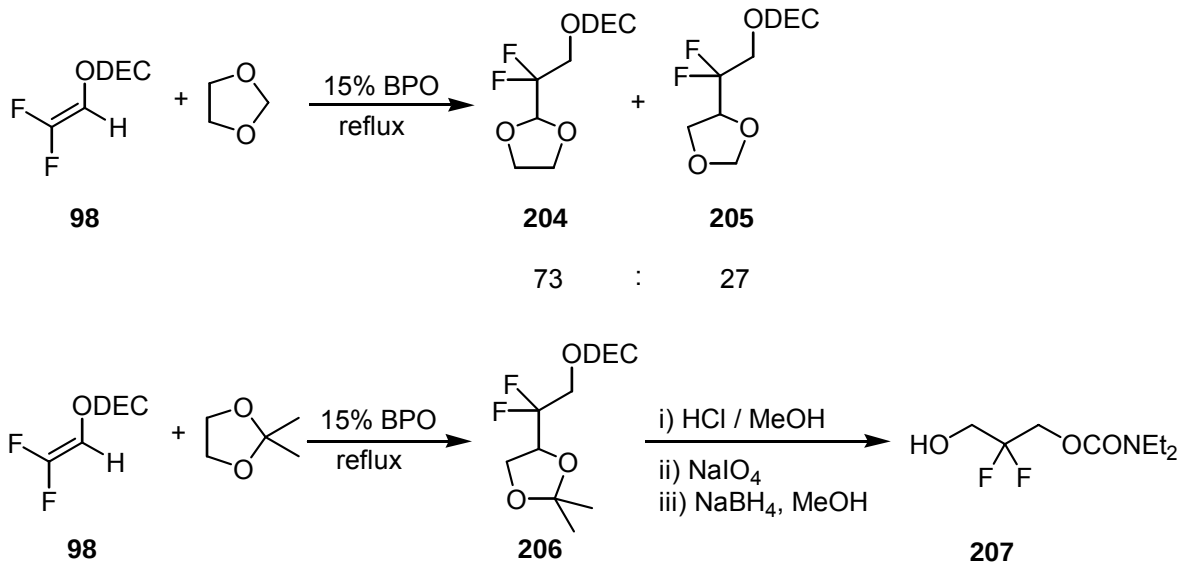


94 (±)-**202** (±)-**203**

Scheme 119: Successful addition of a THF radical to difluoroalkenoate **94**

Okano *et al.* have published work regarding the successful addition of 1,3-dioxolane and 2,2-dimethyl-1,3-dioxolane to enol carbamate **98**.[225] Reaction with 1,3-dioxolane

afforded a 73:27 mixture of acetals **204** and **205**. However, the 1,3-dioxolane unit in **204** could not be deprotected, even with concentrated HCl, due to the development of positive charge *alpha* to the CF_2 centre. The poor regioselectivity in hydrogen atom abstraction from tetrahydrofuran is also much lower than expected. However, reaction with 2,2-dimethyl-1,3-dioxolane afforded acetonide **206** (no problem of regioselectivity) which could be deprotected with acid, and converted through to the alcohol **207** *via* oxidative cleavage to the aldehyde by sodium periodate and subsequent reduction with sodium borohydride (**Scheme 120**).



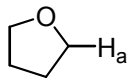
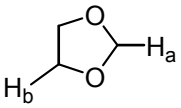
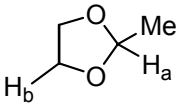
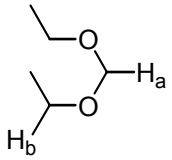
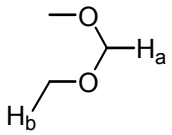
Scheme 120: Addition of cyclic acetal linkages to enol carbamate **98**

The stability of acetal **204** to acid is a major problem. The poor regioselectivity is also a concern. Of more concern is the compatability of the MEM acetal linkage to radical conditions using 2,2-dimethyl-1,3-dioxolane.

Malatesta and Ingold[226] have studied stereoelectronic effects in hydrogen atom abstraction from various cyclic and acyclic ethers using electron paramagnetic

resonance (EPR) spectroscopy. **Table 14** shows the experimental ρ values (relative reactivities per equivalent hydrogen type) for key ethers toward *t*-butoxyl radical at -60°C.

Table 14: Relative reactivities (to THF) per equivalent hydrogen atom (ρ) of cyclic and acyclic ethers toward $Me_3CO\bullet$ at -60°C

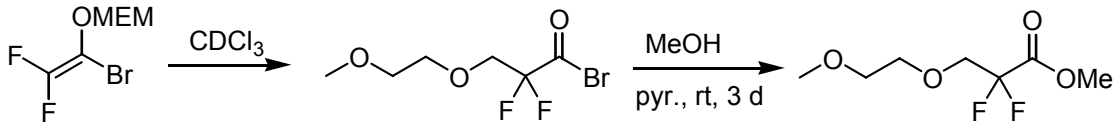
	Ether	H	ρ
1		H_a (4)	(1.0)
2		H_a (2) H_b (4)	8.8 0.32
3		H_a (1) H_b (4)	5.2 0.19
4		H_a (2) H_b (4)	0.29 0.11
5		H_a (2) H_b (6)	0.25 0.05

Entry 2 indicates that an H_a in a 1,3-dioxolane unit is much more easily abstracted than either an H_a of tetrahydrofuran or an H_b of a 1,3-dioxolane. Entry 3 indicates that an H_b of 2,2-dimethyl-1,3-dioxolane is comparable to that of an H_b in 1,3-dioxolane. Of most importance is that entries 4 and 5 indicate that the ease of abstraction of an H_a in an acyclic acetal (such as MEM) is comparable to that of an H_b in 1,3-dioxolanes. This would suggest that the MEM protecting group is incompatable with

the use of 2,2-dimethyl-1,3-dioxolane as a formyl radical equivalent. An alternative formyl equivalent would therefore have to be found.

O to C protecting group transfer

During studies by Thomas on the application of 1-bromo-2,2-difluoro-1-(2-methoxyethoxymethoxy)-ethene **208** as a substrate for styrene synthesis *via* palladium-catalysed cross-coupling, it was discovered that this material was prone to acid-catalysed ($CDCl_3$ from NMR solvent) rearrangement to acid bromide **209** (trapped by MeOH to form ester **210**), resulting from transfer of the MEM group (**Scheme 121**).[169]

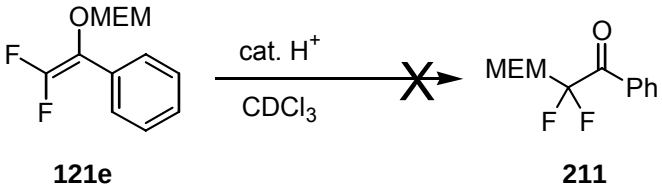


208 **209** **210**

Scheme 121: Observed migration of a MEM group in vinyl bromide **208**

Indeed, during these studies, certain styrene derivatives also underwent rearrangement if left at ambient temperature for extended periods. No detailed studies have been performed on this intriguing reaction, so it was decided to use styrene **121e** to test conditions to promote such a rearrangement.

Initially, a sample was stirred with Amberlyst-15 for 18 hours in deuterated chloroform. NMR analysis indicated, however, the absence of any ketone **211** (**Scheme 122**).

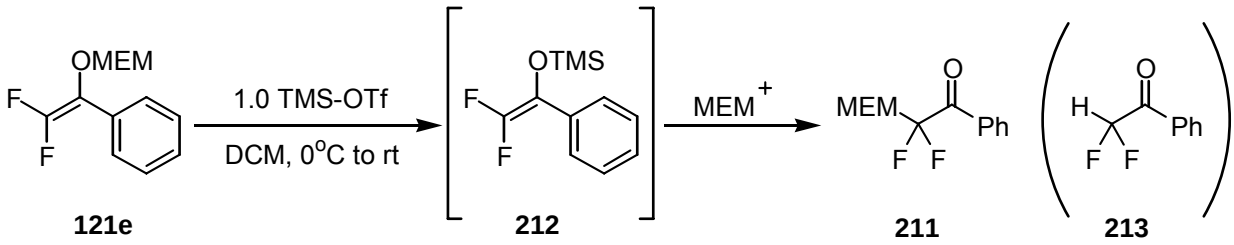


121e **211**

Scheme 122: Attempted MEM transfer using catalytic Brønsted acid sources

The use of trifluoroacetic acid led, conversely, to a multitude of fluorinated products, none of which could be properly assigned, although signals consistent with ketone **211** could be seen.

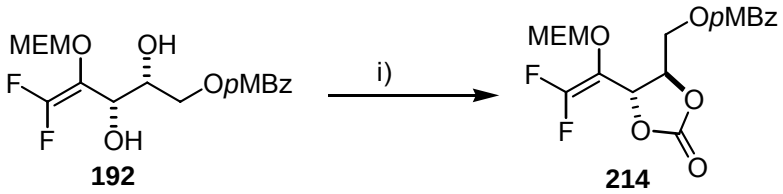
On the other hand, treatment of styrene **121e** with trimethylsilyl triflate successfully promoted the formation of ketone **211** (δ_F -107.40, t, $^3J_{HF}$ 14.0 Hz) as well as difluoromethylketone **213** (δ_F -122.25, d, $^2J_{HF}$ 53.4 Hz), resulting from hydrolysis of the intermediate TMS enol ether **212** (**Scheme 123**).



121e **212** **211** **213**

Scheme 123: Successful promotion of MEM transfer using a Lewis acid

Having established a protocol to induce the desired O to C protecting group transfer, incorporation into aldohexose synthesis was attempted. The diol **192** was protected as the carbonate **214** using triphosgene,[227] so as to tie up the diol unit as a Lewis-acid-stable protecting group (**Scheme 124**).

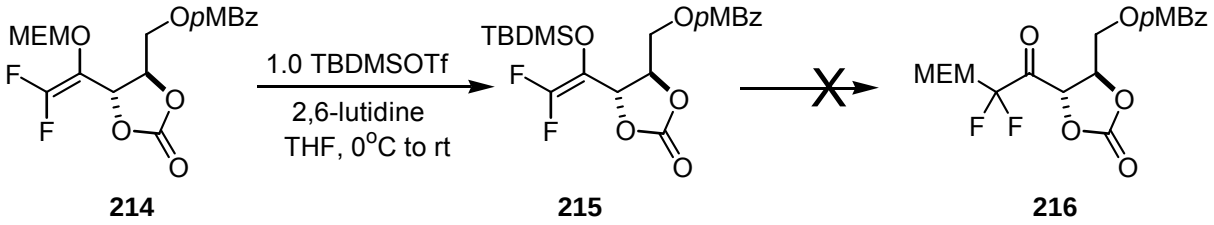


Reagents and Conditions: i) 1.0 eq. triphosgene, DCM, 2,6-lutidine, reflux, 18 h, 66%

Scheme 124: Conversion of diol **192** to cyclic carbonate **214**

Attempts to use 1,1-carbonyldiimidazole also led to carbonate **214**. ^{19}F NMR and mass spectral analysis also detected traces of the addition of imidazole to the difluoromethylene centre. Treatment with ethylene carbonate only returned starting material. Carbonate **214** was found to be unstable for long periods.

When carbonate **214** was treated with *tert*-butyldimethylsilyl trifluoro-methanesulfonate in the presence of 2,6-lutidine (to scavenge traces of acid), a 14:86 mixture of starting material **214** and a new difluoroolefin was observed, as indicated by the new chemical shifts at -99 and -114 ppm. None of the desired ketone **216** was observed. The shifts correlated very well with those expected for silyl difluoroenol ethers, suggesting that cleavage had occurred, but that the TBDMS enol ether **215**, under these conditions, was insufficiently reactive to trap the resulting MEM cation. Unfortunately, attempted column chromatography failed to afford silyl difluoroenol ether **215** to confirm its identity (**Scheme 125**).



214 **215** **216**

Scheme 125: Formation of TBDMS enol ether **215** from carbonate **214**

However, this is an important observation since silyl difluoroenol ethers are useful species and a Mukaiyama aldol process may be applicable (using paraformaldehyde) to install the required hydroxymethyl group.[228]

Chapter Three

Conclusions

The Stille coupling of a range of difluorovinyl *C*-stannanes with aryl, vinyl, heteroaryl and allyl halides has been developed. It was also possible to employ a difluorovinyl iodide to access the same targets, giving scope to the synthesis of certain styrene derivatives. It was also possible to generate biarylethenes through coupling of aryl triflates under Stille and Suzuki-Miyaura conditions. Sonogashira coupling was also possible. With the correct choice of enol protecting group, these materials could be cleaved under mild electrophilic conditions with a range of electrophiles. The methodology developed offers the possibility of generating a diverse array of aryl difluoromethyl ketones for the first time.

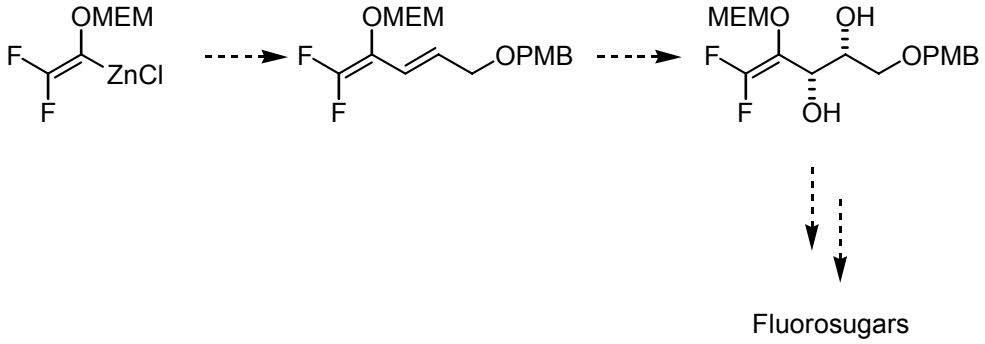
Limitations to the methodology are that a stannane is required as the metal, leading to toxicity issues. In addition, the MEM enol ethers are fairly labile and are therefore difficult to purify and cannot be stored for long periods. Also, the first coupling protocol is only amenable to aryl iodides as the organic electrophiles, although it should be stressed that only a small range of commonly used palladium catalysts were studied.

Future work in this area could look at the possibility of using either a difluorovinylzinc reagent or a difluorovinylsilane as the coupling component. Early indications are that couplings, in one pot from the MEM ether of trifluoroethanol, using a zinc reagent are feasible. The extension to the use of bromo- and chloroarenes could also be studied. Although the range of electrophiles studied is fairly extensive, it would be instructive to further probe the possibility of using an aldol reaction to construct β-hydroxy-α,α-difluoroketones.

It has been demonstrated, for the first time, that fluorinated 1,4-dienes and 1,3-dienes are useful precursors to the synthesis of fluorinated carbohydrate analogues.

The Sharpless Asymmetric Dihydroxylation of a limited range of 1,1-difluoro-1,3-dienes has been studied and it has been found that the reaction is highly dependent upon the electronic nature of the olefinic substituents. Through the use of a special protecting group (*p*MBz) and controlled pH conditions, it has been possible to dihydroxylate a 1,1-difluoro-1,3-dien-5-ol with high levels of regio- and enantioselection. This sequence has afforded an intermediate with high synthetic potential for the synthesis of enantiomerically enriched oxygenated fluorine-containing materials. Its use was exemplified in the short asymmetric synthesis of a fluorinated deoxyxylulose of current interest.

Possible future work could look at the use of a difluorozinc reagent to form the key diene **190** in order to be able to allow telescoping of the reaction. It may also be beneficial to use a PMB group for allylic alcohol protection to possibly increase the stability of both the diene and the diol product to the basic reaction conditions (**Scheme 126**).

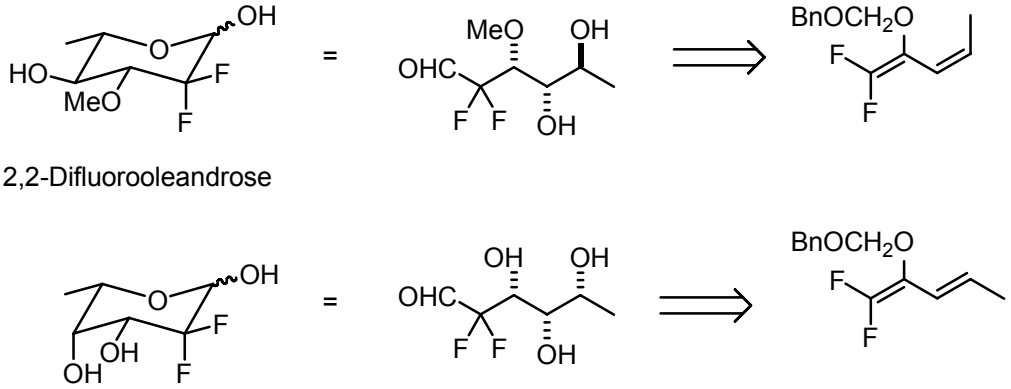


Scheme 126: Possible future developments using a MEM protecting group

A successful outcome to this initial work would see the synthesis of a difluorinated hexose analogue. This requires a more thorough study of the use of an enol

protecting group transfer strategy. The use of a benzyloxymethyl protecting group could be beneficial to allow easier deprotection strategies to be employed.

Possible targets using the methodology developed could be 2,2-difluorinated analogues of oleandrose and fucose (**Scheme 127**).



Scheme 127: Possible targets using the methodology developed to date

Chapter Four

Experimental

General Procedures:

NMR Spectroscopy:

All NMR spectra were recorded on Bruker AC-300, AV-300, AMX-400 or DRX-500 spectrometers. ^{1}H NMR and ^{13}C NMR were recorded using deuterated solvent as the lock and residual protic solvent as the internal standard. ^{13}C NMR were recorded using the PENDANT pulse sequence unless otherwise stated. The central peak of the $CDCl_3$ resonance (δ 77.0) was used as an external reference. The multiplicities of the signals have been indicated as Cq, CH, CH_2 and CH_3. ^{19}F NMR spectra were recorded relative to chlorotrifluoromethane as the internal standard over the range -40 to -180 ppm. Multiplicities are represented in the following manner: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets etc., envelope= overlapping multiplets of different nuclei. All coupling constants are recorded in hertz (Hz). *J* (italic) represents homonuclear coupling (i.e H-H or F-F). Square brackets ([ ]) represent groups of resonances for a single nucleus resulting from rotamers. The numbering used to aid interpretation of NMR data does not necessarily correlate with the IUPAC numbering in the given name.

Mass Spectrometry:

Chemical ionisation (CI) and Electron Impact (EI) mass spectra were recorded on a VG Prospec or Kratos MS-80 mass spectrometer with a DS-90 data system. Chemical Ionisation methods used ammonia as the carrier gas. Fast Atom Bombardment (FAB) mass spectra were recorded using a VG Zabspec instrument. A micromass LCT mass spectrometer was used for both low-resolution (ES-TOF) mass spectra (using methanol as the mobile phase) and HRMS measurements (using a

lock mass incorporated into the mobile phase). HRMS measurements were also obtained from either the VG Prospec spectrometer or a VG autospec instrument.

Chromatography:

Thin layer chromatography was performed on either pre-coated aluminium-backed silica gel plates (E.Merck, A.G.Darmstadt, Germany. Silica gel 60 F_{254}, thickness 0.2 mm), pre-coated aluminium-backed alumina gel plates (E.Merck, A.G.Darmstadt, Germany. Alumina gel 60 F_{254}, thickness 0.2 mm) or plastic-backed RP-C18 plates. Visualisation was achieved using potassium permanganate staining, ammonium molybdate staining and UV detection at 254 nm.

Column chromatography was performed on silica gel (E.Merck, A.G. Kieselgel 60, Art. 9385), alumina (pH 9-11, Brockmann 1, Fisher) or florasil. Column fractions were collected and monitored by thin layer chromatography upon the appropriate plates.

GC analysis was carried out on a Carlo Erba GC 8000 Series with Flame Ionisation Detection (FID). An SPE BPX-5 Megabore column (15 m $\times$ 0.53 mm ID/Split Mode 20:1) was used with helium as the carrier gas. Chromcard was used as the software.

Analytical HPLC analysis was performed on a Dionex Summit HPLC system with chromeleon software using a Summit P580 quaternary low-pressure gradient pump with built-in vacuum degasser. A Summit UVD 170s UV/VIS multi-channel detector with an analytical flow cell was used for detection. A Luna 10μ C18(2) column (250 mm $\times$ 4.6 mm) was used as the stationary phase unless otherwise stated. Semi-preparative HPLC of diols 192 was performed on an identical system accept that a Prep flow cell was used in conjunction with a Luna 10μ C18(2) column (250 mm $\times$ 10

mm). Chiral HPLC of alcohols 157 and 159 was performed on a Chiralcel OD column (0.46 cm × 25 cm) using a 90% hexane: 10% *iso*propanol eluent.

Elemental analyses were performed on a Carlo Erba 1110 CHNS microelemental analysis machine. Optical rotations were performed on a PolAAr 2001 optical activity Ltd automatic polarimeter using 0.25 dm (1 ml) cells. IR spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer using sodium chloride plates. Melting points were recorded on a Stuart scientific SMP1 melting point apparatus and are uncorrected. UV spectra were recorded on a Thermospectronic UV 500 UV-Vis spectrometer using 10.00 mm quartz glass cuvettes.

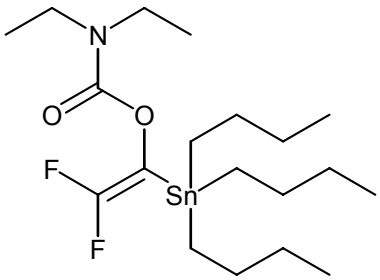
Solvents and Reagents:

Tetrahydrofuran was dried by heating under reflux with sodium metal and benzophenone, under dry nitrogen, until a deep purple colour persisted. The solvent was then collected by syringe as required. DMF was distilled from barium oxide under reduced pressure and stored under nitrogen. Dioxane was distilled from diphosphorous pentoxide. DCM was distilled from calcium hydride. Di*iso*propylamine was distilled from calcium hydride and stored over 4Å molecular sieves. Dichloromethane was distilled from calcium hydride. 2,6-Lutidine was distilled from KOH and stored over KOH pellets. pH Measurements were taken using a pH tester ('Checker', Hanna instruments) available from Fisher chemicals. Degassing of solvents for couplings was performed by purging with dry nitrogen or dry argon for 20 min prior to use. *n*-Butyllithium was titrated against either 4-benzylidene benzylamine[235] or *N*-pivaloyl-*o*-toluidine[236] before use.

Zinc(II) bromide was dried by powdering using a pestle and mortar, followed by heating at 200°C under high vacuum (0.1 mmHg). All crude coupling products were diluted with diethyl ether and aqueous KF (1 M, > 3 molar equivalents) added and stirred rapidly for 30 minutes. The solution was then filtered and extracted with the appropriate solvent.

All materials were purchased from Aldrich, Lancaster, Acros (Fisher) or Avocado and used as received unless otherwise stated. (*R*)-(-)-α-(Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (Chiraselect, >99%) was purchased from the Aldrich chemical company PLC and stored in a drikold freezer whilst not in use. 4-Iodoanisole was recrystallised from ethanol prior to use. Copper(I) iodide was recrystallised from potassium iodide according to the method of Taylor *et al.*.[237] Allyl bromide was distilled prior to use. *Tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct was prepared according to the method of Cotton.[238] 5-Bromo-2-iodopyridine was prepared according to the method of Song.[188] 1-(*N,N*-Diethylcarbamoyloxy)-2,2,2-trifluoroethane was prepared according to the method of Howarth.[99] 1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene was prepared according to the method of Haworth.[99] *N*-Pivaloyl-*o*-toluidine was prepared according to the method of Suffert.[236] (*E*)-2-[3-(Tributylstannyl)-prop-2-enyloxy]-tetrahydropyran was prepared according to the method of Corey.[168]

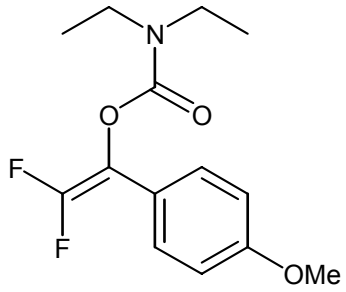
1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-1-(tributylstannyl)ethene 81



n-Butyllithium (24.6 ml of a 2.0 M solution in pentane, 49.2 mmol) was added dropwise over 20 min to a –78°C solution of di*iso*propylamine (6.8 ml, 51.1 mmol) in THF (45 ml) to afford a pale yellow solution. The solution was allowed to warm slightly by removal from the Dewar flask for 5 min, then re-cooled to –78°C. 2,2,2-Trifluoroethyl *N,N*-diethylcarbamate **96** (4.0 ml, 24.6 mmol) was added over 25 min and the mixture was stirred for a further 30 min. During this time the colour of the mixture changed from yellow through red to a deep blue. Tributyltin chloride (7.5 ml, 27.6 mmol) was added in one portion and the reaction mixture stirred for 1 h at –78°C, before being allowed to warm to room temperature, affording a yellow solution. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (100 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 50 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded enol stannane **81** as a colourless oil (10.75 g, 93%); R_f (5% diethyl ether in light petroleum) 0.48; δ_H (300 MHz, $CDCl_3$) 3.29 (4H, q, ^3J 7.4, $N(CH_2CH_3)_2$), 1.54-1.43 (6H, m), 1.35-1.23 (6H, m), 1.15-1.09 (6H, m, $N(CH_2CH_3)_2$), 1.01-0.96 (6H, m), 0.88 (9H, t, ^3J 7.4, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_F (282 MHz, $CDCl_3$)

-83.64 (1F, d, ^2J 64.1), - 110.27 (1F, d, ^2J 64.1, satellite peaks due to Sn coupling were also observed). NMR Data agreed with those reported by Howarth.[99]

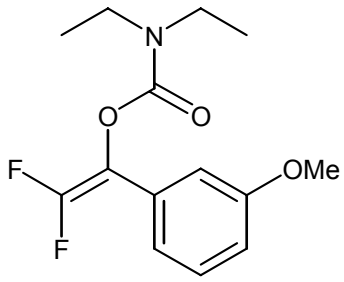
4-[1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-1-methoxybenzene 95a



A mixture of copper(I) iodide (27 mg, 0.14 mmol), triphenylphosphine (53 mg, 0.20 mmol), 4-iodoanisole (286 mg, 1.22 mmol) and *tris*(dibenzylideneacetone) dipalladium(0)-chloroform adduct (27 mg, 52 μmol Pd) in dry, degassed DMF (8 ml) was heated to 50°C. A solution of stannane 81 (514 mg, 1.10 mmol) in DMF (2 ml) was added and the reaction mixture heated at 50-65°C for 16 h under a nitrogen atmosphere. After cooling, the mixture was diluted with diethyl ether (10 ml) and water (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole 95a as a pale yellow oil (261 mg, 83%); R_f (20% diethyl ether in light petroleum) 0.24; ν (film/cm^{-1}) 1729 s (C=O), 1611 m, 1515 m, 1425 m, 1269 s, 1147 s, 1035 m, 983 m, 838 w, 824 w, 786 w, 756 w; λ_{max} 250.2 nm (10^{-4} M in MeOH), (log ε = 4.24); δ_H (300 MHz, $CDCl_3$) 7.34 (2H, d, ^3J 8.8, ArH), 6.90 (2H, d, ^3J 8.8, ArH), 3.80 (3H, s, OCH_3), 3.42 (2H, q, ^3J 7.2, CH_2NCH_2), 3.34 (2H, q, ^3J 7.2, CH_2NCH_2), 1.24 (3H, t, ^3J

7.2, EtNCH$_2$*Me*), 1.16 (3H, t, ^3J 7.2, *Me*CH$_2$NEt); δ_C (75 MHz, $CDCl_3$) 159.4 (t, $^6J_{CF}$ 1.6, Cq-OMe), 154.5 (dd, $^2J_{CF}$ 290.5, 287.7, CF_2), 152.9 (dd, $^4J_{CF}$ 3.2, 2.0, CO), 127.0 (dd, $^4J_{CF}$ 6.0, 3.7, CH), 122.4 (dd, $^3J_{CF}$ 6.3, 0.6, Cq), 113.9 (CH), 112.1 (d, $^2J_{CF}$ 39.2, 19.3, *C*=CF_2), 55.1 (OCH_3), [42.4, 41.8] (CH_2), [14.1, 13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -95.78 (1F, d, ^2J 53.9), -105.85 (1F, d, ^2J 53.9); [HRMS (ES-TOF, M+Na) Found: 308.1078; Calc. for $C_{14}H_{17}NO_3F_2Na$: 308.1074]; *m/z* (EI) 285 (53%, M), 186 (18%), 169 (21%, M-ODEC), 135 (62%), 108 (33%), 100 (100%, $CONEt_2$), 92 (34%), 77 (36%), 72 (88%), 56 (37%), 44 (74%). Data are in agreement with those reported by Thomas.[169]

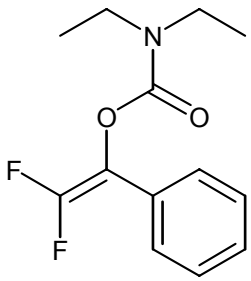
3-[1-(*N,N*-diethylcarbamoyloxy-2,2-difluoro)-vinyl]-1-methoxybenzene 95b



Anisole **95b** was prepared as for **95a** using palladium(II) acetate (13 mg, 58 μmol), CuI (21 mg, 0.11 mmol), triphenylarsine (69 mg, 0.23 mmol), 3-iodoanisole (253 mg, 1.08 mmol) and stannane **81** (549 mg, 1.17 mmol) in DMF (5 ml) at 100°C. After 2 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole **81** as a colourless oil (152 mg, 49%); R_f (20% diethyl ether in light petroleum) 0.22; ν (film/cm^{-1}) 1733 s, 1602 m, 1581 s, 1422 s, 1382 m, 1270 s, 1219 m, 1142 s, 1096 m, 1043 m, 1007 m, 952 m, 931 m, 843 m, 782 m, 755 m, 690 m; δ_H (300 MHz, $CDCl_3$)

7.29 (1H, t, ^{3}J 8.1, ArH), 7.01 (1H, d, ^{3}J 7.7, ArH), 6.95 (1H, s, ArH), 6.84 (1H, dd, ^{3}J 8.5, ^{4}J 2.6, ArH), 3.79 (3H, s, OCH_3), 3.44 (2H, q, ^{3}J 7.2, NCH_2Me), 3.35 (2H, q, ^{3}J 7.2, NCH_2Me), 1.26 (3H, t, ^{3}J 7.2, NCH_2CH_3), 1.17 (3H, t, ^{3}J 7.2, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 159.6 (Cq-OMe), 154.9 (t, $^{1}J_{CF}$ 289.9, CF_2), 152.8 (t, $^{4}J_{CF}$ 2.8, CO), 131.5 (dd, $^{3}J_{CF}$ 6.8, 1.1, Cq), 129.6 (CH), 117.8 (dd, $^{4}J_{CF}$ 6.8, 3.4, CH), 113.6 (CH), 112.0 (dd, $^{2}J_{CF}$ 37.3, 18.1, C=CF_2), 111.2 (dd, $^{4}J_{CF}$ 6.2, 3.4, CH), 55.1 (OCH_3), [42.5, 41.9] (CH_2), [14.1, 13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -93.39 (1F, d, ^{2}J 48.0), -103.00 (1F, d, ^{2}J 48.0); [HRMS (ES-TOF, [M+Na]) Found: 308.1059; Calc. for $C_{14}H_{17}NO_3F_2Na$: 308.1074]; *m/z* (CI) 303 (100%, M+NH_4), 286 (48%, M+H), 74 (53%, H_2NEt_2), 72 (20%), 52 (9%), 44 (16%). Data are in agreement with those reported by Thomas.[169]

[1-(*N,N*-Diethylcarbamoyloxy-2,2-difluoro)-vinyl]-benzene 95d



Method A:

Styrene **95d** was prepared as for **95a** using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd), triphenylphosphine (53 mg, 0.20 mmol), CuI (24 mg, 0.13 mmol), iodobenzene (240 mg, 1.17 mmol) and stannane **81** (517 mg, 1.10 mmol). After 20 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded

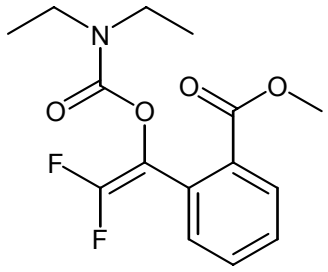
styrene **95d** as a pale yellow oil (225 mg, 80%); R_f (20% ether in light petroleum) 0.32; ν (film/cm^{-1}) 1732 s, 1424 m, 1382 w, 1269 s, 1224 w, 1148 s, 1098 w, 1077 w, 1036 w, 984 m, 951 w, 928 w, 788 w, 759 m, 693 m; δ_H (300 MHz, $CDCl_3$) 7.44-7.25 (5H, m, ArH), 3.44 (2H, q, ^3J 7.0, NCH_2CH_3), 3.40 (2H, q, ^3J 7.0, NCH_2CH_3), 1.26 (3H, t, ^3J 7.0, NCH_2CH_3), 1.17 (3H, t, ^3J 7.0, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 154.9 (t, $^1J_{CF}$ 289.9, CF_2), 152.9 (CO), 130.1 (d, $^3J_{CF}$ 6.8, Cq), 128.5 (CH), 128.1 (t, $^5J_{CF}$ 1.7, CH), 125.4 (dd, $^4J_{CF}$ 6.2, 3.4, CH), 112.4 (dd, $^2J_{CF}$ 37.9, 19.2, C=CF_2), [42.5, 41.9] (CH_2), [14.1,13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -93.66 (1F, d, ^2J 49.1), -103.73 (1F, d, ^2J 49.1); *m/z* (CI) 273 (32%, M+NH_4), 256 (100%, M+H), 100 (19%, $CONEt_2$). Data are in agreement with those reported by Thomas.[169]

Method B:

A flask containing *tetrakis*(triphenylphosphine)palladium(0) (54 mg, 47 μmol) and copper(I) iodide (179 mg, 0.94 mmol) was pump-purged with nitrogen. Dry, degassed THF (3 ml) was added followed by iodobenzene (210 mg, 1.03 mmol). The reaction mixture was stirred and warmed to 30°C. A solution of stannane **81** (477 mg, 0.94 mmol based on 92% purity) in THF (1 ml) was added and the heterogeneous reaction mixture heated under reflux for 18 h. The resulting black reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml). This mixture was transferred to a conical flask and an aqueous solution of KF (10 ml of a 1 M soln) added with vigorous stirring. After 25 min, the grey solids were removed by suction filtration. The ethereal layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil, in addition to

some solids. This crude material was taken up in acetone (ca. 15 ml) and concentrated onto silica gel to afford an orange powder. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded styrene **95d** as a pale yellow oil (182 mg, 76%); 98% by GC; R_f (20% diethyl ehter in hexanes) 0.28. NMR data (^{19}F and ^{1}H) were in agreement with those reported by Thomas.[169]

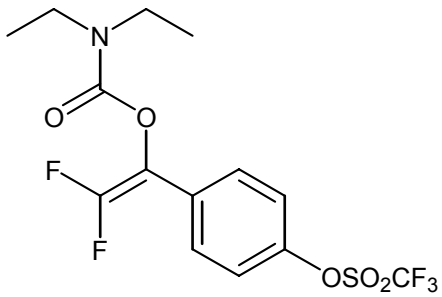
Methyl 2-[(1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro)-vinyl)-benzenecarboxylate 95f



Ester **95f** was prepared as for **95a** using *tris*(dibenylideneacetone)dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), CuI (19 mg, 0.10 mmol), triphenylarsine (63 mg, 0.21 mmol), methyl 2-iodobenzoate (641 mg, 2.44 mmol) and stannane **81** (476 mg, 1.02 mmol) in DMF (10 ml) at 100°C. After 1.5 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded ester **95f** as a pale orange oil (174 mg, 55%); R_f (20% ethyl acetate in light petroleum) 0.38; ν (film/cm^{-1}) 1758 m, 1729 s, 1599 w, 1575 w, 1423 s, 1382 m, 1271 s, 1146 s, 1088 m, 1042 w, 984 m, 954 w, 929 w, 768 m, 712 m; δ_H (300 MHz, $CDCl_3$) 7.87 (1H, dd, ^3J 7.4, ^4J 1.5, ArH), 7.60-7.57 (1H, m, ArH), 7.52 (1H, td, ^3J 7.4, ^4J 1.5, ArH), 7.42 (1H, td, ^3J 7.4, ^4J 1.5, ArH), 3.89 (3H, s, OCH_3), 3.28 (2H, q, ^3J 7.0, NCH_2Me), 3.24

(2H, q, ^3J 7.0, NCH_2Me), 1.12 (3H, t, ^3J 7.0, NCH$_2$CH_3), 1.08 (3H, t, ^3J 7.0, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 167.4 (CO ester), 154.5 (t, $^1J_{CF}$ 283.1, CF_2), 153.5 (CO carbamate), 131.9 (CH), 131.6 (t, $^4J_{CF}$ 2.8, CH), 130.3 (CH), 129.3 (CH), 52.2 (OCH_3), [42.3, 41.7] (CH_2), [13.9 13.2] (CH_3), 2 × Cq too weak to assign with confidence and *C*=CF_2 too weak to assign; δ_F (282 MHz, $CDCl_3$) -96.57 (1F, d, ^2J 53.9), -106.73 (1F, d, ^2J 53.9); [HRMS (ES-TOF, M+Na) Found: 336.1012; Calc. for $C_{15}H_{17}NO_4F_2Na$: 336.1023]; *m/z* (CI) 314 (100 %, M+H), 216 (10%), 198 (7%), 74 (84 %, H_2CONEt_2), 72 (67%), 52 (12%), 44 (22%).

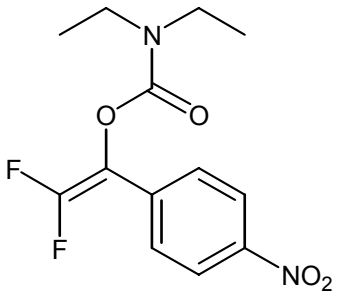
4-[(1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro)-vinyl]-phenyl trifluoromethane-sulfonate 95e



Triflate 95e was prepared as for 95a using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (109 mg, 210 μmol Pd), triphenylphosphine (263 mg, 1.00 mmol), CuI (102 mg, 0.54 mmol), 4-iodophenyl trifluoromethanesulfonate 120a (1.98 g, 5.62 mmol) and stannane 81 (2.61 g, 5.57 mmol) in DMF (10 ml). After 16 h, the usual work-up afforded a red oil. Purification by column chromatography over silica gel (5% diethyl in light petroleum ⇒ 10% diethyl ether in light petroleum) afforded triflate 95e as a pale yellow oil (1.79 g, 82%); 69% by GC; R_f (10% diethyl ether in light

petroleum) 0.17; ν (film/cm^{-1}) 2982 w, 1736 sm, 1598 wm, 1505 wm, 1426 m, 1275 m, 1216 sm, 1146 sm, 989 w, 888 m, 849 w, 826 wm, 786 w, 759 w; δ_H (300 MHz, $CDCl_3$) 7.50-7.46 (2H, m, ArH), 7.30-7.25 (2H, m, ArH), 3.40 (2H, q, ^3J 7.2, NCH_2CH$_3$), 3.32 (2H, q, ^3J 7.2, NCH_2CH$_3$), 1.21 (3H, t, ^3J 7.2, NCH$_2$CH_3), 1.13 (3H, t, ^3J 7.2, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 155.0 (dd, $^1J_{CF}$ 292.7, 291.6, Cq, CF_2), 152.5 (dd, $^4J_{CF}$ 3.3, 2.1, Cq, CO), 148.7 (t, $^6J_{CF}$ 2.3, Cq), 130.7 (dd, $^3J_{CF}$ 6.9, 1.1, Cq), 127.2 (dd, $^4J_{CF}$ 7.1, 3.4, CH), 121.5 (CH), 118.6 (q, $^1J_{CF}$ 321.0, Cq, CF_3), 111.2 (dd, $^2J_{CF}$ 37.9, 20.3, Cq, *C*=CF_2), [42.6, 41.9] (CH_2), [14.0, 13.0] (CH_3); δ_F (282 MHz, $CDCl_3$) -72.92 (3F, s), -91.75 (1F, d, ^2J 45.2), -101.98 (1F, d, ^2J 45.2); [HRMS (ES-TOF, M+Na) Found: 426.0413; Calc. for $C_{14}H_{14}NO_5F_5NaS$: 426.0411]; *m/z* (ES-TOF) 426.0 (100%, M+Na).

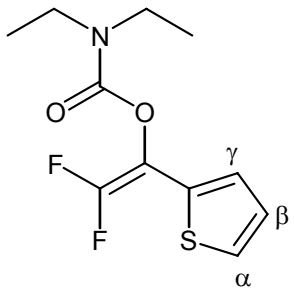
4-[1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro-vinyl]-1-nitrobenzene 95g



Nitrobenzene **95g** was prepared as for **95a** using palladium(II) acetate (22 mg, 98 μmol), triphenylphosphine (105 mg, 0.40 mmol), CuI (38 mg, 0.20 mmol), 1-iodo-4-nitrobenzene (498 mg, 2.00 mmol) and stannane **81** (936 mg, 2.00 mmol) in DMF (5 ml). After 3 h, the usual work-up afforded orange crystals in addition to a supernatant orange oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes ⇒ 60% diethyl ether in light petroleum) afforded nitrobenzene **95g** as a

orange semi-solid (99 mg, 18%); 92% by GC; mp 40°C; R_f (20% diethyl ether in hexanes) 0.16; ν (film/cm^{-1}) 1731 s, 1600 m, 1522 s, 1476 m, 1460 m, 1427 m, 1383 m, 1350 s, 1332 m, 1270 s, 1223 m, 1151 s, 988 m, 951 w, 928 w, 854 m, 826 w, 788 w, 753 m, 693 w; δ_H (300 MHz, $CDCl_3$) 8.23-8.18 (2H, m, ArH), 7.57-7.51 (2H, m, ArH), 3.44 (2H, q, ^3J 7.1, CH_2NCH_2), 3.33 (2H, q, ^3J 7.1, CH_2NCH_2), 1.25 (3H, t, ^3J 7.1, NCH_2CH_3), 1.15 (3H, t, ^3J 7.1, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 155.5 (dd, $^1J_{CF}$ 294.5, 293.3, Cq, CF_2), 152.4 (dd, $^4J_{CF}$ 3.2, 2.0, Cq, CO), 146.9 (t, $^6J_{CF}$ 2.0, Cq-NO_2), 136.8 (dd, $^3J_{CF}$ 7.5, 1.7, Cq), 125.9 (dd, $^4J_{CF}$ 7.5, 3.7, CH), 123.8 (d, $^5J_{CF}$ 0.7, CH), 111.5 (dd, $^2J_{CF}$ 36.9, 20.4, C=CF_2), [42.8, 42.1] (CH_2), [14.1, 13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -88.51 (1F, d, ^2J 36.9), -98.54 (1F, d, ^2J 36.9); [HRMS (ES-TOF, M+Na) Found: 323.0830; Calc. for $C_{13}H_{14}N_2O_4F_2Na$: 323.0819]. A satisfactory mass spectrum (ES) could not be obtained.

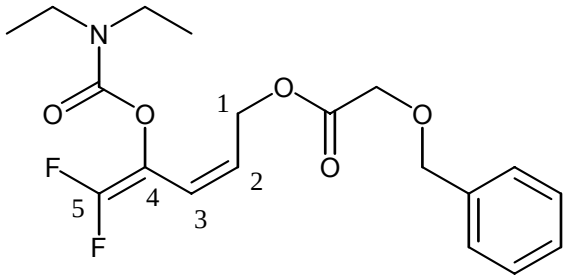
2-[1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro)-vinyl]-thiophene 99a



Thiophene **99a** was prepared as for **95a** using *tris*(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd), CuI (23 mg, 0.12 mmol), triphenylphosphine (53 mg, 0.20 mmol), 2-iodothiophene (232 mg, 1.10 mmol) and stannane **81** (539 mg, 1.15 mmol). After 45 h, the usual work-up afforded an orange oil. Purification by column chromatography over alumina (10% diethyl ether in light

petroleum) afforded thiophene **99a** as a colourless oil (127 mg, 44%); R_f (20% diethyl ether in light petroleum) 0.30; ν (film/cm^{-1}) 1732 s, 1423 s, 1304 m, 1260 s, 1222 m, 1149 s, 1098 m, 1033 m, 965 m, 913 m, 850 m, 821 m, 786 m, 753 m, 700 m; δ_H (300 MHz, $CDCl_3$) 7.28 (1H, dd, ^3J 4.8, ^4J 1.1, H-α), 7.06-7.05 (1H, m, H-β), 7.01-6.99 (1H, m, H-γ), 3.39 (2H, q, ^3J 7.2, NCH_2Me), 3.32 (2H, q, ^3J 7.2, NCH_2Me), 1.22 (3H, t, ^3J 7.2, NCH_2CH_3), 1.15 (3H, t, ^3J 7.2, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 154.1 (dd, $^1J_{CF}$ 292.2, 289.9, CF_2), 152.4 (CO), 132.5 (Cq), 127.5 (CH), 125.7 (dd, J_{CF} 5.1, 3.4, CH), 124.8 (dd, J_{CF} 6.2, 5.1, CH), [42.7, 42.1] (CH_2), [14.2, 13.3] (CH_3), *C*=CF_2 too weak to assign; δ_F (282 MHz, $CDCl_3$) -95.77 (1F, d, ^2J 45.5), -101.04 (1F, d, ^2J 45.5); *m/z* (CI) 279 (94%, M+NH_4), 262 (38%, M+H), 100 (12%), 74 (100%, H_2NEt_2), 72 (29%), 58 (20%), 52 (16%). This material decomposed to the [2+2] dimer before a HRMS measurement could be obtained.

(*Z*)-[4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro-penta-2,4-dienyl] (benzyloxy)-acetate 99b



Method A:

Ester **99b** was prepared as for **95a** using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), CuI (19 mg, 0.10 mmol), triphenylarsine (63 mg, 0.21 mmol), (*Z*)-3-iodopropen-2-yl benzyloxyacetate (271 mg, 0.81 mmol) and

stannane **81** (463 mg, 0.99 mmol). After 18.5 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl in light petroleum) afforded pentadienyl ester **99b** as a pale orange oil (145 mg, 46%); R_f (10% ethyl acetate in light petroleum) 0.15; ν (film/cm^{-1}) 1732 s, 1476 m, 1456 m, 1428 m, 1383 m, 1267 s, 1194 s, 1128 s, 1085 s, 1030 m, 752 m, 700 m; [Found: C, 59.22; H, 6.04; N, 3.48; Calc. for $C_{19}H_{23}O_5NF_2$: C, 59.52; H, 6.05; N, 3.65%]; δ_H (300 MHz, $CDCl_3$) 7.35-7.25 (5H, m, ArH), 6.00 (1H, ddt, ^3J 12.2, $^4J_{HF}$ 3.7, ^4J 2.4, H-3), 5.59 (1H, dtdd, ^3J 12.1, 6.3, $^5J_{HF}$ 1.5, 0.8, H-2), 4.85 (2H, ddd, ^3J 6.2, ^4J 2.4, $^6J_{HF}$ 1.5, H-1), 4.61 (2H, s, CH_2OBn), 4.09 (2H, s, OCH_2Ph), 3.37 (2H, q, ^3J 7.2, NCH_2Me), 3.32 (2H, q, ^3J 7.0, NCH_2Me), 1.18 (3H, t, ^3J 7.2, NCH_2*Me*), 1.15 (3H, t, ^3J 7.2, NCH_2*Me*); δ_C (75 MHz, $CDCl_3$) 169.9 (CO ester), 154.6 (dd, $^1J_{CF}$ 295.0, 293.3, CF_2), 152.2 (d, $^4J_{CF}$ 2.3, CO carbamate), 136.9 (Cq), 128.4 (CH), 127.9 (CH), 127.9 (CH), 125.3 (dd, $^3J_{CF}$ 11.0, 3.7, C-3), 118.4 (d, $^4J_{CF}$ 4.5, C-2), 111.2 (dd, $^2J_{CF}$ 39.0, 19.2, *C*=CF_2), 73.2 (OCH_2), 66.9 (OCH_2), 61.3 (OCH_2), [42.4, 41.8] (CH_2), [13.8, 13.1] (CH_3); δ_F (282 MHz, $CDCl_3$) -94.18 (1F, d, ^2J 35.7), -102.19 (1F, d, ^2J 35.7); *m/z* (CI) 401 (56%, M+NH_4), 237 (16%), 218 (49%, M-$OCOCH_2$OBn), 184 (23%), 106 (28%), 74 (100%, H_2NEt_2), 52 (59%).

Method B:

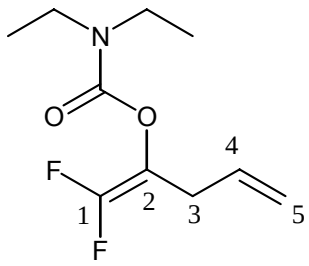
Ester **99b** was prepared as for **95a** using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (27 mg, 52 μmol Pd), CuI (21 mg, 0.11 mmol), triphenylphosphine (55 mg, 0.21 mmol), (*Z*)-3-iodopropen-2-yl benzyloxyacetate (267 mg, 0.81 mmol) and stannane **81** (519 mg, 1.11 mmol) in DMF (10 ml) at 50°C. After 20 h, the usual work-up afforded a crude orange oil. Purification by column chromatography over

silica gel (20% diethyl ether in light petroleum ⇒ 10% ethyl acetate in light petroleum) afforded dienyl ester **99b** as a pale brown oil (192 mg, 62%); R_f (10% ethyl acetate in light petroleum) 0.15. ^{19}F and ^{1}H NMR in agreement with those found for method A.

(*E*)-2-[4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoropenta-2,4-dienyloxy]-tetrahydro-pyran 99c

Pyran **99c** was prepared as for **95a** using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (27.5 mg, 53 μmol Pd), CuI (26 mg, 0.14 mmol), triphenylphosphine (54 mg, 0.21 mmol), (*E*)-3-iodopropenol THP ether (99 mg, 0.37 mmol) and stannane **81** (519 mg, 1.11 mmol) in DMF (3 ml). After 16 h, the usual work-up afforded a brown solid. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded protected 2,4-dien-1-ol **99c** (29 mg, 25%) as a pale yellow oil. NMR data was in close agreement with those obtained from the coupling of iodoalkene **82** and stannane **100b** (see pg 172).

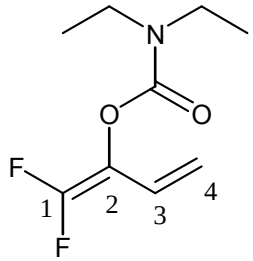
2-(*N,N*-Diethylcarbamoyloxy) -1,1-difluoro-1,4-pentadiene 99d



1,4-Diene **99d** was prepared as for **95a** using *tris*(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (26 mg, 50 μmol Pd), CuI (29 mg, 0.15 mmol),

triphenylphosphine (60 mg, 0.23 mmol), freshly distilled allyl bromide (100 μl, 1.16 mmol) and stannane **81** (519 mg, 1.11 mmol). After 18 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,4-diene **99d** as a pale yellow oil (213 mg, 87%); R_f (10% diethyl ether in light petroleum) 0.32; ν (film/cm^{-1}) 3085 w, 1782 s (C=CF_2), 1730 s (C=O), 1643 m (C=C), 1476 m, 1460 m, 1426 s, 1383 m, 1288 s, 1246 s, 1211 s, 1157 s, 1074 s, 1036 m, 992 m, 958 m, 924 m, 785 m, 757 m; δ_H (300 MHz, $CDCl_3$) 5.79-5.66 (1H, m, H-4), 5.14-5.04 (2H, m, H-5), 3.30-3.20 (4H, m, C*H*$_2$NC*H*$_2$), 3.00-2.95 (2H, m, H-3), 1.10 (6H, t, ^3J 7.0, (*Me*CH_2)$_2$N); δ_C (75 MHz, $CDCl_3$) 154.2 (dd, $^1J_{CF}$ 288.0, C-1), 152.7 (CO), 132.0 (t, $^4J_{CF}$ 3.0, C-4), 117.6 (C-5), 110.6-109.8 (m, C-2), [42.2, 41.7] (CH_2), 31.2 (d, $^3J_{CF}$ 2.3, C-3), [13.7, 13.0] (CH_3); δ_F (282 MHz, $CDCl_3$) -99.32 (1F, dt, ^2J 63.6, $^4J_{HF}$ 2.5), -111.49 (1F, dt, ^2J 63.6, $^4J_{HF}$ 3.8); [HRMS (EI, M+H) Found: 220.1159; Calc. for $C_{10}H_{16}NO_2F_2$: 220.1149]; *m/z* (EI) 237 (35%, M+NH_4), 220 (100%, M+H), 170 (24%), 100 (66%, ODEC), 74 (69%, NH_2Et_2), 58 (23%), 44 (12%). Data are in close agreement with those reported by Howarth.[189a]

2-(*N,N*-Diethylcarbamoyloxy)-1,1-difluoro-1,3-butadiene 99e

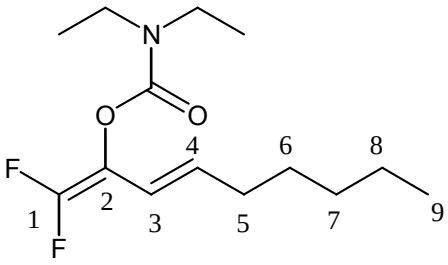


1,3-Diene **99e** was prepared as for **95a**, using CuI (94 mg, 0.50 mmol), triphenylarsine (331 mg, 1.08 mmol), palladium(II) acetate (593 mg, 0.26 mmol), 2-

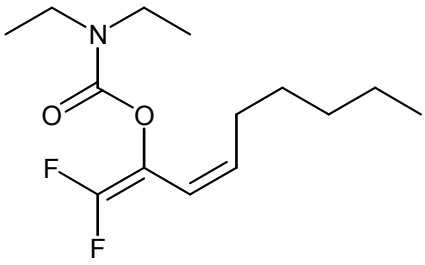
(*N,N*-diethylcarbamoyloxy)-1,1-difluoro-2-iodoethene **82** (1.56 g, 5.11 mmol) and tributylvinyltin (1.77 g, 5.58 mmol) in dry, degassed DMF (10 ml) at 100°C. The solution had an initial yellow colour, which changed to black after 6 min leaving a Pd black suspension. TLC after 80 min indicated no starting iodoalkene **82**. The mixture was diluted with diethyl ether (10 ml) and decanted from the Pd into a separating funnel. Water (30 ml) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded 1,3-diene **99e** as a pale yellow oil (925 mg, 88%); 88% by G.C; R_f (10% diethyl ether in light petroleum) 0.29; δ_H (300 MHz, $CDCl_3$) 6.34 (1H, dddd, $^3J_{trans}$ 17.3, $^3J_{cis}$ 11.2, $^4J_{HF}$ 3.3, 1.8, H-3), 5.21 (1H, d, $^3J_{trans}$ 17.3, H-4a), 5.17-5.12 (1H, m, H-4b), [3.42-3.30] (4H, m, two overlapping q, $N(CH_2CH_3)_2$), [1.23-1.13] (6H, m, two overlapping t, $N(CH_2CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 154.2 (dd, $^1J_{CF}$ 294.4, 292.2, CF_2), 152.3 (CO), 124.1 (d, $^3J_{CF}$ 5.1, *C*H=CH_2), [113.3, 113.1] (2 × d, $^4J_{CF}$ 4.5, =CH_2), 112.3 (dd, $^2J_{CF}$ 40.7, 18.1, *C*=CF_2), [42.5, 41.9] (CH_2), [14.0, 13.20] (CH_3); δ_F (282 MHz, $CDCl_3$) -95.50 (1F, d, ^2J 40.7), -105.50 (1F, dd, ^2J 40.7, $^4J_{HF}$ 3.8); [HRMS (CI, M+H) Found: 206.0995; Calc. for $C_9H_{14}NO_2F_2$: 206.0993]; *m/z* (CI) 223 (47%, $M+NH_4$), 206 (100%, M+H), 100 (11%, $CONEt_2$). This material decomposed before full characterisation could be achieved.

(*E*)-2-(*N,N*-Diethylcarbamoyloxy)-1,1-difluoro-1,3-nonadiene and

(*Z*)-2-(*N,N*-diethylcarbamoyloxy)-1,1-difluoro-1,3-nonadiene 99f



E

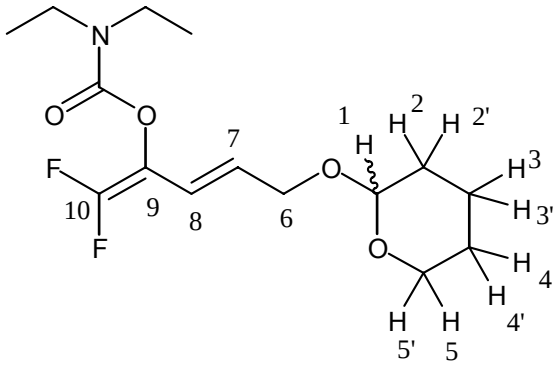


Z

1,3-Dienes **99f** were prepared as for **95a** using palladium(II) acetate (12.7 mg, 56.5 μmol), CuI (21.3 mg, 0.11 mmol), triphenylarsine (66 mg, 0.22 mmol), iodoalkene **82** (321 mg, 1.1 mmol) and 1-heptenyltributyltin (439 mg, 1.1 mmol, 5:1 *E*:*Z*) in dry DMF (5 ml). After 3 h, the usual work-up afforded a pale yellow oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded inseparable 1,3-dienes **99f** as pale yellow oils (205 mg, 71%, 5:1 *E*:*Z*); R_f (5% diethyl ether in light petroleum) 0.11; δ_H (300MHz, $CDCl_3$) 6.02-5.94 (0.83H, m, H-3, *E*-isomer), 5.81-5.74 (0.17H, m, H-3, *Z*-isomer), 5.70-5.59 (0.83H, unres. dt, H-4, *E*-isomer), 5.58-5.47 (0.17H, m, H-4, *Z*-isomer), 3.41-3.31 (4H, m, $N(CH_2CH_3)_2$ *E* and *Z* isomers), 2.21-2.07 (2H, m, H-5, *E* and *Z* isomers), 1.65-1.13 (12H, envelope, H-6, H-7, H-8 and $N(CH_2CH_3)_2$, *E* and *Z*-isomers), 0.94-0.85 (3H, envelope, H-9, *E* and *Z*-isomers); δ_C (75 MHz, $CDCl_3$)(*E*-isomer only, *Z*-isomer too weak to assign) 153.8 (t, $^1J_{CF}$ 289.9, Cq, C-1), 152.6-152.5 (m, Cq, CO), 130.6 (dd, $^3J_{CF}$ 11.6, 4.5, CH, C-3), 117.0-116.9 (m, CH, C-4), 112.0 (dd, $^2J_{CF}$ 40.7, 18.1, Cq, C-2), [42.5, 41.9] (CH_2, NCH_2CH_3), 32.5 (CH_2), 31.3 (CH_2), 28.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3), [14.1, 13.2] (CH_3, NCH_2CH_3); δ_F (282 MHz, $CDCl_3$) -98.14 (1F, d, ^2J 48.3, *E* and *Z* isomers), -104.56 to -104.73 (0.17F, m, *Z* isomer), -107.87 (0.83F, d, ^2J 47.0, *E* isomer);

[HRMS (EI, M) Found: 275.1692; Calc. for $C_{14}H_{23}NO_2F_2$: 275.1697]; *m/z* (EI) 275 (13%, M), 100(100%, $CONEt_2$), 72 (74%, H_2NEt_2), 55 (14%), 44 (32%).

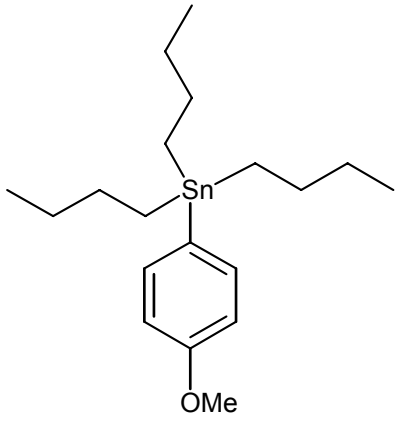
(*E*)-2-[4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoropenta-2,4-dienyloxy]-tetrahydro-pyran 99c



Pyran **99c** was prepared as for **95a** using palladium(II) acetate (12.8 mg, 57.0 μmol), triphenylarsine (68 mg, 0.22 mmol), CuI (22.3 mg, 0.12 mmol), iodoalkene **82** (340 mg, 1.11 mmol based upon 81% purity (enol carbamate **98** impurity)) and (*E*)-2-[3-(tributylstannyl)-prop-2-enyloxy]-tetrahydropyran (460 mg, 1.07 mmol) in DMF (10 ml). After 6.5 h, the usual work-up afforded a yellow oil. Purification over silica gel (20% diethyl ether in light petroleum) afforded 1,3-diene **99c** as a pale yellow oil (90 mg, 31%); R_f (20% diethyl ether in light petroleum) 0.05; δ_H (300 MHz, $CDCl_3$) 6.31-6.22 (1H, dm, H-8), 5.74 (1H, dt, ^3J 15.4, 5.9, H-7), 4.62 (1H, t, ^3J 3.3, H-1), 4.34-4.26 (1H, dm, H-6), 4.08-4.00 (1H, dm, H-6'), 3.87-3.80 (1H, m, H-5), 3.52-3.45 (1H, m, H-5'), 3.40-3.29 (4H, m, $N(CH_2CH_3)_2$), 1.87-1.45 (6H, envelope, H-2, H-2', H-3, H-3', H-4, H-4'), 1.21-1.13 (6H, envelope, $N(CH_2CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 154.2 (dd, $^1J_{CF}$ 293.9, 291.6, Cq, C-10), 152.3 (Cq, CO), 125.6 (dd, $^3J_{CF}$ 11.9, 4.3, CH, C-8), 119.0 (d, $^4J_{CF}$ 5.1, CH, C-7), 111.7 (dd, $^2J_{CF}$ 40.7, 18.6, Cq, C-9), 97.9 (CH, C-1), 66.7

(CH_2O), 62.1 (CH_2O), [42.5, 41.9] (CH_2), 30.5 (CH_2), 25.3 (CH_2), 19.3 (CH_2), [14.0, 13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -95.66 (1F, d, ^2J 41.9), -105.72 (1F, dd, ^2J 41.9, $^4J_{HF}$ 3.2); [HRMS (ES-TOF, M+Na) Found: 342.1490; Calc. for $C_{15}H_{23}NO_4F_2Na$: 342.1493]; *m/z* (CI) 337.7 (49%, M+NH_4), 319.0 (3%, M), 253.5 (100%, M+NH_4-THP), 218.4 (32%, M-OTHP), 102.3 (13%, OTHP+H).

Tributyl-(4-methoxyphenyl)-tin 100c



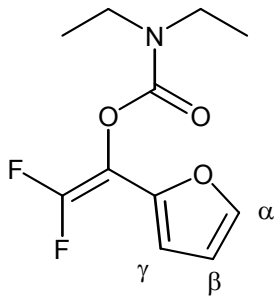
4-Iodoanisole (582 mg, 2.0 mmol) was dissolved in dry diethyl ether (20 ml) under a nitrogen atmosphere and the solution cooled to -85°C using a diethyl ether/solid CO_2 bath. After stirring for 5 min, ^{t}BuLi (2.6 ml of a 1.6 M solution in hexanes, 4.2 mmol) was dispensed *via* syringe into the reaction vessel, and the subsequent solution stirred for 30 min at this temperature. Tributyltin chloride (0.4 ml, 1.8 mmol) was then added and the solution allowed to stir for 1 h, then allowed to warm to room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic

extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over alumina (100% toluene) afforded aryl stannane **100c** as a pale yellow oil (555 mg, 76%); est. 90% purity by ^{1}H NMR; R_f (100% toluene) 1.00; δ_H (300 MHz, $CDCl_3$) 7.45-7.30 (2H, m, ArH, weak satellite peaks due to Sn coupling were also observed), 6.94-6.88 (2H, m, ArH), 3.81 (3H, s, OCH_3), 1.58-1.48 (6H, m), 1.39-1.27 (6H, m), 1.07-0.98 (6H, m), 0.89 (9H, t, ^{3}J 7.4, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 159.7 (Cq-OMe), 137.5 (CH), 132.0 (Cq), 113.9 (CH), 55.0 (OCH_3), 29.1 (CH_2), 27.4 (CH_2), 13.7 (CH_3), 9.6 (CH_2); *m/z* (EI) 397 (13%, M(^{118}Sn)+1), 341 (73%, M(^{120}Sn)-Bu), 285 (46%, M(^{120}Sn)-2Bu+1), 227 (84%, M(^{120}Sn)-3Bu), 135 (26%), 108 (77%, M+1-$SnBu_3$), 91 (26%), 78 (39%), 65 (38%), 56 (73%), 41 (100%), 32 (88%). This material was used without further characterisation.

4-[1-(*N,N*-Diethylcarbamoyloxy-2,2-difluoro)-vinyl]-1-methoxybenzene 95a from iodoalkene 82

Anisole **95a** was prepared using *tris*(dibenzylideneacetone)dipalladium (0)-chloroform adduct (25 mg, 48.3 μmol Pd), CuI (22 mg , 0.12 mmol), triphenylphosphine (51 mg, 0.19 mmol), (4-methoxyphenyl)tributyltin **100c** (487 mg, 1.2 mmol) and iodide **82** (305 mg, 1.0 mmol) in DMF (10 ml). After 45 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded anisole **95a** as a pale yellow oil (99 mg, 35%); R_f (20% ether in light petroleum) 0.19. NMR data were in agreement with those found for the Stille coupling protocol from stannane **81** (see pg 158).

2-[(1-(*N*,*N*-Diethylcarbamoyloxy)-2,2-difluoro)-vinyl]-furan 99g



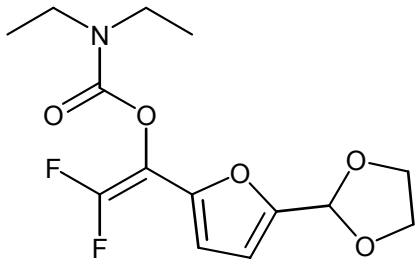
A mixture of copper(I) iodide (23 mg, 0.12 mmol), triphenylarsine (68 mg, 0.22 mmol), palladium(II) acetate (15 mg, 67 μmol) and iodoalkene **82** (280 mg, 0.93 mmol) in dry, degassed DMF (10 ml) was stirred at ambient temperature for 2 min under nitrogen. 2-(Tributylstannyl)furan (370 mg, 1.04 mmol) was added and the reaction heated at 100°C for 16 h. The solution had an initial orange colour, which changed to straw yellow upon stannane addition. The reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml) and water (30 ml). The ethereal phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded furan **99g** as a pale yellow oil (180 mg, 81%); R_f (10% diethyl ether in light petroleum) 0.23; ν (film/cm^{-1}) 1741 m, 1610 m, 1562 s, 1423 w, 1269 w, 1171 m, 982 s; δ_H (300 MHz, $CDCl_3$) 7.43 (1H, d, ^3J 1.5, H-α), 6.43 (1H, dd, ^3J 3.3, 1.5, H-β), 6.37 (1H, d, ^3J 3.3, H-γ), 3.43-3.32 (4H, two overlapping q, ^3J 7.0, CH_2NCH_2), 1.25-1.15 (6H, two overlapping t, ^3J 7.0, $N(CH_2CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 154.6 (t, $^1J_{CF}$ 291.0, CF_2), 152.8 (CO), 144.0 (d, $^3J_{CF}$ 10.2, Cq), 142.9 (HetArH), 111.5 (HetArH), 111.2-111.0 (m, C=CF_2), 108.6-108.4

(m, HetArCH), [42.9, 42.2] (CH_2), [14.2, 13.5] (CH_3); δ_F (282 MHz, $CDCl_3$) -95.94 (1F, d, ^2J 44.5), -101.38 (1F, d, ^2J 44.5); [HRMS (ES-TOF, M+Na) Found: 268.0761; Calc. for $C_{11}H_{13}NO_3F_2Na$: 268.0761]; *m/z* (ES-TOF) 268.1 (100%, M+Na).

2-[1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluoro)-vinyl]-thiophene 99a from iodo-alkene 82

Thiophene **99a** was prepared as for **99g** using *tris*(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (26 mg, 49.1 μmol Pd), CuI (26 mg, 0.14 mmol), triphenylphosphine (53 mg, 0.20 mmol), iodoalkene **82** (308 mg, 1.01 mmol) and 2-(tributylstannyl)thiophene (421 mg, 1.13 mmol) in DMF (10 ml), except that the stannane was added over 1 h *via* a syringe pump. After 30 h, the usual work-up afforded an orange oil (1.17 g). Purification by column chromatography over alumina (10 % diethyl ether in light petroleum) afforded thiophene **99a** as a colourless oil (94 mg, 36%); R_f (10 % ether in light petroleum) 0.31. NMR data were in agreement with those found using the Stille protocol from stannane **81** (see pg 166).

Attempted preparation of 1-[1-(*N,N*-diethylcarbamoyloxy-2,2-difluoro)-vinyl]-3-(1,3-dioxacyclopent-2-yl)-furan 99k



A mixture of CuI (240 mg, 0.13 mmol), triphenylarsine (70 mg, 0.23 mmol), palladium (II) acetate (12.5 mg, 56 μmol Pd) and 1-(*N,N*-diethylcarbamoyloxy)-2,2-difluoro-1-iodoethene **82** (341 mg, 0.92 mmol based on 82% purity (enol carbamate **98** impurity)) in dry DMF (10 ml) was stirred at ambient temperature for 2 min under nitrogen. 5-(Tributylstannyl)-2-(2,5-dioxacyclopentyl)-furan **100f** (614 mg, 1.03 mmol based on 72% purity) was added and the reaction mixture heated at 100°C for 16 h. The solution had an initial orange colour which changed to straw yellow upon addition of the stannane. A black mixture was observed by the end of the reaction, leaving a palladium black deposit. The mixture was diluted with diethyl ether (10 ml), decanted from the Pd and washed with water (20 ml), allowing the DMF to enter the aqueous phase. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 15 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford an orange oil. Analysis by ^{19}F NMR indicated the presence of furan **99k** (61%), enol carbamate **98** (28%) and dimer **97** (11%), in addition to several baseline fluorinated products, including those resulting from [2+2] cycloaddition reactions. Attempted purification by column chromatography

over silica gel (20% diethyl ether in light petroleum) failed to afford any of the desired product.

Data for crude **99k**; δ_F (282 MHz, $CDCl_3$) -95.96 (1F, d, ^2J 43.2), -101.66 (1F, d, ^2J 43.2). Shifts are in agreement with those found for furan **99g** and thiophene **99a**.

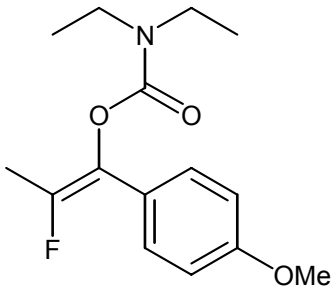
Procedure for Negishi coupling of 1-(*N*,*N*-diethylcarbamoyloxy)-2,2-difluorovinylzinc halides*:*

[1-(*N,N*-Diethylcarbamoyloxy)-2,2-difluorovinyl]-benzene 95d

n-Butyllithium (0.84 ml of a 2.38 M solution in hexanes, 2.0 mmol) was added dropwise by syringe to a –78°C solution of di*iso*propylamine (0.28 ml, 2.0 mmol) in THF (3 ml). The pale yellow solution was warmed to –30°C for 5 min to allow complete LDA formation, then re-cooled to –78°C. Trifluoroethyl *N,N*-diethylcarbamate **96** (0.16 ml, 0.99 mmol) was added dropwise over 15 min to afford an orange solution. After stirring for a further 20 min, a deep red solution was observed which changed to light orange upon addition of a solution of vacuum-dried zinc bromide (230 mg, 1.02 mmol) in THF (2 ml). After stirring for 1 h at –78°C, the solution was allowed to warm to room temperature, with no loss of the pale orange colour. Iodobenzene (0.12 ml, 1.07 mmol) was added in one portion, followed by triphenylphosphine (26.8 mg, 0.26 mmol) and *tris*(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (11.5 mg, 22.1 μmol Pd). The resulting heterogeneous mixture was stirred for 48 h at ambient temperature under a nitrogen atmosphere. Diethyl ether (5 ml) was added, followed by water (10 ml). The organic

phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded styrene **95d** as a colourless oil (134 mg, 54%); R_f (20% diethyl ether in light petroleum) 0.36. The data obtained agreed with those found for the Stille coupling, but the sample was found to be slightly cleaner by ^{1}H NMR owing to the absence of tin residues.

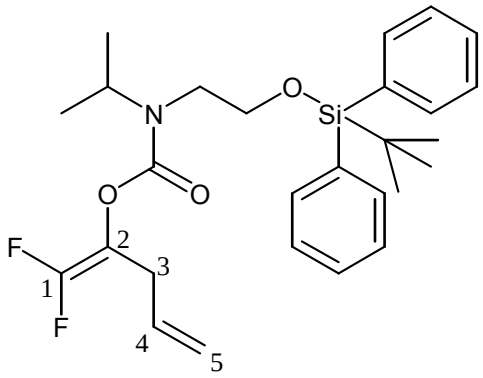
(*E*)-4-(1-(*N,N*-Diethylcarbamoyloxy)-2-fluoro-prop-1-enyl)-1-methoxybenzene 104



Methyllithium (2.8 ml of a 1.29 M solution in hexanes, 3.61 mmol) was added to a –78°C solution of styrene **95a** (338 mg, 1.19 mmol) in THF (15 ml) to afford a brown solution. After stirring for 1 h at this temperature, TMEDA (0.7 ml, 4.62 mmol) was added and the resulting solution stirred for 15 min. Chlorotrimethylsilane (0.5 ml, 3.94 mmol) was added and the reaction allowed to warm to ambient temperature over 1 h. A saturated solution of ammonium chloride (10 ml) was added and the phases separated. The aqueous phase was extracted with diethyl ether (3 × 10 ml). The combined organic extracts were consecutively washed with brine (15 ml) and a saturated solution of sodium bicarbonate (15 ml), then dried and concentrated under

reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded fluoroalkene **104** as pale yellow crystals (213 mg, 64%); 86% by GC; 97% by HPLC at 225 nm; HPLC t_r (20% water in MeCN, 1ml/min) 4.83 min; R_f (20% diethyl ether in light petroleum) 0.14; mp. 57-60°C; [Found: C, 64.11; H, 7.05; N, 4.76; Calc. for $C_{15}H_{20}FNO_3$: C, 64.04; H, 7.17; N, 4.98%]; ν (nujol mull/cm^{-1}) 1730 w, 1610 w, 1514 w, 1294 w, 1262 w, 1221 w, 1126 w, 1076 w, 936 w, 922 w; δ_H (300 MHz, $CDCl_3$) 7.31 (2H, d, ^3J 9.2, ArH), 6.87 (2H, d, ^3J 9.2, ArH), 3.78 (3H, s, OCH_3), [3.39-3.26] (4H, two overlapping q, CH_2NCH_2), 2.07 (3H, d, $^3J_{HF}$ 17.7, =CFCH_3), [1.21-1.10] (6H, two overlapping t, $N(CH_2CH_3)_2$); δ_C (75 MHz, $CDCl_3$) 159.3 (Cq-OMe), 153.5 (d, $^4J_{CF}$ 1.7, CO), 148.9 (d, $^1J_{CF}$ 252.1, CF), 130.4 (d, $^2J_{CF}$ 17.5, *C*=CF), 129.6 (d, $^4J_{CF}$ 2.8, CH), 125.7 (d, $^3J_{CF}$ 2.8, Cq), 113.6 (CH), 55.1 (OCH_3), [42.1, 41.7] (NCH_2), 14.9 (d, $^2J_{CF}$ 27.1, =CFCH_3), [14.0, 13.2] (NCH_2CH_3); δ_F (282 MHz, $CDCl_3$) -113.45 (q, $^3J_{HF}$ 17.8); [HRMS (ES-TOF, M+Na) Found: 304.1331; Calc. for $C_{15}H_{20}FNO_3Na$: 304.1325]; *m/z* (EI) 281 (18%, M), 153 (4%), 151 (4%), 135 (16%), 100 (100%, $CONEt_2$), 72 (39%, H_2NEt_2), 44 (8%); *m/z* (ES) 304.1 (100%, M+Na).

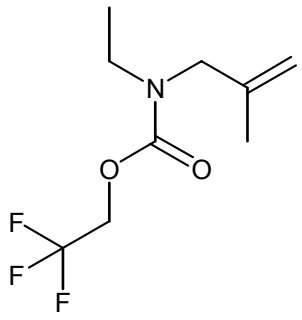
1,1-Difluoro-2-[(*N*-*iso*propyl-*N*-(*tert*-butyldiphenylsilyloxyethyl))-carbamoyloxy]-penta-1,4-diene 108



A mixture of copper(I) iodide (21 mg, 0.11 mmol), triphenylphosphine (54 mg, 0.21 mmol) and *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (25 mg, 48 μmol Pd) was pump-purged twice with argon, then degassed DMF (5 ml) was added. A solution of allyl bromide (90 μl, 1.08 mmol) in DMF (2 ml) was added and the mixture heated to 50°C under an argon atmosphere. A solution of 1,1-difluoro-2-[(*N*-*iso*propyl-*N*-(*tert*-butyldiphenylsilyloxyethyl))-carbamoyloxy]-1-(tributylstannyl)-ethene (660 mg, 0.91 mmol) in DMF (2 ml) was added in one portion and the reaction mixture heated at 50-65°C until TLC indicated consumption of starting material. The reaction was diluted with diethyl ether (10 ml) and water (20 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded a yellow oil (230 mg, 73%) consisting of an inseparable mixture of 1,4-diene **108** (60%) and enol carbamate (13%). Purification by preparative HPLC afforded diene **108** as a colourless oil; R_f (20% diethyl ether in light petroleum) 0.66; δ_H (300 MHz, $CDCl_3$) 7.67 (4H, d, ^3J 6.2, ArH), 7.44-7.36 (6H, m, ArH), [5.81-5.69,

5.67-5.54] (1H, 3:7, m, H-4), [5.16-4.95] (2H, m, H-5), [4.21-4.12, 4.09-4.00] (1H, 7:3, m, NC*H*Me_2), 3.78-3.69 (2H, m, $NCH_2C\mathit{H}_2O$), [3.38-3.33, 3.30-3.25] (2H, 3:7, m, $NC\mathit{H}_2CH_2O$), [3.05-3.01, 2.95-2.89] (2H, 3:7, m, H-3), 1.12-1.09 (6H, m, $NCH\mathit{Me}_2$), 1.06 (9H, s, ^{t}Bu-Si); δ_c (75 MHz, $CDCl_3$) 154.3 (dd, $^1J_{CF}$ 288, 287, C-1), [152.9, 152.8] (CO), 135.5 (ArCH), 133.4 (Cq), 132.1 (ArCH), 129.8 (CH), 127.7 (ArCH), 117.8 (CH2), 110.5-109.9 (m, $^2J_{CF}$ 46.8, C-2), 62.7 (CH_2O, major rotamer), 62.0 (CH_2O, minor rotamer), 49.0 ($Me_2\mathit{C}HN$, minor rotamer), 48.7 ($Me_2\mathit{C}HN$, major rotamer), 46.0 (CH_2N, minor rotamer), 44.7 (CH_2N, major rotamer), 31.4 (CH_2, C-3), 26.8 (CH_3, $C(\mathit{C}H_3)_3$), 20.9 (CH_3, $(\mathit{C}H_3)_2CHN$, minor rotamer), 20.2 (CH_3, $(\mathit{C}H_3)_2CHN$, major rotamer), 19.2 (Cq, $\mathit{C}(CH_3)_3$); δ_F (282 MHz, $CDCl_3$) major rotamer (66%*)* -98.8 (1F, m), -111.30 to -111.56 (1F, m, ^2J 62.3); minor rotamer (34%*)* -99.1 (1F, d, ^2J 64.9), -111.18 to -111.44 (1F, m, ^2J ca. 64.0); [HRMS (ES-TOF, M+Na) Found 510.2258; Calc. for $C_{27}H_{35}NO_3F_2NaSi$: 510.2252]. A satisfactory mass spectrum could not be obtained.

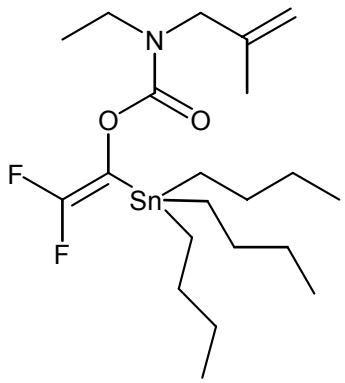
2,2,2-Trifluoroethyl N-ethyl-N-(2-methylallyl)carbamate 109b



2,2,2-Trifluoroethanol (7.25 ml, 100.4 mmol) was added to a solution of 1,1-carbonyldiimidazole (16.25 g, 100.4 mmol) in DCM (220 ml) at ambient temperature and the resulting solution stirred for 16 h. Imidazole (7.76 g, 114.0 mmol) and *N*-(2-

methylallyl)-ethylamine (14.5 ml, 110.1 mmol) were added and the resulting solution stirred for a further 16 h. The reaction mixture was concentrated under reduced pressure to half volume. The residual mixture was transferred to a separating funnel and washed twice with HCl (2 × 100 ml of a 0.5M aqueous solution). The organic layer was separated, dried and concentrated under reduced pressure to afford carbamate **109b** as a pale yellow oil (21.70 g, 96%). Purification by distillation under reduced pressure afforded **109b** as a colourless oil (21.63 g, 96%); 100% by GC; bp. 51°C/ 11 mmHg; [Found: C, 47.97; H, 6.08; N, 6.21; Calc. for $C_9H_{14}O_2NF_3$: C, 48.00; H, 6.27; N, 6.22%]; ν (film/cm^{-1}) 2979 m, 2941 m, 1720 m, 1659 w, 1476 m, 1432 m, 1381 m, 1290 m, 1254 m, 1170 m, 1099 m, 975 m, 903 w, 763 w; δ_H (300 MHz, $CDCl_3$) 4.85 (1H, bd s, =C$H_a$$H_b$), [4.78, 4.76] (1H, =C$H_a$$H_b$), [4.53-4.41] (2H, two overlapping q of two rotamers, CH_2CF_3), 3.80 (2H, d, ^2J 12.0, NCH_2vinyl), [3.27-3.23] (2H, two overlapping q, NCH_2Me), 1.66 (3H, s, =C(CH_3)vinyl), [1.10-1.09] (3H, two overlapping t, NCH_2*Me*); δ_c (75 MHz, $CDCl_3$) [154.6, 154.1] (CO), 140.8 (Cq), 123.3 (q, $^1J_{CF}$ 277.5, CF_3), [112.4, 112.3] (=CH_2), 61.3 (q, $^2J_{CF}$ 36.1, CH_2CF_3), [52.9, 52.1] (CH_2), [42.0, 41.2] (CH_2CH_3), 19.7 (CH_3), [13.1, 12.6] (CH_2CH_3); δ_F (282 MHz, $CDCl_3$) [-74.39, -74.46] (3F, t, $^3J_{HF}$ 8.9); [HRMS (ES-TOF, M+Na) Found: 248.0866; Calc. for $C_9H_{14}O_2NF_3Na$: 248.0874]; *m/z* (EI) 225 (100%, M), 210 (50%, M-Me), 184 (61%, M-MeC=CH_2), 170 (12%), 156 (17%), 142 (10%, 126 (16%), 110 (5%), 98 (46%, N(Et)CH_2C(Me)=CH_2), 92 (11%), 83 (41%, CH_2CF_3), 55 (75%, CH_2C(Me)=CH_2).

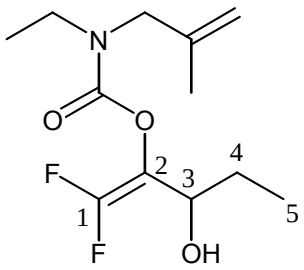
1-Tributylstannyl-1-[(*N*-ethyl-*N*-(2-methylallyl))carbamoyloxy]-2,2,2-trifluoro-ethene 112



n-Butyllithium (2.8 ml of a 2.4 M solution in pentanes, 6.8 mmol) was added over 20 min to a -78°C solution of di*iso*propylamine (0.9 ml, 6.8 mmol) in dry THF (5 ml). The pale yellow solution was allowed to warm slightly by removal from the Dewar flask for 5 min then re-cooled to -78°C. Carbamate **109b** (759 mg, 3.4 mmol) was added over 25 min, affording a brown solution, which was left to stir at this temperature for 2 h. Tributyltin chloride (1.0 ml, 3.6 mmol) was added in one portion and the reaction mixture stirred for 1 h at -78°C, before being allowed to warm to room temperature, affording a yellow solution. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (15 ml), then diluted with diethyl ether (30 ml) and water (30 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude orange oil. Diethyl ether (10 ml) was added followed by KF (10 ml of a 1 M aqueous soln) and the resulting mixture stirred rapidly for 30 min. The suspension was filtered and the filtrate extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried

and concentrated under reduced pressure. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded stannane **112** as a colourless oil (1.27 g, 76%); 88% by GC; R_f (5% diethyl ether in light petroleum) 0.68; ν (film/cm^{-1}) 3081 w, 2925 s, 1705 s, 1462 s, 1425 s, 1378 m, 1259 s, 1193 m, 1151 s, 1108 m, 1003 m, 966 w, 900 w, 797 w, 761 w; δ_H (300 MHz, $CDCl_3$) 4.86 (1H, s, =C*H*$_a$H$_b$), 4.80 (1H, s, =CH$_a$*H*$_b$), 3.82 (2H, s, NC*H*$_2$vinyl), [3.30-3.20] (2H, m, NC*H*$_2$CH$_3$), 1.69 (3H, s, C(C*H*$_3$)=CH$_2$), 1.55-1.44 (6H, m, 3 × CH$_2$), 1.36-1.24 (6H, m, 3 × CH$_2$), 1.14-0.97 (9H, envelope, 3 × CH$_2$, NCH$_2$C*H*$_3$), 0.88 (9H, t, ^3J 7.4, 3 × CH$_3$); δ_C (75 MHz, $CDCl_3$) 162.1-155.0 (triplet of multiplets, centred around 158.5, CF_2), 157.9-157.9 (m, CO), 154.6-154.3 (doublet of multiplets, *C*=CF$_2$), 140.9 (=CH$_2$), [112.4, 112.1] (*C*=CH$_2$), [52.5, 52.2] (NCH$_2$C(Me)=CH$_2$), [41.7, 41.0] (NCH$_2$CH$_3$), 28.8 (CH$_2$, satellite peaks due to Sn coupling were also observed), 27.2 (CH$_2$, satellite peaks due to Sn coupling were also observed), 19.8 (C(*C*H$_3$)=CH$_2$), 13.7 (CH$_3$), [13.1, 12.7] (CH$_3$), 11.4 (CH$_2$); δ_F (282 MHz, $CDCl_3$) [-83.13, -83.18] (1F, d, ^2J 63.6), [-110.07, -110.13] (1F, d, ^2J 63.6; satellite peaks due to Sn coupling were also observed); [HRMS (ES-TOF, M(^{120}Sn)+Na) Found: 518.1874; Calc. for $C_{21}H_{39}NO_2F_2Na^{120}Sn$: 518.1869]; *m/z* (ES-TOF) 550.3 (6%, M(^{120}Sn)+Na+MeOH), 518.2 (100%, M(^{120}Sn)+Na), 517.2 (19%, M(^{119}Sn)+Na), 516.2 (67%, M(^{118}Sn)+Na), 515.2 (23%, M(^{117}Sn)+Na), 514.2 (34%, M(^{116}Sn)+Na).

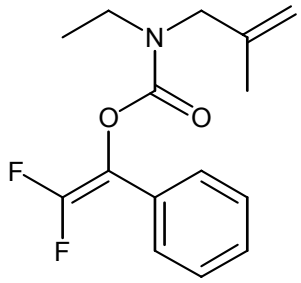
(3*RS*)-2-(*N*-Ethyl-*N*-2-methallylcarbamoyloxy)-1,1-difluoro-pent-1-en-3-ol 113



n-Butyllithium (6.30 ml of a 1.6 M in hexane, 10.08 mmol) was added dropwise to a -78°C solution of di*iso*propylamine (1.33 ml, 10.23 mmol) in THF (20 ml). Following the addition, the solution was removed from the Dewar for 5 min to complete LDA formation, before being recooled to -78°C. 2,2,2-Trifluoroethyl *N*-ethyl-*N*-2-methallylcarbamate **109b** (1.1 ml, 5.0 mmol) was added dropwise *via* syringe over 25 min. During this period, the solution changed from pale yellow, through to a deeper yellow colour. After stirring for 30 min, freshly distilled propanal (0.4 ml, 5.51 mmol) was added in one-portion and the resulting pale yellow solution maintained at -78°C for 1 h, affording a pale orange solution. After this period, boron trifluoride-diethyl ether complex (0.70 ml, 5.52 mmol) was added, which immediately discharged the orange colour, affording a pale yellow solution. The solution was allowed to warm to 0°C by use of an ice bath, then stirred for a further 1 h at this temperature. The pale yellow solution was then quenched with a saturated aqueous solution of ammonium chloride (50 ml). Diethyl ether (50 ml) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 40 ml) and the combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil (1.6 g). Purification by column chromatography over silica gel (20% ethyl acetate in light petroleum) afforded allylic alcohol **113** as a colourless oil (858

mg, 65%); 98% by GC; R_f (20% ethyl acetate in light petroleum) 0.33; ν (film/cm^{-1}) 3450 bd (OH), 3082 w, 2974 m, 2941 m, 2881 m, 1770 s (C=CF_2), 1712 s (C=O), 1460 m, 1427 m, 1381 m, 1297 m, 1231 m, 1134 m, 1071 m, 1016 m, 972 wm 897 m, 838 w, 797 w, 756 w, 735 w; δ_H (300 MHz, $CDCl_3$) 4.88 (1H, s, =C$H_a$$H_b$), 4.80 (1H, s, =$CH_a$$H_b$), 4.33-4.21 (1H, m, C*H*OH), 3.82 (2H, s, NCH_2All), [3.59, 3.55] (1H, d, ^3J 5.4, OH), 3.28 (2H, q, ^3J 7.1, NCH_2Me), [1.69, 1.67] (3H, 2 × s, C(CH_3)=CH_2), 1.24-1.09 (5H, envelope, CHCH_2Me, NCH_2CH_3), [0.90, 0.87] (3H, t, ^3J 6.7, CH_2CH_3); δ_C (300 MHz, $CDCl_3$) 155.4 (CO), 154.8 (dd, $^1J_{CF}$ 295.9, 287.4, C-1), 154.7 (dd, $^1J_{CF}$ 291.4, 286.8, C-1 rotamer), [140.4, 140.2] (*C*(Me)=CH_2), 113.2-113.0 (m, C-2), [112.7, 112.3] (=*C*H_2), 68.4-68.3 (m, C-3), [53.1, 52.7] (NCH_2C(Me)=CH_2), [42.4, 41.8] (NCH_2Me), [26.7, 26.6] (C-4), [19.7, 19.7] (C(*C*H_3)=CH_2) [13.2, 12.4] (NCH_2CH_3), 9.7 (C-5); δ_F (282 MHz, $CDCl_3$) [-95.52, -95.94] (1F, d, ^2J 52.8), -106.17 (1F, d, ^2J 52.8); [HRMS (ES, M+Na) Found: 286.1235; Calc. for $C_{12}H_{19}O_3NF_2Na$: 286.1231]; *m/z* (ES-TOF) 286.1 (100%, M+Na).

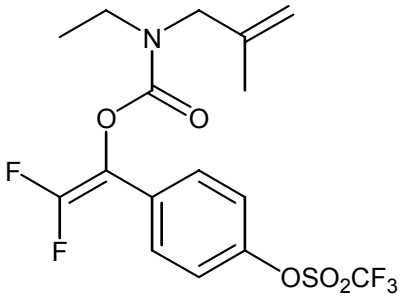
[((1-(*N*-Ethyl-*N*-2-methylallyl)-carbamoyloxy)-2,2-difluoro)-vinyl]-benzene 114



Styrene **114** was prepared as for **95a** using palladium(II) acetate (61 mg, 273 μmol), CuI (426 mg, 2.23 mmol), triphenylphosphine (265 mg, 1.03 mmol), iodobenzene

(1.2 ml, 10.7 mmol) and stannane **112** (4.94 g, 8.78 mmol based on 88% purity) in DMF (20 ml). After 16 h, the usual work-up afforded an orange oil. Flash column chromatography over silica gel (15% diethyl ether in light petroleum) removed baseline colour to afford a colourless oil (2.30 g). Purification by distillation under reduced pressure (60°C/11 mmHg $\Rightarrow$ 95°C/13 mmHg $\Rightarrow$ 95°C/2 mmHg $\Rightarrow$ 104°C/0.03 mmHg) afforded styrene **114** as a colourless oil (1.85 g, 72%); 95% by GC; bp. 104°C/0.03 mmHg; ν (film/cm^{-1}) 3081 w, 1736 s, 1658 w, 1422 m, 1275 s, 1147 s, 1130 m, 982 s; δ_H (300 MHz, $CDCl_3$) 7.44-7.27 (5H, m, ArH), [4.95, 4.90, 4.90, 4.88] (2H, s, =C*H*$_2$), [3.97, 3.88] (2H, s, NCH_2), [3.42, 3.34] (2H, q, ^3J 7.1, NC*H*$_2$Me), [1.78, 1.71] (3H, s, C(C*H*$_3$)=CH_2), [1.24, 1.15] (3H, t, ^3J 7.2, NCH_2CH_3); δ_C (75 MHz, ,$CDCl_3$) 155.0 (t, $^1J_{CF}$ 289.9, CF_2 of rotamer), 155.0 (t, $^1J_{CF}$ 289.5, CF_2 of rotamer), 153.7 (CO of rotamer), 153.1 (CO of rotamer), 140.8 (*C*Me=CH_2 of rotamer), 140.6 (*C*Me=CH_2 of rotamer), [130.2, 130.1] (C_q), [128.6, 128.6] (CH), 128.2 (CH), 125.7-125.4 (m, CH), [112.7, 111.9] (=*C*H_2), [53.0, 52.4] (*C*H_2 of allyl), [42.4, 41.5] (N*C*H_2Me), [20.0, 19.7] (CH_3), [13.5, 12.7] (CH_2CH_3); δ_F (282 MHz, $CDCl_3$) [-93.39, -93.70] (1F, d, ^2J 49.6), [-103.72, -103.77] (1F, d, ^2J 49.6); [HRMS (ES-TOF, M+Na) Found: 304.1134; Calc. for $C_{15}H_{17}NO_2F_2Na$: 304.1125]; *m/z* (ES) 304.1 (100%, M+Na).

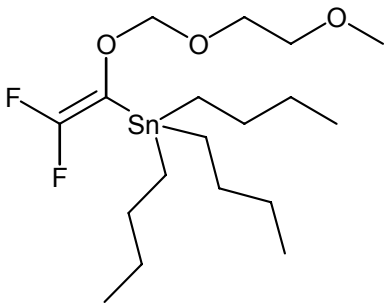
[4-((1-(*N*-Ethyl-*N*-2-methylallyloxy)-2,2-difluoro)-vinyl)-phenyl] trifluoromethane-sulfonate 115



Triflate **115** was prepared as for **114** using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (48 mg, 92 μmol Pd), triphenylphosphine (107 mg, 0.41 mmol), CuI (42 mg, 0.22 mmol), triflate **120a** (792 mg, 2.00 mmol) and stannane **112** (960 mg, 2.10 mmol) in DMF (5 ml). After 16 h, the usual work-up afforded a yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded triflate **115** as a colourless oil (490 mg, 59%); 100% by GC; R_f (10% diethyl ether in light petroleum) 0.23; ν (film/cm^{-1}) 3083 w, 2981 m, 2936 m, 1738 s, 1505 m, 1426 s, 1281 s, 1251 s, 1216 s, 1145 s, 1019 w, 987 m, 889 s, 847 m, 791 w, 756 w, 607 m; δ_H (300 MHz, $CDCl_3$) [7.50, 7.49] (2H, 2 × d, ^3J 8.8, ArH), [7.31-7.26] (2H, m, ArH), [4.95, 4.91, 4.87, 4.84] (2H, 4 × s, $=CH_aH_b$), [3.95, 3.88] (2H, 2 × s, $NCH_2C(Me)=CH_2$), [3.45-3.30] (2H, m, NCH_2CH_3), [1.77, 1.70] (3H, 2 × s, $C(CH_3)=CH_2$), [1.23, 1.16] (3H, 2 × t, ^3J 7.4, NCH_2CH_3); δ_C (75 MHz, $CDCl_3$) 159.0-151.2 (triplet of multiplets, centred at 155.1, CF_2), [153.3-152.7] (m, CO), 148.8 (t, $^3J_{CF}$ 2.3, Cq), 140.4 ($=CH_2$), 130.7-130.6 (m, Cq), [127.4-127.2] (m, CH), [121.6, 121.5] (CH), 118.7 (q, $^1J_{CF}$ 321.0, CF_3), [112.7, 111.7] ($C(Me)=CH_2$), [53.0, 52.4] (CH_2), [42.6, 41.6] (CH_2), [19.9, 19.7] (CH_3), [13.5, 12.6] (CH_3), $C=CF_2$ too weak to

assign; δ_F (282 MHz, $CDCl_3$) -72.75 (3F, s, CF_3), [-91.18, -91.54] (1F, d, ^2J 44.4), -101.72 (1F, d, ^2J 44.4); [HRMS (ES-TOF, M+H) Found: 430.0755; Calc. for $C_{16}H_{16}NO_5F_5S$: 430.0748]; *m/z* (ES-TOF) 452.1 (30%, M+Na), 430.1 (100%, M+H).

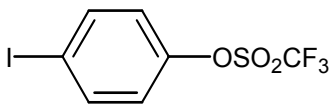
2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-1-(tributylstannyl)-ethene 118



n-Butyllithium (16.8 ml of a 2.38 M solution in hexanes, 40.0 mmol) was added to a –78°C solution of di*iso*propylamine (5.4 ml, 40.0 mmol) in THF (30 ml). The flask was removed from the dewar for 5 min to complete LDA formation, then recooled to –78°C. 1,1,1-Trifluoro-2-(2-methoxy-ethoxymethoxy)ethane **119** (3.2 ml, 20.0 mmol) was added dropwise over 10 min to afford a pale yellow solution. The reaction mixture was then allowed to stir for a further 20 min to afford a thick brown solution. Tributyltin chloride (5.6 ml, 20.0 mmol) was added in one portion and the reaction allowed to warm to ambient temperature over 3 h. The reaction was quenched with a saturated solution of ammonium chloride (50 ml), then diethyl ether (50 ml) added. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a yellow oil. Diethyl ether (20 ml) was added followed by KF (15 ml of a 1 M solution in water) and the resulting solution stirred rapidly for 30

min. The suspension was filtered using suction filtration and the organic phase separated. The ether phase was dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by flash column chromatography over a 5 cm pad of silica gel (5% diethyl ether in light petroleum) afforded stannane **118** as a colourless oil (8.12 g, 89%); R_f (5% diethyl ether in light petroleum) 0.50; δ_H (300 MHz, $CDCl_3$) 4.74 (2H, s, OCH_2O), 3.76-3.74 (2H, m, CH_2O), 3.56-3.53 (2H, m, CH_2O), 3.38 (3H, s, OCH_3), 1.55-1.44 (6H, m), 1.37-1.24 (6H, m), 1.04-0.99 (6H, m), 0.88 (9H, t, ^3J 7.4, $Sn(CH_2CH_2CH_2CH_3)_3$); δ_C (75 MHz, $CDCl_3$) 159.7 (dd, $^1J_{CF}$ 317.2, 267.5, CF_2), 96.2-96.1 (m, OCH_2O), 71.6 (CH_2O), [67.7, 67.7] (CH_2O), 59.0 (OCH_3), 28.7 (s, satellite peaks due to Sn coupling were also observed, CH_2), 27.2 (s, satellite peaks due to Sn coupling were also observed, CH_2), 13.6 (CH_3), 10.2 (dd, $^4J_{CF}$ 2.0, 1.1, CH_2), C=CF_2 too weak to assign; δ_F (282 MHz, $CDCl_3$) -84.96 (1F, d, ^2J 66.1, satellite peaks due to Sn coupling were also observed), -109.34 (1F, d, ^2J 66.1, satellite peaks due to Sn coupling were also observed). NMR data were in close agreement with those reported by Patel.[101]

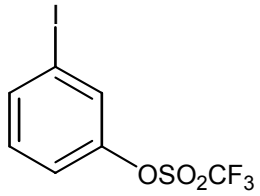
4-Iodophenyl trifluoromethanesulfonate 120a



4-Iodophenol (7.80 g, 35.5 mmol) was dissolved in pyridine (20 ml) and cooled to 0°C under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (6.0 ml, 35.5 mmol) was added dropwise and the resulting solution allowed to warm to room

temperature. The solution was stirred overnight until TLC indicated complete consumption of starting iodophenol. The mixture was quenched with water (30 ml) and diluted with diethyl ether (50 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were sequentially washed with water (30 ml), 3M HCl (30 ml) and brine (30 ml), then dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate **120a** as a colourless oil (11.60 g, 93%); 100% by GC; R_f (100% light petroleum) 0.30; ν (film/cm^{-1}) 1479 m, 1427 m, 1396 w, 1251 m, 1214 m, 1179 w, 1141 m, 1957 w, 1010 m, 885 m, 829 m, 747 m; δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, ^3J 8.5, ArH), 7.01 (2H, d, ^3J 8.5, ArH); δ_C (75 MHz, $CDCl_3$) 149.4 (Cq), 139.4 (ArCH), 123.4 (ArCH), 118.7 (q, $^1J_{CF}$ 320.8, CF_3), 93.2 (Cq); δ_F (282 MHz, $CDCl_3$) -72.7 (3F, s). NMR data were in agreement with those reported by Qing *et al.*.[179]

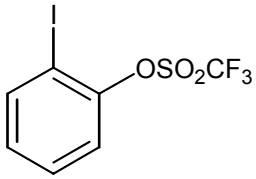
3-Iodophenyl trifluoromethanesulfonate 120b



Triflate **120b** was prepared as for **120a**, using 3-iodophenol (5.17 g, 23.5 mmol), pyridine (13 ml) and trifluoromethanesulfonic anhydride (5 ml, 29.7 mmol). After the usual work-up, a crude yellow oil was isolated. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate **120b** as a

colourless oil (7.85 g, 95%); 100% by GC; R_f (100% light petroleum) 0.47; ν (film/ cm^{-1}) 1588 m, 1574 s, 1465 s, 1428 s, 1249 s, 1214 s, 1169 m, 1142 s, 1089 w, 1060 w, 999 w, 893 s, 792 s, 753 m, 679 w, 606 s, 569 s; [Found: C, 23.99; H, 1.00; Calc: C, 23.88; H, 1.15%]; %]; δ_H (300 MHz, $CDCl_3$) 7.73 (1H, dd, ^3J 7.7, ^4J 1.1, ArH), 7.63 (1H, t, ^4J 2.0, ArH), 7.29-7.24 (1H, m, ArH), 7.18 (1H, t, ^3J 8.1, ArH); δ_C (75 MHz, $CDCl_3$) 149.2 (Cq), 137.6 (CH), 131.4 (CH), 130.4 (d, J 0.6, CH), 120.8 (d, J 0.6, CH), 118.6 (q, $^1J_{CF}$ 320.7, CF_3), 93.8 (Cq); δ_F (282 MHz, $CDCl_3$) -72.55 (3F, d, J 3.8). NMR data were in agreement with those reported by Qing *et al.*.[179]

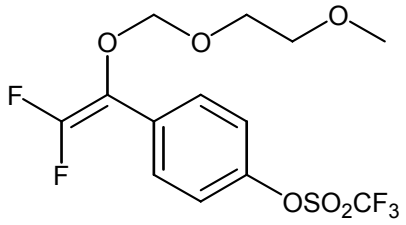
2-Iodophenyl trifluoromethanesulfonate 120c



Triflate **120c** was prepared as for **120a**, using 2-iodophenol (5.15 g, 23.4 mmol), pyridine (13 ml) and trifluoromethanesulfonic anhydride (4.0 ml, 23.8 mmol). After the usual work-up, a crude yellow oil was isolated. Purification by column chromatography over silica gel (100% light petroleum) afforded triflate **120c** as a colourless oil (7.77 g, 94%); 100% by GC; R_f (100% light petroleum) 0.24; ν (film/ cm^{-1}) 1573 w, 1463 m, 1427 s, 1248 s, 1213 s, 1167 m, 1138 s, 1118 w, 1042 w, 1022 w, 946 w, 886 s, 780 m, 765 m, 739 m, 702 w; [Found: C, 23.82; H, 1.16; S, 9.26; Calc: C, 23.88; H, 1.15; S, 9.11%]; δ_H (300 MHz, $CDCl_3$) 7.91 (1H, dd, ^3J 7.9, ^4J 1.7, ArH), 7.42 (td, ^3J 7.8, ^4J 1.7, ArH), 7.32 (1H, dd, ^3J 8.2, ^4J 1.4, ArH), 7.11 (1H, td,

^{3}J 7.7, ^{4}J 1.5, ArH); δ_C (75 MHz, $CDCl_3$) 150.2 (Cq), 140.8 (ArCH), 130.0 (ArCH), 129.6 (ArCH), 122.1-122.0 (m, ArCH), 118.7 (q, $^{1}J_{CF}$ 320.7, CF_3), 89.0 (Cq); δ_F (282 MHz, $CDCl_3$) -73.14 (3F, s, CF_3). NMR data were in agreement with those reported by Qing *et al.*.[179]

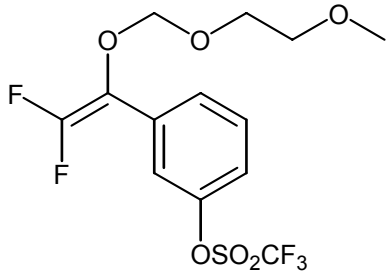
4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl)-phenyl] trifluoromethane-sulfonate 121a



A mixture of copper(I) iodide (756 mg, 3.97 mmol), triphenylphosphine (469 mg, 1.79 mmol) and palladium(II) acetate (107 mg, 0.48 mmol) was pump-purged twice with argon, then dry, degassed DMF (45 ml) added. A solution of 4-iodophenyl triflate **120a** (6.53 g, 18.54 mmol) in DMF (2 ml) was added and the mixture heated to 50°C. Stannane **118** (8.12 g, 17.76 mmol) was subsequently added and the mixture stirred for 16 h at this temperature. The mixture was allowed to cool to ambient temperature and diluted with diethyl ether (20 ml) and water (100 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 $\times$ 25 ml). The combined organic extracts were dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum $\Rightarrow$ 20% ethyl acetate in light petroleum) afforded triflate **121a** as a pale orange oil (6.32 g, 96%); 97% by GC; R_f (20% ethyl acetate in light petroleum) 0.44;

ν (film/cm^{-1}) 1731 m, 1504 m, 1428 s, 1271 s, 1251 s, 1215 s, 1179 m, 1142 s, 1103 m, 984 m, 941 m, 889 s, 847 m, 783 w, 758 w; δ_H (300 MHz, $CDCl_3$) 7.50 (2H, d, ^3J 8.9, ArH), 7.24 (2H, d, ^3J 8.9, ArH), 4.82 (2H, s, OCH_2O), 3.80-3.77 (2H, m, OCH_2CH_2O), 3.49-3.46 (2H, m, OCH_2CH_2O), 3.31 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 155.8 (t, $^1J_{CF}$ 292.0, CF_2), 148.9 (t, $^6J_{CF}$ 2.3, Cq), 130.7 (dd, $^3J_{CF}$ 4.7, 1.7, Cq), 128.5 (dd, $^4J_{CF}$ 6.2, 3.4, CH), 121.6 (CH), 118.7 (q, $^1J_{CF}$ 320.0, CF_3), 114.6 (dd, $^2J_{CF}$ 34.4, 19.5, C=CF_2), 95.8 (t, $^4J_{CF}$ 3.0, OCH_2O), 71.5 (OCH_2), 68.7 (OCH_2), 59.0 (OCH_3); δ_F (282 MHz, $CDCl_3$) -73.0 (3F, s, CF_3), -95.79 (1F, d, ^2J 51.5), -104.51 (1F, d, ^2J 51.5); [HRMS (ES-TOF, M+Na) Found: 415.0247; Calc. for $C_{13}H_{13}O_6F_5SNa$: 415.0251]; *m/z* (CI) 410 (100%, M+NH_4), 361 (12%), 346 (43%), 317 (10%), 287 (25%, M-OMEM), 253 (41%), 223 (12%), 189 (8%), 171 (6%), 154 (19%); *m/z* (ES-TOF) 415.1 (100%, M+Na).

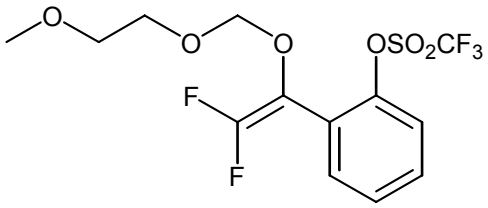
3-[(2,2-Difluoro-1-(2-methoxyethoxymethoxy))-vinyl)-phenyl] trifluoromethane-sulfonate 121b



Triflate **121b** was prepared as for **121a** using copper(I) iodide (440 mg, 2.3 mmol), triphenylphosphine (270 mg, 1.0 mmol), palladium(II) acetate (60 mg, 0.27 mmol), 3-iodophenyl triflate **120b** (3.52 g, 10.0 mmol) and stannane **118** (4.58 g, 10.0 mmol) in DMF (28 ml). After 16 h, the usual work-up afforded an orange oil. Purification by

column chromatography over silica gel (5% diethyl ether in light petroleum ⇒ 20% diethyl ether in light petroleum) afforded triflate **121b** as an orange oil (3.24 g, 86%); 91% by GC; R_f (20% diethyl ether in light petroleum) 0.27; ν (film/cm^{-1}) 2931 m, 2888 m, 1729 s, 1612 m, 1577 m, 1489 m, 1426 s, 1369 w, 1272 s, 1246 s, 1215 s, 1027 m, 1009 m, 946 s, 896 s, 804 s, 762 m, 608 s; δ_H (300 MHz, $CDCl_3$) 7.52-7.43 (2H, envelope, ArH), 7.38 (1H, t, ^4J 1.8, ArH), 7.20 (1H, dt, ^3J 7.4, ^4J 2.2, ArH), 4.88 (2H, s, OCH_2O), 3.86-3.83 (2H, m, CH_2O), 3.54-3.51 (2H, m, CH_2O), 3.36 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$)155.8 (t, $^1J_{CF}$ 292.2, CF_2), 149.7 (Cq), 133.1 (dd, $^3J_{CF}$ 6.9, 2.0, Cq), 130.4 (CH), 126.3 (dd, $^4J_{CF}$ 7.2, 3.2, CH), 120.9-120.8 (m, CH), 119.3 (dd, $^4J_{CF}$ 5.8, 3.7, CH), 118.7 (q, $^1J_{CF}$ 320.7, CF_3), 114.5 (dd, $^2J_{CF}$ 34.2, 19.8, *C*=CF_2), 96.0 (t, $^4J_{CF}$ 2.9, OCH_2O), 71.5 (CH_2O), 68.7 (d, $^6J_{CF}$ 1.7, CH_2O), 58.9 (OCH_3); δ_F (282 MHz, $CDCl_3$) -72.83 (3F, s, CF_3), -94.59 (1F, d, ^2J 49.4), -103.09 (1F, d, ^2J 49.4); [HRMS (M+Na) Found: 415.0244; Calc. for $C_{13}H_{13}O_6F_5SNa$: 415.0251]; *m/z* (ES) 414.9 (100%, M+Na).

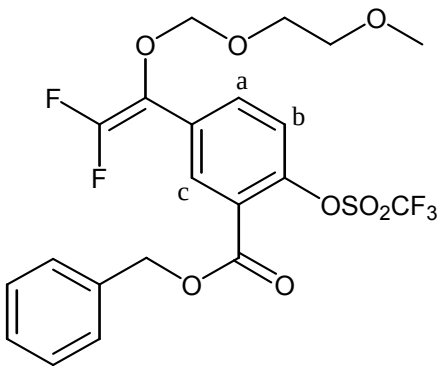
2-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl)-phenyl] trifluoromethane-sulfonate 121c



Triflate **121c** was prepared as for **121a** using palladium(II) acetate (65 mg, 0.29 mmol), triphenylphosphine (266 mg, 1.02 mmol), CuI (433 mg, 2.28 mmol), 2-

iodophenyl triflate **120c** (3.53 g, 10.03 mmol) and stannane **118** (4.58 g, 10.02 mmol). After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded triflate **121c** as an orange oil (810 mg, 21%); 97% by GC; R_f (10% diethyl ether in light petroleum) 0.15; ν (film/cm^{-1}) 2932 m, 2898 m, 1748 s, 1612 w, 1490 m, 1426 s, 1279 s, 1248 s, 1215 s, 1179 s, 1141 s, 1102 s, 986 s, 949 s, 886 s, 783 s, 779 s; δ_H (300 MHz, $CDCl_3$) 7.57-7.30 (4H, envelope, ArH), 4.79 (2H, s, OCH_2O), 3.81-3.78 (2H, m, OCH_2CH_2O), 3.53-3.50 (2H, m, OCH_2CH_2O), 3.36 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 154.9 (dd, $^1J_{CF}$ 292.2, 286.2, CF_2), 147.3 (dd, $^4J_{CF}$ 3.1, 1.7, Cq), 132.3 (t, $^4J_{CF}$ 2.9, CH), 131.3 (CH), 128.3 (CH), 123.5 (dd, $^3J_{CF}$ 4.8, 2.8, Cq), 122.0 (dd, $^5J_{CF}$ 2.3, 1.1, CH), 118.5 (q, $^1J_{CF}$ 319.9, CF_3), 110.8 (dd, $^2J_{CF}$ 40.7, 21.5, C=CF_2), 94.8 (t, $^4J_{CF}$ 2.6, OCH_2O), 71.4 (CH_2O), 68.2 (d, $^6J_{CF}$ 1.7, CH_2O), 59.0 (OCH_3); δ_F (282 MHz, $CDCl_3$) -73.85 (3F, s, CF_3), -97.28 (1F, d, ^2J 52.1), -104.94 (1F, d, ^2J 52.1); [HRMS (ES-TOF, M+Na) Found: 415.0263; Calc. for $C_{13}H_{13}O_6F_5Na$ S: 415.0251]; *m/z* (ES) 415 (100%, M+Na).

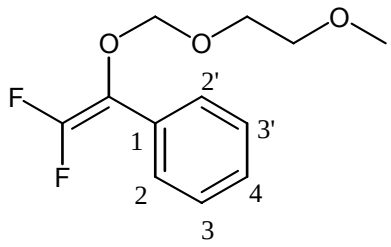
Benzyl 5-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-2-trifluoro-methanesulfonoxy-benzenecarboxylate 121d



Triflate **121d** was prepared as for **121a** using palladium(II) acetate (17 mg, 76 μmol), CuI (12 mg, 63 μmol), triphenylphosphine (75 mg, 292 μmol), benzyl 5-iodo-2-(trifluoromethanesulfonoxy)-benzene-carboxylate (1.30 g, 2.68 mmol) and stannane **118** (1.25 g, 2.74 mmol) in DMF (8 ml) at 50°C. After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (30% diethyl ether in light petroleum) afforded triflate **121d** as a pale yellow oil (986 mg, 70%); 96% by GC; R_f (30% diethyl ether in light petroleum) 0.21; ν (film/ cm^{-1}) 2930 m, 2891 m, 1733 s (CO), 1607 w, 1588 w, 1491 m, 1429 s, 1248 s, 1213 s, 1178 s, 1141 s, 1103 m, 1072 s, 1026 w, 945 m, 894 m, 758 w, 699 w; δ_H (300 MHz, $CDCl_3$) 8.18 (1H, d, ^3J 2.5, H-c), 7.71 (1H, ddd, ^3J 8.8, ^3J 2.5, $^5J_{HF}$1.1, H-a), 7.47-7.44 (2H, envelope, ArH), 7.40-7.29 (4H, envelope, ArH), 5.41 (2H, s, CH_2Ph), 4.87 (2H, s, OCH_2O), 3.84-3.79 (2H, m, OCH_2CH_2O), 3.50-3.44 (2H, m, OCH_2CH_2O), 3.33 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 163.1 (CO ester), 156.0 (t, $^1J_{CF}$ 293.0, CF_2), 147.5 (Cq-OTf), 135.1 (Cq of Bn), 132.0 (dd, $^4J_{CF}$ 7.2, 3.4, CH), 131.3 (dd, $^3J_{CF}$ 7.1, 1.5, Cq), 130.7 (dd, $^4J_{CF}$ 6.2, 4.0, CH), 128.8 (CH), 128.6 (CH), 128.6 (CH), 124.9 (Cq-CO), 123.2 (d, $^5J_{CF}$ 1.1, CH), 118.7 (q, $^1J_{CF}$ 320.8, CF_3), 114.3 (dd, $^2J_{CF}$ 33.9, 19.8, *C*=CF_2),

96.2 (t, $^{4}J_{CF}$ 2.8, OCH_2O), 71.5 (OCH_2), 68.8 (d, $^{6}J_{CF}$ 2.3, OCH_2), 67.8 (OCH_2Ph), 59.0 (OCH_3); δ_F (282 MHz, $CDCl_3$) -73.41 (s, CF_3), -94.18 (d, ^{2}J 49.4), -103.06 (d, ^{2}J 49.7); [HRMS (ES-TOF, M+Na) Found: 549.0605; Calc. for $C_{21}H_{19}O_8F_5NaS$: 549.0619]; *m/z* (ES-TOF) 549.1 (100%, M+Na).

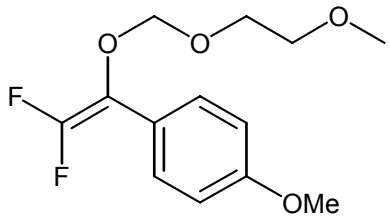
2-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-benzene 121e



Styrene **121e** was prepared as for **121a** using palladium(II) acetate (25 mg, 0.11 mmol), triphenylphosphine (107 mg, 0.41 mmol), CuI (172 mg, 0.90 mmol), iodobenzene (0.45 ml, 4 mmol) and stannane **118** (1.83 g, 4 mmol) in DMF (9 ml) at 50°C. After completion of the reaction as judged by TLC (2.5 h) the reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (10 ml), followed by KF (6 ml of a 0.91 M aqueous solution). The mixture was stirred rapidly for 30 min, then filtered under suction to remove the grey precipitate. Usual work-up from this stage afforded a crude brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded styrene **121e** as a colourless oil (427 mg, 44%); 100% by GC; R_f (20% diethyl ether in light petroleum) 0.27; [Found: C, 58.93; H, 5.97; Calc. for $C_{12}H_{14}O_3F_2$: C, 59.01; H, 5.78%]; ν (film/ cm^{-1}) 2929 m, 2884 m, 1735 s, 1498 w, 1449 m, 1265 s, 1201 m, 1177 s, 1153 s, 1103 s, 1070 s, 1032 m, 980 s, 948 s, 850 w, 767 s, 715 s, 697 s; δ_H (300 MHz,

$CDCl_3$) 7.47-7.42 (2H, envelope, ArH), 7.39-7.32 (2H, envelope, ArH), 7.31-7.24 (1H, m, H-4), 4.86 (2H, s, OCH_2O), 3.86-3.82 (2H, m, OCH_2CH_2O), 3.54-3.51 (2H, m, OCH_2CH_2O), 3.35 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 155.4 (dd, $^1J_{CF}$ 289.9, 289.0, CF_2), 129.8 (dd, $^3J_{CF}$ 6.3, 1.7, C-1), 128.4 (C-4), 128.3 (t, $^5J_{CF}$ 1.4, C-3, C-3'), 126.7 (dd, $^4J_{CF}$ 5.6, 3.4, C-2, C-2'), 115.5 (dd, $^2J_{CF}$ 35.2, 18.1, C=CF_2), 95.2 (t, $^4J_{CF}$ 2.9, OCH_2O), 71.4 (CH_2O), 68.3 (d, $^6J_{CF}$ 2.0, CH_2O), 58.8 (OCH_3); δ_F (282 MHz, $CDCl_3$) -97.85 (1F, d, ^2J 55.9), -106.34 (1F, d, ^2J 55.9); [HRMS (ES-TOF, M+Na) Found: 267.0814; Calc. for $C_{12}H_{14}O_3F_2Na$: 267.0809]; *m/z* (ES-TOF) 267.0 (100%, M+Na).

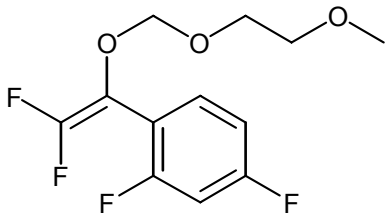
4-[2,2-Difluoro-1-(2-methoxyethoxymethoxy)-vinyl]-1-methoxybenzene 121f



Anisole **121f** was prepared as for **121a** using palladium(II) acetate (24 mg, 0.11 mmol), triphenylphosphine (105 mg, 0.40 mmol), copper(I) iodide (170 mg, 0.89 mmol), 4-iodoanisole (936 mg, 4.0 mmol) and stannane **118** (1.83 g, 4.0 mmol) in DMF (5 ml). After 1.5 h, the usual work-up afforded an orange oil containing a red sediment. Purification by column chromatography over silica gel (20 % diethyl ether in hexanes $\Rightarrow$ 20% ethyl acetate in hexanes) afforded anisole **121f** as a pale yellow oil (761 mg, 71%); 100% by GC; R_f (20% diethyl ether in hexanes) 0.12; ν (film/ cm^{-1}) 2936 m, 1737 m, 1611 m, 1576 w, 1515 m, 1465 m, 1257 s, 1179 m, 1151 m, 1035 m, 979 m, 950 m, 836 m; δ_H (300 MHz, $CDCl_3$) 7.39-7.33 (2H, m, ArH), 6.92-

8.86 (2H, m, ArH), 4.83 (2H, s, OCH_2O), 3.85-3.82 (2H, m, CH_2O), 3.79 (3H, s, ArOMe), 3.55-3.52 (2H, m, CH_2O), 3.36 (3H, s, $CH_2OC\mathit{H_3}$); δ_C (75 MHz, $CDCl_3$) 159.5 (t, $^6J_{CF}$ 1.3, Cq-OMe), 155.0 (dd, $^1J_{CF}$ 288.5, 286.5, CF_2), 128.2 (dd, $^4J_{CF}$ 5.2, 3.4, CH), 121.9 (dd, $^3J_{CF}$ 6.0, 1.4, Cq), 115.2 (dd, $^2J_{CF}$ 36.1, 18.4, C=CF_2), 113.9 (CH), 94.9 (t, $^4J_{CF}$ 2.9, OCH_2O), 71.5 (CH_2O), [68.3, 68.2] (CH_2O), [58.8, 58.8] (CH_2OCH_3), [55.1, 55.1] ($ArOCH_3$); δ_F (282 MHz, $CDCl_3$) -100.38 (1F, d, ^2J 61.0), -108.94 (1F, d, ^2J 61.0); [HRMS (ES-TOF) Found: 297.0901; Calc. for $C_{13}H_{16}O_4F_2Na$: 297.0914]; *m/z* (ES-TOF) 297.1 (100%, M+Na).

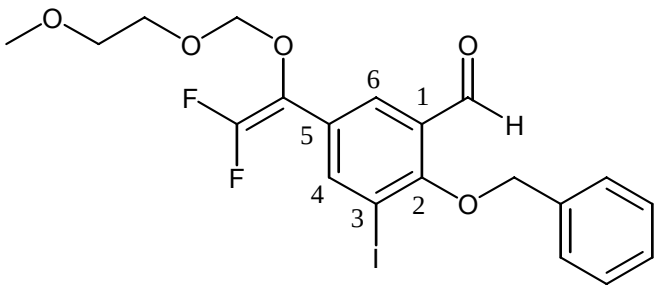
2,4-Difluoro-1-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-benzene 121g



Styrene **121g** was prepared as for **121a** using palladium(II) acetate (3 mg, 13.4 μmol), triphenylphosphine (14 mg, 53.4 μmol), CuI (20 mg, 0.11 mmol), 2,4-difluoro-1-iodobenzene (120 mg, 0.5 mmol) and stannane **118** (274 mg, 0.6 mmol) in DMF (3 ml) at 50°C. After 3.7 h, the usual work-up afforded a yellow oil. Purification by column chromatography over silica gel (10% ethyl acetate in hexanes) afforded styrene **121g** as a colourless oil (77 mg, 55%); 99% by GC; R_f (10% ethyl acetate in hexanes) 0.34; ν (film/cm^{-1}) 2898 m, 1754 m, 1615 m, 1596 m, 1508 s, 1456 w, 1427 m, 1369 w, 1344 w, 1276 s, 1243 s, 1155 s, 1105 s, 988 s, 969 m, 947 m, 853 m, 821 m; δ_H (300 MHz, $CDCl_3$) 7.38 (1H, dt, $^3J_{HF}$ 8.1, ^4J 6.6, ArH), 6.94-8.81 (2H,

envelope, ArH), 4.78 (2H, s, OCH_2O), 3.80-3.77 (2H, m, CH_2O), 3.53-3.50 (2H, m, CH_2O), 3.36 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.3-158.6 (unresolved 2 × Cq-F), 158.6-150.8 (m, CF_2), 132.0-131.7 (m, ArCH), 111.8-111.5 (m, ArCH), 104.5 (t, $^2J_{CF}$ 25.6, ArCH), 94.7 (t, $^4J_{CF}$ 2.6, OCH_2O), 71.5 (CH_2O), 68.2 (d, $^6J_{CF}$ 1.4, CH_2O), 59.0 (OCH_3), Cq and *C*=CF_2 too weak to assign due to multiple F-coupling; δ_F (282 MHz, $CDCl_3$) -98.33 (1F, d, ^2J 54.7), -105.90 (1F, dd, ^2J 54.0, ^5J 20.3), -107.39 to -107.64 (2F, envelope, ArF); *m/z* (ES-TOF) 303 (100%, M+Na); *m/z* (CI) 298 (100%, $M+NH_4$), 94 (3%), 89 (2%).

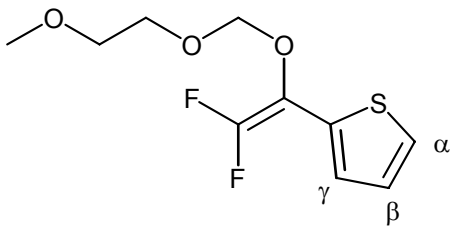
2-Benzyloxy-5-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-3-iodo-benzaldehyde 121h



Benzaldehyde **121h** was prepared as for **121a** using copper(I) iodide (44 mg, 0.23 mmol), triphenylphosphine (26 mg, 99 μmol), palladium(II) acetate (6 mg, 27 μmol), 3,5-diiodo-2-benzyloxy-benzaldehyde (466 mg, 1.01 mmol) and stannane **118** (461 mg, 1.01 mmol) in DMF (3 ml) at 50°C. Usual KF work-up afforded a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded iodide **121h** as a white solid (131 mg, 26%); 98% by HPLC at 225 nm; HPLC t_r (20% water in MeCN, 1ml/min) 7.73 min; R_f (20% diethyl ether in

light petroleum) 0.08; m.p. 90-92°C; [Found: C, 47.83; H, 3.72; Calc. for $C_{20}H_{19}O_5IF_2$: C, 47.64; H, 3.80%]; ν (nujol mull/cm^{-1}) 1728 w, 1692 w, 1589 w, 1279 m, 1262 m, 1228 w, 1189 w, 1164 m, 1110 m, 1078 w, 1032 w, 937 m, 911 w, 692 w; δ_H (300 MHz, $CDCl_3$) 10.06 (1H, s, CHO), 8.17 (1H, s, H-4), 7.89 (1H, s, H-6), 7.50-7.38 (5H, envelope, OCH_2*Ph*), 5.08 (2H, s, C*H*$_2$Ph), 4.87 (2H, s, OCH_2O), 3.87-3.84 (2H, m, CH_2O), 3.57-3.53 (2H, m, CH_2O), 3.37 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 188.0 (CO), 160.4 (t, $^6J_{CF}$ 1.6, C-2), 155.6 (dd, $^1J_{CF}$ 292.2, 291.1, CF_2), 143.1 (dd, $^4J_{CF}$ 6.6, 3.4, C-4), 134.9 (Cq of Ph), 130.5 (C-1), 129.0 (CH of Ph), 128.8 (CH of Ph), 128.7 (CH of Ph), 127.1 (dd, $^4J_{CF}$ 6.0, 3.7, C-6), 113.7 (dd, $^2J_{CF}$ 34.8, 19.5, *C*=CF_2), 95.9 (t, $^4J_{CF}$ 2.9, OCH_2O), 93.6 (C-3), 78.4 (O*C*H_2Ph), 71.5 (OCH_2), [68.7, 68.7] (OCH_2), 59.0 (OCH_3), C-5 not observed as a distinct resonance and possibly lies under the signal at 129.0; δ_F (282MHz, $CDCl_3$) -95.11 (1F, d, ^2J 51.1), -103.78 (1F, d, ^2J 51.4); [HRMS (ES-TOF, M+Na) Found: 527.0133; Calc. for $C_{20}H_{19}O_5F_2NaI$: 527.0143]; *m/z* (ES) 559.1 (42%, M+Na+MeOH), 527.1 (100%, M+Na).

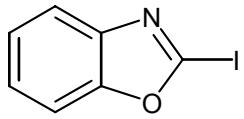
2-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-thiophene 121j



A flask containing palladium(II) acetate (24 mg, 0.11 mmol), triphenylphosphine (105 mg, 0.40 mmol) and copper(I) iodide (170 mg, 0.89 mmol) was pump-purged twice with argon. Dry, degassed DMF (3 ml) was added followed by 2-iodothiophene (0.44

ml, 4.0 mmol). The mixture was heated to 30°C, then stannane **118** (1.83 g, 4.0 mmol) was added as a solution in DMF (1 ml). After stirring at 50°C for 2 h, the dark red mixture was allowed to cool to ambient temperature, then diluted with diethyl ether (5 ml). The mixture was transferred to a conical flask and aqueous KF (15 ml of a 1 M soln) was added. The resulting mixture was stirred rapidly for 30 min, then filtered to remove the cream precipitate. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude reddish oil containing a red sediment. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded thiophene **121j** as a pale yellow oil (430 mg, 45%); 96% by GC; R_f (20% diethyl ether in hexanes) 0.23; ν (film/cm^{-1}) 3108 w, 2925 m, 1730 s, 1453 w, 1436 w, 1354 w, 1292 m, 1256 s, 1228 w, 1201 w, 1175 m, 1152 s, 1102 s, 1045 w, 1029 w, 962 m, 911 m; δ_H (300 MHz, $CDCl_3$) 7.31 (1H, dd, ^3J 5.1, ^4J 1.1, H-□), 7.10 (1H, d, ^3J 3.7, H-□), 7.03-7.00 (1H, m, H-□), 4.97 (2H, s, OCH_2O), 3.88-3.85 (2H, m, CH_2O), 3.57-3.54 (2H, m, CH_2O), 3.37 (3H, s, OCH_3); δ_C (300 MHz, $CDCl_3$) 154.6 (dd, $^1J_{CF}$ 291.6, 290.2, CF_2), 132.7 (dd, $^3J_{CF}$ 8.6, 1.4, Cq), 127.3 (d, $^6J_{CF}$ 0.6, C-α), 125.9 (dd, $^5J_{CF}$ 4.9, 2.9, C-β), 125.4 (dd, $^4J_{CF}$ 6.6, 4.9, C-γ), 112.5 (dd, $^2J_{CF}$ 38.2, 22.2, *C*=CF_2), 96.1 (dd, $^4J_{CF}$ 3.2, 2.7, OCH_2O), 71.5 (CH_2O), 68.6 (d, $^6J_{CF}$ 2.0, CH_2O), 58.9 (OCH_3); δ_F (282 MHz, $CDCl_3$) -98.79 (1F, dd, ^2J 51.5, $^5J_{HF}$ 3.2), -102.43 (1F, dd, ^2J 52.1, $^5J_{HF}$ 3.8); [HRMS (ES-TOF, M+Na) Found: 273.0366; Calc. for $C_{10}H_{12}O_3F_2NaS$: 273.0373]; *m/z* (ES) 273.0 (100%, M+Na).

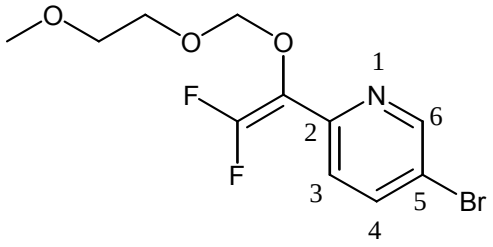
2-Iodobenzoxazole 124



n-Butyllithium (6.25 ml of a 1.6 M solution in hexanes, 10.0 mmol) was added dropwise to a solution of benzoxazole (1.19 g, 10.0 mmol) in THF (30 ml) at -78°C to afford a deep orange solution. After stirring for 15 min, with thickening of the solution, zinc chloride (20 ml of a 0.5 M solution in THF, 10.0 mmol) was added and the resulting brown solution stirred for 15 min before being allowed to warm to 0°C over 20 min. A solution of iodine (2.79 g, 11.0 mmol) in THF (10 ml) was added in one portion and the reaction stirred for a further 2 h whilst warming to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride (20 ml). The contents were transferred to a separating funnel and washed with a saturated solution of sodium thiosulfate (60 ml). Diethyl ether (50 ml) was added and the organic phase separated. The aqueous phase was extracted with diethyl ether (3 x 30 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a deep red solid. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded 2-iodobenzoxazole **124** (CAUTION: severe irritant to eyes and skin) as a sand-textured solid (1.79 g, 73%), in addition to colourless crystals which collected on the rims of the tubes (240 mg, 10%). The sand-textured solid was triturated with hexane (3 × 10 ml) to afford a light brown solid (1.68 g, 69%, total = 2.03 g, 79%). Recrystallisation by vapour diffusion (acetone/hexane) afforded further 2-iodobenzoxazole as colourless crystals; [Found: C, 34.23; H, 1.44; N, 5.55; Calc. for C_7H_4NOI: C, 34.31; H, 1.65; N, 5.72%]; R_f (20%

diethyl ether in light petroleum) 0.50; δ_H (300 MHz, $CDCl_3$) 7.74-7.67 (1H, m, ArH), 7.57-7.51 (1H, m, ArH), 7.34-7.27 (2H, envelope, ArH); δ_C (75 MHz, $CDCl_3$) 154.0 (Cq), 142.6 (Cq), 125.3 (CH), 124.7 (CH), 119.3 (CH), 110.1 (CH), 108.1 (Cq); *m/z* (CI) 247 (6%, M(^{13}C)+H), 246 (100%, M+1), 245 (1%, M), 135 (4%), 120 (24%, M+2H-^{127}I), 80 (4%). This material was found to be relatively unstable, even in a refridgerated (-5°C) environment and should therefore be used immediately.

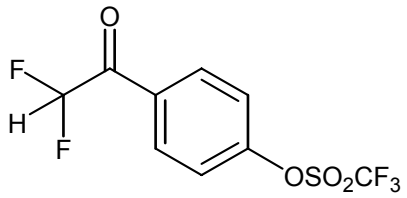
5-Bromo-2-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-pyridine 121m



Bromopyridine **121m** was prepared as for **121a** using palladium(II) acetate (34 mg, 0.15 mmol), CuI (14 mg, 80 μmol), triphenylphosphine (118 mg, 0.45 mmol), 2,5-dibromopyridine (640 mg, 2.70 mmol) and stannane **118** (1.36 g, 2.98 mmol) in DMF (4 ml) at 50°C. After 16 h, the usual work-up afforded an orange oil. Purification by column chromatography over silica gel (30% diethyl ether in light petroleum) afforded pyridine **121m** as a pale yellow oil (290 mg, 33%); R_f (30% diethyl ether in light petroleum) 0.19; δ_H (300 MHz, $CDCl_3$) 8.66 (1H, d, ^4J 2.2, H-6), 7.80 (1H, dd, ^3J 8.5, ^4J 2.2, H-4), 7.36 (1H, d, ^3J 8.5, H-3), 4.96 (2H, s, OCH_2O), 3.85 (2H, t, ^3J 4.8, OCH_2CH_2O), 3.52 (2H, t, ^3J 4.8, OCH_2CH_2O), 3.35 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 157.1 (dd, $^1J_{CF}$ 297.3, 293.3, CF_2), 150.7 (C-6), 148.5 (dd, $^3J_{CF}$ 7.9, 4.0, C-2), 139.1 (C-4), 123.1 (dd, $^4J_{CF}$ 8.2, 3.7, C-3), 119.5 (t, $^5J_{CF}$ 2.3, C-5), 115.3 (dd, $^2J_{CF}$

30.8, 18.9, *C*=CF_2), 96.4 (t, $^4J_{CF}$ 2.8, OCH_2O), 71.5 (OCH_2), 68.7 (d, $^6J_{CF}$ 2.3, OCH_2), 59.0 (OCH_3); δ_F (282 MHz, $CDCl_3$) -91.69 (d, ^2J 38.2), -99.03 (d, ^2J 38.2); HRMS [ES-TOF (M+Na) Found: 345.9861; Calc. for $C_{11}H_{12}O_3NBrF_2Na$: 345.9866]; *m/z* (ES) 348 (100%, M(^{81}Br)+Na), 346 (100%, M(^{79}Br)+Na). This material decomposed before full characterisation could be achieved.

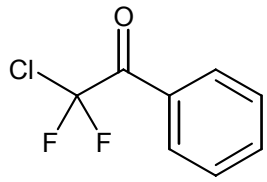
4-(2,2-Difluoroacetyl)-phenyl trifluoromethanesulfonate 132



Chlorotrimethylsilane (0.15 ml, 1.17 mmol) was added to a solution of enol acetal **121a** (249 mg, 630 μmol) in methanol (5 ml) at 0°C. The solution was allowed to warm to ambient temperature and the colourless solution stirred for 18 h, with monitoring by TLC. The reaction mixture was concentrated under reduced pressure to afford a mixture of the ketone **132** and its methanol hemiketal. Toluene (5 ml) was added and the methanol removed by azeotropic distillation with toluene, affording the ketone **132** as the sole fluorinated product. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded ketone **132** as a colourless oil (42 mg, 22%); 98% by GC; R_f (20% diethyl ether in light petroleum) 0.14; ν (film/cm^{-1}) 1715 s, 1600 s, 1502 s, 1430 s, 1348 m, 1291 m, 1252 s, 1219 s, 1141 s, 1067 s, 1017 m, 983 w, 889 s, 781 w, 750 w; δ_H (300 MHz, $CDCl_3$) 8.20 (2H, d, ^3J 9.0, ArH), 7.45 (2H, d, ^3J 9.0, ArH), 6.24 (1H, t, $^3J_{HF}$ 53.5, HCF_2); δ_C (75 MHz,

$CDCl_3$) 153.4 (Cq), 132.1 (t, $^4J_{CF}$ 2.6, CH), 131.0 (t, $^3J_{CF}$ 2.6, Cq), 122.1 (CH), 120.7 (Cq), 111.3 (t, $^1J_{CF}$ 251.7, CF_2H), CF_3 too weak to assign; δ_F (282 MHz, $CDCl_3$) -72.65 (3F, s, CF_3), -121.35 (2F, d, $^2J_{HF}$ 53.5, HCF_2). Satisfactory mass spectral analysis could not be obtained for this compound.

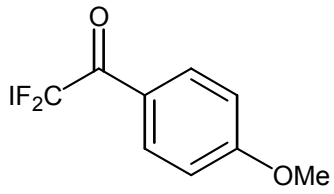
2-Chloro-2,2-difluoro-1-phenyl-ethanone 133b



Sulfuryl chloride (80 μl, 1 mmol) was added to a solution of styrene **121e** (244 mg, 1 mmol) in DCM (3 ml) at ambient temperature. An intense red colouration was observed for a few seconds, before being discharged with the evolution of a gas (SO_2) to afford a pale yellow solution. After stirring for 2.5 h, with monitoring by TLC, the reaction mixture was concentrated under reduced pressure to afford a pale green oil. This material was diluted with acetone (10 ml) and concencentrated on to silica gel. Purification by flash column chromatography over silica gel (100% light petroleum) afforded chlorodifluoromethyl ketone **133b** as a colourless oil (68 mg, 60%) 97% by GC; R_f (100% light petroleum) 0.22; δ_H (300 MHz, $CDCl_3$) 8.13-8.10 (2H, m, ArH), 7.69 (1H, tt, ^3J 7.5, ^4J 1.3, ArH), 7.56-7.50 (2H, m, ArH); δ_C (75 MHz, $CDCl_3$) 135.2 (CH), 130.5 (t, $^4J_{CF}$ 2.3, CH), 129.3 (Cq), 128.9 (CH), 120.1 (t, $^1J_{CF}$ 304.9, CF_2); CO too weak to assign; δ_F (282 MHz, $CDCl_3$) -60.79 (s); *m/z* (EI) 193 (<1%, M(^{37}Cl)+1), 192 (<1%, M(^{37}Cl)), 191 (<1%, M(^{35}Cl)+1), 192 (<1%, M(^{35}Cl)), 155

(<1%, M-Cl), 106 (7%), 105 (100%, COPh), 77 (57%, Ph), 51 (24%), 50 (11%). ^{19}F and ^{1}H NMR data in agreement with those reported by Kuroboshi.[239]

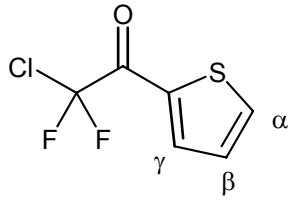
2,2-Difluoro-2-iodo-1-(4'-methoxyphenyl)-ethanone 133c



A solution of iodine (550 mg, 2.18 mmol) in DCM (5 ml) was added to a solution of anisole **121f** (570 mg, 2.08 mmol) in DCM (3 ml) at ambient temperature. The intense violet colour of the iodine solution was quenched upon initial addition, ultimately affording a red solution. The reaction was stirred in the absence of light for 18 h and monitored by TLC. The reaction mixture was washed with 10% sodium thiosulfate solution (20 ml) to afford a pale yellow solution. The organic phase was separated and the aqueous phase extracted with DCM (3 × 10 ml). The combined organic extracts were dried concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (in the dark; 20% diethyl ether in hexanes) afforded iodoketone **133c** as a colourless oil that partly solidifed on standing (420 mg, 65%); 98% by GC on mixture; R_f (20% diethyl ether in hexanes) 0.40; mp 35-38°C; ν (nujol mull/cm^{-1}) 1682 m, 1601 m, 1572 m, 1511 m, 1463 m, 1425 m, 1378 m, 1318 m, 1263 m, 1184 m, 1122 m, 957 m, 942 m, 860 m, 732 m, 686 m, 637 m; δ_H (300 MHz, $CDCl_3$) 8.16-8.13 (2H, m, ArH), 7.00-6.94 (2H, m, ArH), 3.90 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 164.9 (Cq), 133.4 (d, $^{4}J_{CF}$ 13.2, CH), 121.4

(Cq, coupling unresolved), 114.3 (CH), 95.9 (t, $^{1}J_{CF}$ 325.8, CF_2), 55.7 (OCH_3), CO too weak to assign; δ_F (282 MHz, $CDCl_3$) -53.52 (2F, s); *m/z* (CI) 330 (81%, M+NH_4), 313 (7%, M+1), 204 (100%, $COCF_2I$), 186 (24%, M+1-I), 169 (9%), 152 (14%), 135 (45%, M-CF_2I).

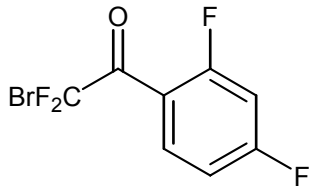
2-Chloro-2,2-difluoro-1-(thien-2-yl)-ethanone 133d



Sulfuryl chloride (91 μl, 1.1 mmol) was added to a solution of thiophene **121j** (282 mg, 1.1 mmol) in DCM (4 ml) at ambient temperature. An intense red colour was observed upon the addition of the first few drops, which then dissipated to afford a pale yellow solution. The resulting solution was stirred for 18 h until TLC indicated the consumption of starting material. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (100% hexanes) afforded volatile ketone **133d** as a colourless oil (80 mg, 36%); 99% by GC; R_f (100% hexanes) 0.13; ν (film/cm^{-1}) 3110 m, 1686 bds, 1514 s, 1411 s, 1358 s, 1287 m, 1244 m, 1223 m, 1168 s, 1066 s, 1048 m, 1021 s, 964 s, 874 s, 853 m, 825 s, 770 s, 725 s, 674 s, 617 s; δ_H (300 MHz, $CDCl_3$) 8.00-7.98 (1H, m, H-α), 7.88 (1H, dd, ^{3}J 5.1, ^{4}J 1.0, H-γ), 7.23 (1H, dd, ^{3}J 4.8, 4.0, H-β); δ_C (75 MHz, $CDCl_3$) 174.8-174.8 (m, CO), 137.7 (d, $^{5}J_{CF}$ 0.9, C-β), 136.5 (t, $^{4}J_{CF}$ 3.7, C-γ), 135.3 (t, $^{3}J_{CF}$ 0.9, Cq), 129.0 (C-α), 119.9 (t, $^{1}J_{CF}$ 304.0, CF_2); δ_F (282 MHz,

$CDCl_3$) -61.88 (2F, s); *m/z* (CI) 216 (6%, M(^{37}Cl)+NH_4), 214 (17%, M(^{37}Cl)+NH_4), 145 (19%), 128 (10%), 111 (100%, M-CF_2Cl).

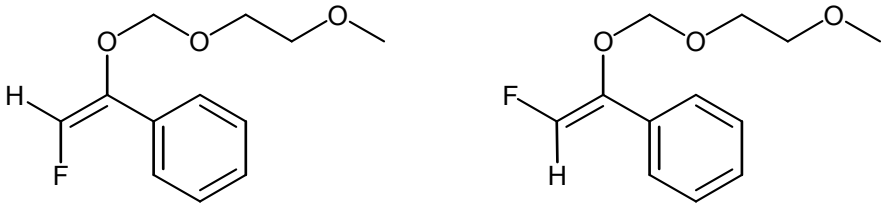
2-Bromo-2,2-difluoro-1-(2,4-difluorophenyl)-ethanone 133f



Bromine (1 ml of a 0.98 M solution in DCM, 1.02 mmol) was added dropwise to a solution of styrene **121g** (282 mg, 1.0 mmol) in DCM (3 ml) at 0°C under a dry nitrogen atmosphere. The intense colour of bromine was initially quenched upon addition. The reaction was allowed to warm to ambient temperature and stirred for 22 h, with monitoring by TLC. The reaction mixture was concentrated under reduced pressure to afford a pale brown oil. Purification by column chromatography over silica gel (10% ethyl acetate in hexanes) afforded bromodifluoromethyl ketone **133f** as a colourless oil (98 mg, 36%); 97% by GC; R_f (10% ethyl acetate in hexanes) ~0.30 (streaks); ν (film/cm^{-1}) 1715 s, 1612 s, 1502 s, 1432 s, 1312 m, 1272 s, 1230 m, 1156 s, 1101 s, 986 s, 859 s, 814 m, 734 m, 685 w; δ_H (300 MHz, $CDCl_3$) 7.96 (1H, dd, $^3J_{HF}$ 14.7, ^3J 8.5, ArH), 7.04-6.90 (2H, envelope, ArH); δ_C (75 MHz, $CDCl_3$) 179.1-179.0 (m, CO), 166.9 (dd, $^1J_{CF}$ 260.9, $^3J_{CF}$ 12.4, Ar*C*F), 162.9 (dd, $^1J_{CF}$ 266.0, $^3J_{CF}$ 12.7, Ar*C*F), 133.8 (ddt, $^3J_{CF}$ 10.9, 2.6, $^4J_{CF}$ 2.6, ArCH), 115.8-115.6 (m, Cq), 113.2 (t, $^1J_{CF}$ 318.1, $BrCF_2$), 112.4 (dd, $^2J_{CF}$ 21.8, $^4J_{CF}$ 3.7, CH), 105.8 (t, $^2J_{CF}$ 25.6,

CH); δ_F (282 MHz, $CDCl_3$) -60.75 (2F, d, ^2J 15.6), -97.62 to -97.75 (1H, m), -99.75 to -99.96 (1F, m); *m/z* (EI) 140 (100%, M-1-$BrCF_2$), 112 (24%), 63 (17%).

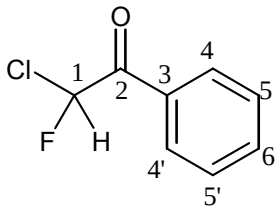
(*E*)-[2-Fluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene and (*Z*)-[2-fluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene 134



Sodium *bis*(2-methoxyethoxy)aluminium hydride (Red-Al®, 0.38 ml of a 65% w/w solution in toluene, 1.2 mmol) was added to a solution of styrene **121e** (244 mg, 1.0 mmol) in hexane (5 ml). The resulting solution was heated under reflux for 3 h, with monitoring by TLC. Upon consumption of styrene **121e**, the solution was cooled to ambient temperature and poured into a conical flask containing ice-water (20 ml). The solution was transferred to a separating funnel and ethyl acetate (10 ml) and Rochelle's salt (20 ml of a 20% w/w aqueous solution) added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Crude ^{19}F NMR indicated the presence of styrenes **134** in a 1:1 ratio, in addition to a trace of residual styrene **121e**. Purification by column chromatography over silica gel (25% diethyl ether in light petroleum) afforded inseparable monofluoroethenes **134** (48:52 *E*:*Z*) as colourless oils (170 mg, 75%); R_f (25% diethyl ether in light petroleum) 0.31; δ_F (282 MHz, $CDCl_3$) -153.7 (d, $^2J_{HF}$ 77.4,

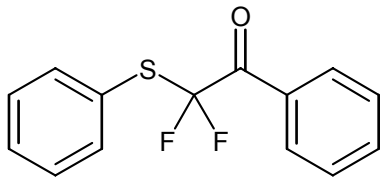
Z-isomer), -162.8 (d, $^{2}J_{HF}$ 79.1, *E*-isomer). Stereochemistry has been assigned based upon the work of Patel.[102a] Due to the unstable nature of this material, the MEM enol ether was cleaved using sulfuryl chloride as the electrophile, without further characterisation (see **133g**).

2-Chloro-2-fluoro-1-phenyl-ethanone 133g



Sulfuryl chloride (22 μl, 0.27 mmol) was added to a solution of monofluoroethenes **134** (48:52, *E*:*Z*) (67 mg, 0.27 mmol) in DCM (3 ml) at ambient temperature. The resulting solution was stirred for 48 h, then concentrated to afford a colourless oil. Purification by column chromatography over silica gel (15% diethyl ehter in light petroleum) afforded chlorofluoromethyl ketone **133g** as a colourless oil (36 mg, 76%); 100% by GC; R_f (15% diethyl ether in light petroleum) 0.55; δ_H (300 MHz, $CDCl_3$) 8.08-8.04 (2H, m, H-4, H-4'), 7.68-7.62 (1H, m, H-6), 7.54-7.48 (2H, m, H-5, H-5'), 6.83 (1H, d, $^{2}J_{HF}$ 50.7, H-1); δ_C (75 MHz, $CDCl_3$) 134.7 (CH), 129.6 (d, $^{4}J_{CF}$ 2.8, C-4, C-4'), 128.9 (CH), 95.1 (d, $^{1}J_{CF}$ 256.6, C-1), C-2 and C-3 too weak to assign; δ_F (282 MHz, $CDCl_3$) -146.58 (d, $^{2}J_{HF}$ 50.8); *m/z* (EI) 105 (100%, COPh), 77 (60%, Ph), 51 (24%). ^{1}H NMR data is in close agreement with those reported by Normant.[240]

2,2-Difluoro-1-phenyl-2-(phenylsulfanyl)-ethanone 137a



Method A:

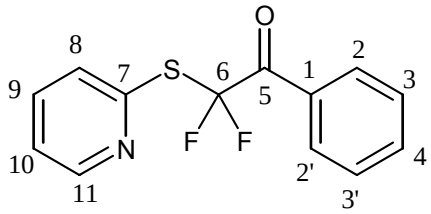
Phenylsulfenyl chloride (30 μl, 0.25 mmol) was added dropwise to a solution of styrene **121e** (61 mg, 0.25 mmol) in DCM (5 ml) at 0°C. After warming to ambient temperature, the reaction was stirred for 16 h. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded (phenylthio)difluoromethyl ketone **137a** as a colourless oil (42 mg, 64%); R_f (20% diethyl ether in light petroleum) 0.68; δ_H (300 MHz, $CDCl_3$) 8.15-8.10 (2H, m, ArH), 7.68-7.58 (3H, m, ArH), 7.52-7.35 (5H, m, ArH); δ_C (75 MHz, $CDCl_3$) 184.6 (t, $^2J_{CF}$ 2.0, CO), 136.7 (CH), 136.6 (CH), 134.6 (CH), 131.0 (Cq), 130.3 (t, $^4J_{CF}$ 1.4, CH), 129.2 (CH), 128.6 (CH), 124.6 (t, $^3J_{CF}$ 2.3, Cq), 123.6 (t, $^1J_{CF}$ 290.8, CF_2); δ_F (282 MHz, $CDCl_3$) -77.14 (s); *m/z* (CI) 282 (48%, M+NH_4), 264 (1%, M), 242 (10%), 154 (3%, M-SPh-1), 105 (100%, PhCO), 94 (7%). ^{1}H and ^{19}F NMR data are in close agreement with those reported by Brigaud and Laurent.[57]

Method B:

Sulfuryl chloride (40 μl, 0.5 mmol) was added to a solution of diphenyl disulfide (110 mg, 0.5 mmol) in DCM (1 ml) at ambient temperature. An orange colouration

appeared immediately, which intensified to a near red solution after 30-40 min of stirring. This solution was added to a solution of styrene **121e** (108 mg, 0.44 mmol) in DCM (1 ml) at 0°C and allowed to warm to ambient temperature overnight. Concentration of the reaction mixture afforded an orange oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum) afforded ketone **137a** (91 mg, 78%) as a colourless oil. Data were in agreement with those previously found above.

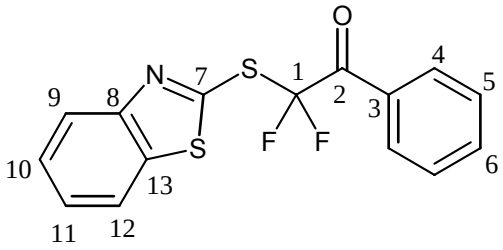
2,2-Difluoro-1-phenyl-2-(pyridin-2'-ylsulfanyl)-ethanone 137b



Sulfuryl chloride (40 μl, 0.5 mmol) was added to a stirred solution of 2,2'-dipyridyl disulfide (110 mg, 0.5 mmol) in DCM (4 ml) at ambient temperature under a nitrogen atmopshere. Pyridine (5 μl, 61.3 μmol) was added and the resulting yellow/orange solution heated under reflux for 1 h. Styrene **121e** (244 mg, 1.0 mmol) was added and the resulting solution heated under reflux for 48 h. The reaction mixture was concentrated under reduced pressure to afford an orange oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded (arylthio)difluoromethyl ketone **137b** as a colourless oil (64 mg, 48%); 100% by GC; R_f (20% diethyl ether in light petroleum) 0.15; ν (film/cm^{-1}) 1705 s (C=O), 1598 m, 1574 s, 1564 m, 1450 s, 1422 s, 1269 s, 1136 s, 1094 m, 1074 m, 1034 m, 989 s,

889 m, 826 m, 765 m, 734 m, 711 s, 687 m, 669 m, 643 m); δ_H (300 MHz, $CDCl_3$) 8.50 (1H, dd, ^3J 4.7, ^4J 1.4, H-11), 8.12 (2H, dd, ^3J 8.4, ^4J 0.8, H-2 and H-2'), 7.69-7.56 (3H, envelope, H-4, H-8, H-9), 7.51-7.45 (2H, m, H-3 and H-3') 7.23 (1H, ddd, ^3J 7.3, 4.7, ^4J 1.1, H-10); δ_C (75 MHz, $CDCl_3$) 150.6 (t, $^3J_{CF}$ 2.8, C-7), 150.4 (CH), 137.4 (CH), 134.6 (CH), 131.4 (t, $^3J_{CF}$ 1.4, C-1), 130.4 (t, $^4J_{CF}$ 2.8, CH), 128.7 (CH), 128.5 (t, $^4J_{CF}$ 2.0, CH), 124.3 (t, $^1J_{CF}$ 291.6, C-6), 123.4 (CH), C-5 too weak to assign; δ_F (282 MHz, $CDCl_3$) -76.78 (s); [HRMS (ES-TOF, M+H) Found: 266.0443; Calc. for $C_{13}H_{10}NOF_2S$: 266.0451]; *m/z* (EI) 265 (0.4%, M), 245 (9%), 237 (3%), 198 (3%), 182 (5%), 155 (3%, M-SPy), 105 (100%, COPh), 77 (59%, Ph), 51 (23%), 39 (8%).

2-(Benzothiazol-2'-ylsulfanyl)-2,2-difluoro-1-phenyl-ethanone 137c

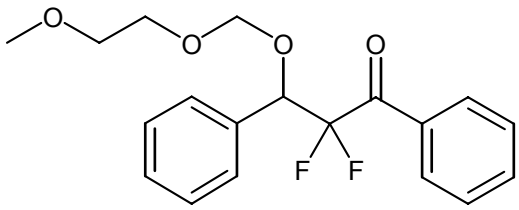


Sulfuryl chloride (80 μl, 0.99 mmol) was added to a yellow heterogeneous solution of benzothiazol-2-yl disulfide (305 mg, 0.91 mmol) and pyridine (10 μl, 0.12 mmol) in DCM (5 ml) at ambient temperature. The mixture began to clear upon the addition of sulfuryl chloride and became a homogeneous orange solution after 5 min. This solution was heated under reflux for 1 h to ensure complete formation of (benzothiazol-2-yl)sulfenyl chloride. A solution of styrene **121e** (443 mg, 1.81 mmol) in DCM (2 ml) was added to afford a yellow solution. The solution was heated under

relux for 21 h, with monitoring by TLC. The reaction mixture was allowed to cool to ambient temperature and then concentrated under reduced pressure to afford an orange solid. Trituration with hexane (3 × 10 ml) afforded orange crystals (542 mg) as a single fluorinated material (by ^{19}F NMR) corresponding to ketone **137c**. Mass spectral analysis (ES) indicated only the presence of ketone **137c**; however, analysis by ^{1}H NMR showed the presence of the desired material in addition to some unidentified impurities. A small sample of the crude material (*ca.* 100 mg) was triturated with ethyl acetate to afford a pale yellow solid (*ca.* 30 mg) which appeared as a single streaking spot by TLC. This material gave satisfactory mass and elemental analyses. The remainder of the crude material was placed in a flask fitted with an air condenser. Hexane (10 ml) was added and the mixture heated gently with a heat gun until it began to boil. The hot hexane solution was decanted on to a petri dish and allowed to evaporate to afford yellow crystals. The brown residue was treated as above twice more. The resulting yellow crystals were dried under vacuum (2.0 mbar) for 5 h to afford a yellow solid (284 mg, 49%). This material proved to still have several minor impurities both by ^{1}H and ^{13}C NMR. This material could not be analysed by GC or by HPLC to give an indication of purity (est. by ^{13}C NMR: 90-95%); R_f (20% diethyl ether in hexanes) 0.42; mp 90-94°C; [Found: C, 55.85; H, 2.71; N, 4.28; Calc. for $C_{15}H_9NOF_2S_2$: C, 56.06; H, 2.82; N, 4.36%]; ν (nujol mull/cm^{-1}) 1694 m, 1595 m, 1578 m, 1552 m, 1410 w, 1311 w, 1282 m, 1235 w, 1188 w, 1169 w, 1136 m, 1049 s, 988 m, 822 m, 763 m, 710 m, 692 m, 677 m, 650m; δ_H (300 MHz, $CDCl_3$) 8.12 (2H, d, ^{3}J 7.7, ArH, H-4, H-4'), 8.07 (1H, d, ^{3}J 8.1, ArH, H-12), 7.85 (1H, d, ^{3}J 8.1, ArH, H-9), 7.64 (1H, t, ^{3}J 7.4, ArH, H-6), 7.52-7.39 (4H, envelope, ArH, H-5, H-5', H-10, H-11); δ_C (75 MHz, $CDCl_3$) 184.4 (t, $^{2}J_{CF}$ 27.6, Cq, C-2), 153.5 (t, $^{3}J_{CF}$ 1.9,

Cq, C-7), 153.0 (Cq, C-13), 137.8 (Cq, C-8), 135.1 (CH, C-6), 130.3 (t, $^{4}J_{CF}$ 2.9, CH, C-4), 130.2 (t, $^{3}J_{CF}$ 2.3, Cq, C-3), 128.8 (CH, C-5), 126.6 (CH, C-10), 126.2 (CH, C-11), 124.8 (t, $^{1}J_{CF}$ 297.1, Cq, C-1), 123.7 (CH, C-9), 121.1 (CH, C-12); δ_F (282 MHz, $CDCl_3$) -72.61 (s); [HRMS (ES-TOF, M+Na) Found: 343.9982; Calc. for $C_{15}H_9NOF_2S_2Na$: 343.9991]; *m/z* (ES-TOF) 376.0 (3%, M+Na+MeOH), 344.0 (100%, M+Na).

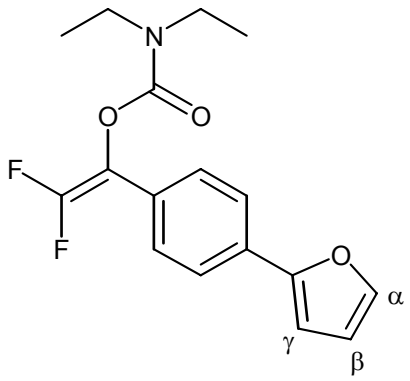
2,2-Difluoro-3-(2-methoxy-ethoxymethoxy)-1,3-diphenyl-propanone 139



Titanium(IV) chloride (1.0 ml of a 1 M soln in DCM, 1.0 mmol) was added to a –20°C solution of styrene **121e** (122 mg, 0.5 mmol) and benzaldehyde (50 μl, 0.5 mmol) in DCM (2 ml). The resulting brown solution was stirred at –20°C for 18 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (5 ml) and diluted with DCM (3 ml). The organic phase was separated and the aqueous phase extracted with DCM (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude yellow oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded MEM-protected aldol **139** as a colourless oil (31 mg, 24%); R_f (20% diethyl ether in light petroleum) 0.13; δ_H (300 MHz, $CDCl_3$) 8.08-8.04 (2H, m, ArH), 7.65-7.59 (1H, m, ArH), 7.51-7.45 (4H, m, ArH), 7.41-7.36 (3H, m, ArH), 5.63

(1H, dd, $^{3}J_{HF}$18.9, 6.5, $CHCF_2$), 4.70-4.61 (2H, m, OCH_2O), 3.51-3.44 (2H, m, CH_2O), 3.40-3.30 (2H, m, CH_2O), 3.29 (3H, s, OCH_3); δc (75 MHz, $CDCl_3$) 134.1 (CH), 130.1 (central resonance for CF_2), 130.0 (dd, $^{4}J_{CF}$ 4.5, 2.8, ArCH), 129.2 (ArCH), 129.1 (ArCH), 128.6 (ArCH), 128.3 (ArCH), 93.3 (OCH_2O), 76.4 (dd, $^{2}J_{CF}$ 30.5, 22.6, *C*HCF_2), 71.3 (CH_2O), 67.4 (CH_2O), 58.9 (OCH_3), CO and 2 × Cq too weak to assign due to weak sample; δ_F (282 MHz, $CDCl_3$) -104.04 (1F, dd, ^{2}J 273.4, $^{3}J_{HF}$ 6.3), -115.99 (1F, dd, ^{2}J 273.4, $^{3}J_{HF}$ 19.1); [HRMS (ES-TOF, M+Na) Found: 373.1224; Calc. for $C_{19}H_{20}O_4F_2Na$: 373.1227]; *m/z* (ES-TOF) 373.1 (100%, M+Na).

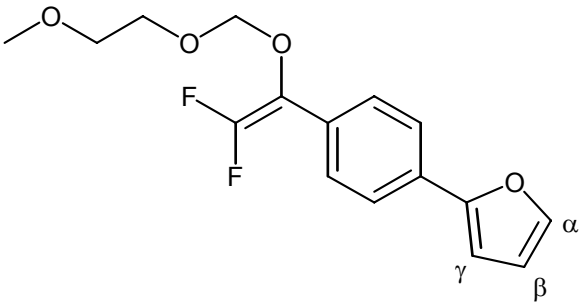
2-{4-[2,2-Difluoro-1-(*N*,*N*-diethylcarbamoyloxy)-vinyl]-phenyl}-furan 138



A flask containing triflate **95e** (283 mg, 0.72 mmol) and *tetrakis*(triphenylphosphine)-palladium(0) (42 mg, 36 μmol) was pump-purged with nitrogen. Dry, degassed DMF (4 ml) was added and the reaction heated to 50°C. A solution of 2-(tributylstannyl)furan (0.34 ml, 1.08 mmol) in DMF (1 ml) was added to the green/yellow solution and the reaction heated at 80°C for 2.7 h. The dark reaction mixture was cooled to ambient temperature and partitioned between diethyl ether (10 ml) and water (10 ml). The organic phase was separated and the aqueous phase

extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude red oil containing a red sediment. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded furan **138** as a pale yellow oil which solidified upon standing to afford an off-white solid (140 mg, 60%); 100% by GC; R_f (20% diethyl ether in hexanes) 0.32; mp. 55-57°C; ν (nujol mull/cm^{-1}) 1725 bd, 1461, 1376, 1269, 1150, 1039, 981, 851, 820, 786, 734, 663; [Found: C, 63.36; H, 5.44; N, 4.18; Calc. for $C_{17}H_{17}NO_3F_2$: C, 63.54; H, 5.33; N, 4.36%]; δ_H (300 MHz, $CDCl_3$) 7.69-7.64 (2H, m, ArH), 7.46-7.39 (3H, envelope, ArH + H-α), 6.65 (1H, d, ^3J 3.3, H-γ), 6.45 (1H, dd, ^3J 3.3, 1.8, H-β), 3.44 (2H, q, ^3J 7.2, N(CH_2CH$_3$)$_2$), 3.35 (2H, q, ^3J 7.2, N(CH_2CH$_3$)$_2$), 1.25 (3H, t, ^3J 7.2, N(CH$_2$CH_3)$_2$), 1.16 (3H, t, ^3J 7.2, N(CH$_2$CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 155.0 (t, $^1J_{CF}$ 291.0, Cq, CF_2), 153.4 (Cq), 152.9 (Cq), 142.4 (CH), 130.5 (d, $^6J_{CF}$ 1.7, Cq), 129.0 (d, $^3J_{CF}$ 6.8, Cq), 125.7 (dd, $^4J_{CF}$ 6.5, 3.7, CH), 123.9 (CH), 112.4 (dd, $^2J_{CF}$ 38.4, 19.6, Cq, *C*=CF_2), 111.8 (CH), 105.7 (CH), [42.7, 42.0] (CH_2N), [14.2, 13.3] (CH_3); δ_F (282 MHz, $CDCl_3$) -93.23 (1F, d, ^2J 47.8), -103.04 (1F, d, ^2J 47.8); [HRMS (ES-TOF, M+Na) Found: 344.1066; Calc. for $C_{17}H_{17}NO_3F_2Na$: 344.1074]; *m/z* (ES-TOF) 344.1 (100%, M+Na).

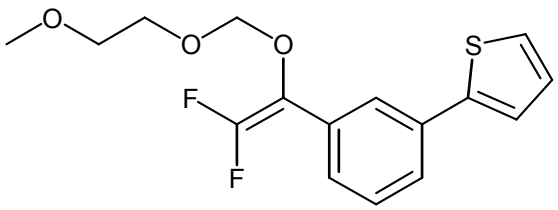
2-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-furan 139a



A flask containing dichloro*bis*(triphenylphosphine)palladium(II) (36 mg, 51.3 μmol) was pump-purged twice with nitrogen, then dry, degassed DMF (3 ml) added to afford a green heterogeneous solution. The mixture was warmed to 60°C and a solution of triflate **121a** (398 mg, 1.02 mmol) in DMF (1 ml) was added in one portion to afford a yellow heterogeneous solution. A solution of 2-(tributylstannyl)furan (362 mg, 1.02 mmol) in DMF (1 ml) was added in one portion at 60°C to afford a deep red solution, which was heated at 60-70°C for 48 h. After cooling to ambient temperature, diethyl ether (5 ml) was added followed by water (10 ml). The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a crude red oil. Purification by column chromatography over silica gel (5% diethyl ether in light petroleum ⇒ 20% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded furan **139a** as a pale orange oil (270 mg, 86%); R_f (20% diethyl ether in light petroleum) 0.19; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, d, ^3J 8.5, ArH), 7.47 (2H, d, ^3J 8.5, ArH), 7.35-7.34 (1H, m, H-α), 6.67-6.65 (1H, m, H-β), 6.46-6.44 (1H, m, H-γ), 4.89 (2H, s, OCH_2O), 3.87-3.84 (2H, m, CH_2O), 3.56-3.52 (2H, m, CH_2O), 3.36 (3H, s, OCH_3); δ_F (282 MHz, $CDCl_3$) -97.29 (1F, d, ^2J 54.6),

-105.52 (1F, d, ^{2}J 54.6). Due to the unstable nature of this material, the MEM enol ether was cleaved under protic conditions without further characterisation (see pg 234).

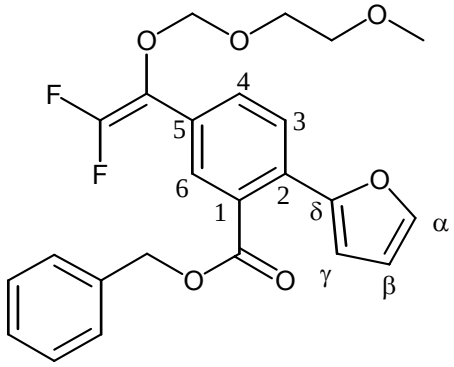
2-{3-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-thiophene 139b



Thiophene **139b** was prepared as for **139a** using dichloro*bis*(triphenylphosphine)-palladium(II) (41 mg, 58.6 μmol), triflate **121b** (393 mg, 1.00 mmol) and 2-(tributylstannyl)thiophene (423 mg, 1.13 mmol) in DMF (3 ml). The reaction was carried out at 60°C for 47 h with TLC indicating a single product spot. After the usual work-up, crude ^{19}F NMR indicated an 89% conversion to a new product. The crude orange oil was diluted with acetone and concentrated on to silica gel to afford an orange powder. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded thiophene **139b** as a colourless oil (230 mg, 71%); 99% by ^{19}F NMR (contamination with triflate **121b**); R_f (10% diethyl ether in light petroleum) 0.11; δ_H (300 MHz, $CDCl_3$) 7.69 (1H, s), 7.52-7.48 (1H, m), 7.35-7.31 (2H, m), 7.29-7.25 (1H, m), 7.25-7.20 (1H, m), 7.04-7.00 (1H, m), 4.87 (2H, s, OCH_2O), 3.85-3.81 (2H, m, CH_2O), 3.52-3.49 (2H, m, CH_2O), 3.32-3.31 (3H, m, OCH_3); δc (75 MHz, $CDCl_3$) 155.6 (dd, $^{1}J_{CF}$ 290.5, 289.3, CF_2), 143.6 (Cq), 134.7 (Cq), 130.6 (dd, $^{3}J_{CF}$ 6.2, 1.7, Cq), 129.1 (CH), 128.0 (CH), 125.8 (t, $^{5}J_{CF}$ 1.4, CH), 125.7 (dd, $^{4}J_{CF}$ 5.9,

3.4, CH), 125.1 (CH), 124.1 (dd, $^{4}J_{CF}$ 5.5, 3.4, CH), 123.5 (CH), 115.3 (dd, $^{2}J_{CF}$ 35.0, 18.7, *C*=CF_2), 95.4 (t, $^{4}J_{CF}$ 2.5, OCH_2O), 71.5 (CH_2O), [68.4, 68.4] (CH_2O), 59.0 (CH_3); δ_F (282 MHz, $CDCl_3$) -97.13 (1F, d, ^{2}J 54.7), -105.55 (1F, d, ^{2}J 54.7). Due to the unstable nature of this material, the MEM enol ether was cleaved to **140c** under protic conditions without further characterisation (see pg 235).

Benzyl 5-[(2,2-difluoro-1-(2-methoxy-ethoxymethoxy))-vinyl]-2-furan-2'-yl benzenecarboxylate 139d



A flask containing dichloro*bis*(triphenylphosphine)palladium(II) (12 mg, 17 μmol) was pump-purged twice with argon. Dry, degassed DMF (4 ml) was added, followed by a solution of triflate **121d** (184 mg, 0.35 mmol) in DMF (1 ml). The resulting yellow solution was warmed to 40°C. 2-(Tributylstannyl)furan (138 mg, 0.39 mmol) was added yellow solution heated for 3 min to 55°C. TLC indicated the consumption of starting material with the formation of a highly UV active material. The resulting colourless solution, containing palladium black was diluted with diethyl ether (5 ml), then an aqueous solution of KF added (5 ml of a 1 M solution). After stirring for 30 min, the grey precipitate was removed by suction filtration. Diethyl ether (5 ml) was

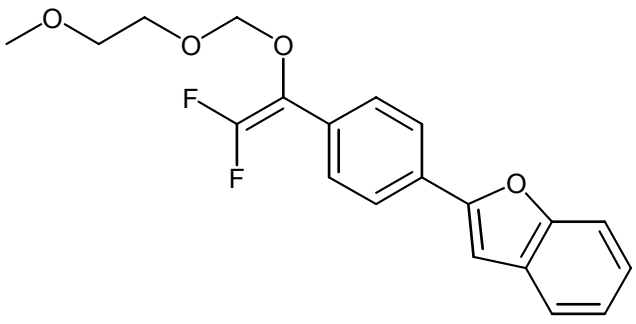
added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5 ml) and the combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Purification by flash column chromatography over silica gel (40% diethyl ether in light petroleum) afforded furan **139d** as a colourless oil (156 mg, 96%); R_f (20% ethyl acetate in light petroleum) 0.28; δ_H (300 MHz, $CDCl_3$) 7.70-7.69 (1H, m, H-α), 7.61-7.50 (2H, m, ArH), 7.30-7.28 (6H, bd. s, envelope, ArH), 6.52 (1H, dd, ^3J 3.3, ^4J 0.7, H-γ), 6.36 (1H, dd, ^3J 3.3, ^3J 1.8, H-β), 5.26 (2H, s, CH_2Ph), 4.84 (2H, s, OCH_2O), 3.82-3.79 (2H, m, OCH_2CH$_2$O), 3.50-3.47 (2H, m, OCH$_2$CH_2O), 3.32 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.6 (CO ester), 155.8 (t, $^1J_{CF}$ 291.4, CF_2), 151.7 (C-δ), 143.1 (C-α), 135.4 (Cq of Ph), 130.3 (C-2), 129.6 (dd, $^3J_{CF}$ 6.8, 1.7, C-5), 129.3 (t, $^5J_{CF}$ 1.4, C-1), 128.7 (dd, $^4J_{CF}$ 6.5, 3.4, CH), 128.6 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.0 (dd, $^4J_{CF}$ 5.8, 3.8, CH), 114.7 (dd, $^2J_{CF}$ 35.9, 16.7, *C*=CF_2), 111.7 (C-β), 108.7 (C-γ), 95.9 (t, $^4J_{CF}$ 2.8, OCH_2O), 71.6 (CH_2O), [68.7, 68.7] (CH_2O), 67.4 (O*C*H_2Ph), 59.1 (OCH_3); δ_F (282 MHz, $CDCl_3$) -95.66 (1F, d, ^2J 52.1), -104.11 (1F, d, ^2J 52.1); [HRMS (ES-TOF, M+Na) Found: 467.1287; Calc. for $C_{24}H_{22}O_6F_2Na$: 467.1282]; *m/z* (ES-TOF) 467.1 (100%, M+Na).

2-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-furan 139a

A mixture of dichloro*bis*(triphenylphosphine)palladium(II) (20 mg, 28 μmol) and benzeneboronic acid (117 mg, 0.96 mmol) was pump-purged twice with nitrogen, then dry, degassed DMF (2 ml) added. The mixture was then warmed towards 90°C. Triethylamine (0.28 ml, 1.99 mmol) was added at 30°C, followed by a solution of

triflate **121a** (205 mg, 0.52 mmol) in DMF (1 ml). The resulting dark red solution was heated at 90°C for 90 h, then cooled to ambient temperature. Diethyl ether (5 ml) and water (10 ml) were added. The organic phase was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were washed with water (10 ml), then dried and concentrated under reduced pressure to afford a brown oil. This oil was diluted with acetone and silica gel added. Concentration under reduced pressure afforded a brown powder. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded furan **139a** as a colourless oil (76 mg, 49%); R_f (20% diethyl ether in light petroleum) 0.21; δ_F (282 MHz, $CDCl_3$) -97.29 (1F, d, ^2J 54.6), -105.52 (1F, d, ^2J 54.6). ^{19}F NMR data is identical to that obtained *via* a Stille coupling. This material was also cleaved to **140b** without further characterisation.

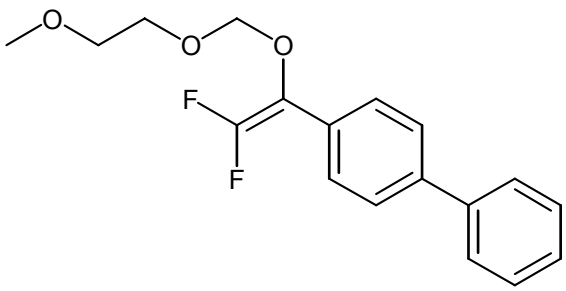
5-{4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-phenyl}-2,3-benzofuran 139f



A flask containing 2-benzofuranboronic acid (520 mg, 3.2 mmol), potassium phosphate (685 mg, 3.2 mmol) and *tetrakis*(triphenylphosphine)palladium(0) (210 mg, 0.18 mmol) was pump-purged with nitrogen. Dry, degassed DMF (6 ml) was

added followed by a solution of triflate **121a** (837 mg, 2.1 mmol) in DMF (2 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 4 h before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were dried and concentrated to afford a dark red oil, which solidified upon cooling. The crude material was dissolved with acetone and concentrated on to silica gel to afford a brown powder. Purification by column chromatography (20% diethyl ether in hexanes) afforded benzofuran **139f** as yellow flakes (616 mg, 80%); mp 48-49°C; ν (nujol mull/cm^{-1}) 1722 s, 1455 s, 1413 m, 1270 s, 1196 m, 1182 m, 1156 m, 1119 m, 1103 m, 1077 m, 1036 m, 982 m, 934 m, 847 m, 800 m, 752 m, 742 m, 726 m; δ_H (300 MHz, $CDCl_3$) 7.87 (2H, d, ^3J 8.5, ArH), 7.59-7.52 (4H, envelope, ArH), 7.33-7.21 (2H, envelope, ArH), 7.04 (1H, s, ArH), 4.92 (2H, s, OCH_2O), 3.90-3.87 (2H, m, CH_2O), 3.59-3.55 (2H, m, CH_2O), 3.39 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 155.6 (t, $^1J_{CF}$ 290.8, CF_2), 155.1 (Cq), 154.9 (Cq), 130.1 (t, $^6J_{CF}$ 1.4, Cq), 130.0 (dd, $^3J_{CF}$ 6.6, 1.4, Cq), 129.0 (Cq), 129.9 (dd, $^4J_{CF}$ 6.2, 3.7, ArCH), 124.9 (ArCH), 124.5 (ArCH), 123.0 (ArCH), 120.9 (ArCH), 115.4 (dd, $^2J_{CF}$ 34.8, 18.7, *C*=CF_2), 111.1 (ArCH), 101.9 (ArCH), 95.6 (t, $^4J_{CF}$ 2.6, OCH_2O), 71.5 (CH_2O), [68.5, 68.5] (CH_2O), 58.9 (OCH_3); δ_F (282 MHz, $CDCl_3$) -96.44 (1F, d, ^2J 53.4), -104.64 (1F, dd, ^2J 53.4); [HRMS (ES-TOF, M+Na) Found: 383.1086; Calc. for $C_{20}H_{18}O_4F_2Na$: 383.1071]; *m/z* (ES) 383.1 (100%, M+Na).

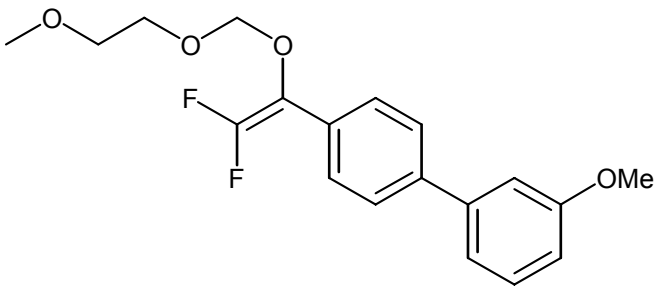
4-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-biphenyl 139g



A mixture of *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (7 mg, 6.6 μmol), triphenylphosphine (13 mg, 49.6 μmol), potassium orthophosphate (159 mg, 0.75 mmol) and phenylboronic acid (7 mg, 0.57 mmol) was pump-purged twice with nitrogen. Degassed dioxane (1 ml) was added, followed by a solution of triflate **121a** (210 mg, 0.51 mmol) in dioxane (1 ml). The mixture was stirred at 85°C for 16 h, then allowed to cool to ambient temperature. The reaction mixture was diluted with diethyl ether (5 ml) and partitioned between water (10 ml) and diethyl ether (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 5 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in light petroleum) afforded biphenyl **139g** as a pale yellow oil (109 mg, 67%); 100% by GC; R_f (20% diethyl ether in light petroleum) 0.30; ν (film/cm^{-1}) 1732 m ($C=CF_2$), 1600 w, 1558 w, 1489 m, 1450 m, 1408 m, 1266 m, 1027 m, 980 m, 945 m, 768 m, 732 m, 698 m; δ_H (300 MHz, $CDCl_3$) 7.64-7.53 (6H, envelope, ArH), 7.48-7.43 (2H, m, ArH), 7.39-7.34 (1H, m, ArH), 4.92 (2H, s, OCH_2O), 3.91-3.88 (2H, m, CH_2O), 3.59-3.56 (2H, m, CH_2O), 3.39 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 155.5 (dd, $^1J_{CF}$ 290.2, 289.6, CF_2), 141.0 (t, $^6J_{CF}$ 1.7, Cq), 140.3 (Cq), 128.9

(d, $^{3}J_{CF}$ 1.4, Cq), 128.8 (CH), 127.5 (CH), 127.2 (CH), 127.1 (dd, $^{4}J_{CF}$ 5.8, 3.4, CH), 127.0 (CH), 115.5 (dd, $^{2}J_{CF}$ 35.1, 18.7, *C*=CF_2), 95.4 (t, $^{4}J_{CF}$ 2.9, OCH_2O), 71.6 (CH_2O), [68.5, 68.5] (CH_2O), 59.0 (OCH_3); δ_F (282 MHz, $CDCl_3$) -97.33 (1F, d, ^{2}J 55.9), -105.72 (1F, d, ^{2}J 55.9); [HRMS (ES-TOF, M+Na) Found: 343.1137; Calc. for $C_{18}H_{18}O_3F_2Na$: 343.1122]; *m/z* (EI) 321 (1%, M+H), 215 (5%), 181 (7%), 152 (10%), 89 (37%), 59 (100%)

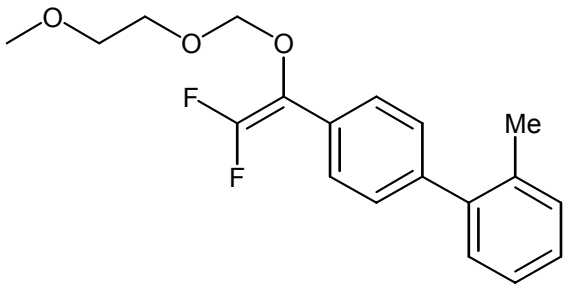
4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-3'-methoxy-biphenyl 139h



A flask containing 3-methoxyphenylboronic acid (230 mg, 1.5 mmol), potassium phosphate (320 mg, 1.5 mmol) and *tetrakis*(triphenylphosphine)palladium(0) (100 mg, 86 μmol) was pump-purged with nitrogen. Dry, degassed DMF (3 ml) was added followed by a solution of triflate **121a** (392 mg, 1.0 mmol) in DMF (1 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 45 min, with monitoring by TLC, before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by

column chromatography over silica gel (20% diethyl ether in hexanes) afforded anisole **139h** as a pale yellow oil (263 mg, 73%); 97% by GC; R_f (20% diethyl ether in hexanes) 0.13; ν (film/cm^{-1}) 1729 m, 1600 m, 1584 m, 1558 w, 1482 m, 1436 w, 1402 w, 1296 m, 1266 s, 1177 m, 1152 s, 1034 m, 981 s, 947 m, 839 m, 781 m, 696 w; δ_H (300 MHz, $CDCl_3$) 7.63-7.52 (4H, AB quartet, ArH), 7.36 (t, ^3J 7.9, ArH), 7.21-7.12 (2H, envelope, ArH), 6.94-6.89 (1H, m, ArH), 4.92 (2H, s, OCH_2O), 3.91-3.88 (2H, m, CH_2O), 3.86 (3H, s, $ArOCH_3$), 3.60-3.56 (2H, m, CH_2O), 3.39 (3H, s, CH_2OCH_3); δ_C (75 MHz, $CDCl_3$) 159.9 (Cq-OMe), 155.5 (t, $^1J_{CF}$ 289.3, CF_2), 141.8-141.7 (m, Cq), 140.8-140.8 (m, Cq), 129.7 (ArCH), 128.9-128.8 (m, Cq), 127.1 (ArCH), 127.0 (dd, $^4J_{CF}$ 5.9, 3.4, ArCH), 119.4 (ArCH), 115.4 (dd, $^2J_{CF}$ 35.1, 18.7, C=CF_2), 112.9 (ArCH), 112.7 (ArCH), 95.5-95.3 (m, OCH_2O), 71.5 (CH_2O), [68.4, 68.4] (CH_2O), 58.9 (CH_2OCH_3), 55.1 ($ArOCH_3$); δ_F (282 MHz, $CDCl_3$) -97.28 (1F, d, ^2J 56.0), -105.66 (1F, d, ^2J 54.7); [HRMS (ES-TOF, M+Na) Found: 373.1243; Calc. for $C_{19}H_{20}O_4F_2Na$: 373.1227]; *m/z* (ES) 373.1 (100%, M+Na).

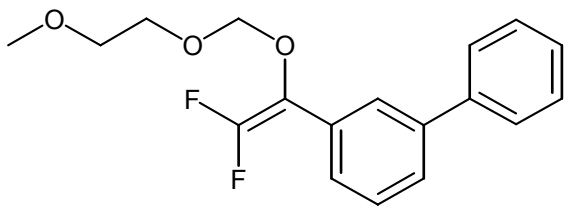
4-[(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-2'-methyl-biphenyl 139j



A flask containing *o*-tolylboronic acid (208 mg, 1.5 mmol), potassium phosphate (320 mg, 1.5 mmol) and *tetrakis*(triphenylphosphine)palladium(0) (100 mg, 86 μmol) was

pump-purged with nitrogen. Dry, degassed DMF (3 ml) was added followed by a solution of triflate **121a** (398 mg, 1.02 mmol) in DMF (1 ml). The heterogeneous yellow mixture was warmed to 85°C with darkening. The reaction mixture was allowed to stir for 2 h, with monitoring by TLC, before being cooled to ambient temperature. The reddish reaction mixture was partitioned between diethyl ether (10 ml) and water (10 ml). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 10 ml). The combined organic extracts were dried and concentrated to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded biphenyl **139j** as a colourless oil (222 mg, 65%); 97% by GC; R_f (20% diethyl ether in hexanes) 0.33; ν (film/cm^{-1}) 1922 w, 1736 s, 1484 s, 1457 s, 1402 m, 1266 s, 1177 s, 1153 s, 1101 s, 1029 m, 980 s, 949 s, 846 s, 765 s; δ_H (300 MHz, $CDCl_3$) 7.54-7.51 (2H, m, ArH), 7.38-7.35 (2H, m, ArH), 7.29-7.23 (4H, envelope, ArH), 4.95 (2H, s, OCH_2O), 3.93-3.90 (2H, m, CH_2O), 3.61-3.58 (2H, m, CH_2O), 3.41 (3H, s, OCH_3), 2.30 (3H, s, $ArCH_3$); δ_C (75 MHz, $CDCl_3$) 155.5 (t, $^1J_{CF}$ 290.2, CF_2), 141.9-141.9 (m, Cq), 141.1 (Cq), 135.2 (Cq), 130.3 (ArCH), 129.6 (ArCH), 129.3 (ArCH), 128.35-128.2 (m, Cq), 127.4 (ArCH), 126.5-126.3 (m, 2 overlapping dd, ArCH), 125.8 (ArCH), 115.9-115.1 (m, *C*=CF_2), 95.4 (t, $^4J_{CF}$ 2.6, OCH_2O), 71.6 (CH_2O), [68.4, 68.4] (CH_2O), 58.9 (OCH_3), 20.4 (CH_3); δ_F (282 MHz, $CDCl_3$) -97.56 (1F, d, ^2J 55.9), -105.98 (1F, d, ^2J 55.9); [HRMS (ES-TOF, M+Na) Found: 357.1284; Calc. for $C_{19}H_{20}O_3F_2Na$: 357.1278]. A satisfactory mass spectrum could not be obtained.

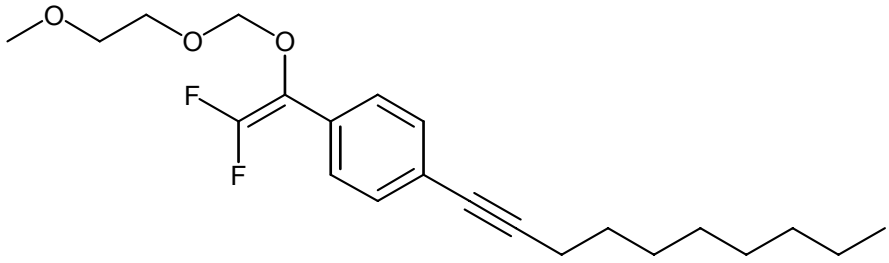
3-[2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-biphenyl 139n



A mixture of dichloro*bis*(triphenylphosphine)palladium(II) (80 mg, 0.11 mmol) and benzeneboronic acid (509 mg, 4.18 mmol) was pump-purged twice with nitrogen, then dry, degassed DMF (4 ml) added. The mixture was then warmed towards 70°C. Triethylamine (1.1 ml, 7.8 mmol) was added at 30°C, followed by a solution of triflate **121b** (0.79 g, 2.01 mmol) in DMF (1 ml). The resulting dark black solution was heated at 70°C for 70 h, with monitoring by TLC and GLC. GLC indicated an 86% conversion after this initial reaction period. Palladium catalyst (40 mg) was re-added and the reaction continued for a further 96 h (total 166 h) to give a 97% conversion by GLC. The reaction mixture was allowed to cool to ambient temperature, then diluted with diethyl ether (10 ml). The contents were added to a saturated aqueous solution of sodium bicarbonate (10 ml). The phases were separated and the aqueous phase extracted with diethyl ether (3 × 20 ml). The combined organic extracts were washed with water (10 ml) and brine (15 ml). The organic extracts were then dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded biphenyl **139n** as a colourless oil (401 mg, 62%); 98% by GC; [Found: C, 67.47; H, 5.75; Calc. for $C_{18}H_{18}F_2O_3$: C, 67.49; H, 5.66%]; ν (film/cm^{-1}) 1952 w, 1886 w, 1732 s, 1600 w, 1481 m, 1453 m, 1414 w, 1278 s, 1241 s, 1176 s, 1152 s, 1030 m, 988 s, 950 s, 760 s, 701 s; δ_H (300 MHz, $CDCl_3$) 7.68-7.66 (1H, m, ArH), 7.57-7.54 (2H, m,

ArH), 7.53-7.48 (1H, m, ArH), 7.45-7.38 (4H, envelope, ArH), 7.36-7.30 (1H, m, ArH), 4.89 (2H, d, $^{5}J_{HF}$ 0.7 Hz, OCH_2O), 3.87-3.84 (2H, m, CH_2O), 3.54-3.51 (2H, m, CH_2O), 3.34 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 154.0 (t, $^{1}J_{CF}$ 289.7, CF_2), 140.0 (Cq), 139.0 (Cq), 128.8 (dd, $^{3}J_{CF}$ 6.3, 1.4, Cq), 127.4 (CH), 127.2 (CH), 126.0 (CH), 125.5 (CH), 124.1 (dd, $^{4}J_{CF}$ 5.9, 3.3, CH), 123.9 (dd, $^{4}J_{CF}$ 5.5, 3.5, CH), 93.7 (t, $^{4}J_{CF}$ 2.7, OCH_2O), 70.0 (CH_2O), [66.8, 66.8] (CH_2O), 57.4 (OCH_3); δ_F (282 MHz, $CDCl_3$) -97.96 (1F, d, ^{2}J 55.6), -106.47 (1F, d, ^{2}J 55.6); [HRMS (ES-TOF, M+Na) Found: 343.1127; Calc. for $C_{18}H_{18}F_2O_3Na$: 343.1122]; *m/z* (ES) 343.0 (100%, M+Na).

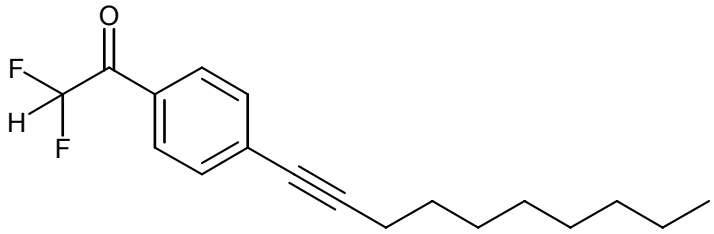
1-Dec-1'-ynyl-4-[2,2-difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl]-benzene 139p



A flask containing dichloro*bis*(triphenylphosphine)palladium(II) (12 mg, 34.2 μmol) was pump-purged twice with argon. Triethylamine (0.56 ml, 3.98 mmol) and a solution of triflate **121a** (205 mg, 0.52 mmol) in DMF (1 ml) were added and the orange solution stirred at ambient temperature for 2 min. 1-Decyne (0.1 ml, 0.55 mmol) was then added *via* syringe, and the resulting brown mixture heated at 90°C, with darkening, for 1 h. The resulting black solution was cooled to ambient temperature and ethyl acetate (5 ml) and water (5 ml) added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 5 ml). The

combined organic extracts were washed once with brine (5 ml), then dried and concentrated under reduced pressure to afford a brown oil, which was diluted with acetone and concentrated onto silica gel to afford a brown powder. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded alkyne **139p** as a pale yellow oil (82 mg, 41%); R_f (10% diethyl ether in light petroleum) 0.21; δ_H (300 MHz, $CDCl_3$) 7.39-7.32 (4H, m, ArH), 4.83 (2H, s, OCH_2O), 3.84-3.80 (2H, m, CH_2O), 3.53-3.50 (2H, m, CH_2O), 3.35 (3H, s, OCH_3), 2.37 (2H, t, ^3J 7.0, Ar-C≡C-CH_2-C_7H_{16}), 1.62-1.52 (2H, m), 1.47-1.35 (2H, m), 1.32-1.15 (8H, envelope), 0.89-0.81 (3H, m); δ_F (282 MHz, $CDCl_3$) -97.48 (1F, d, ^2J 53.7), -105.59 (1F, d, ^2J 53.7). Due to the unstable nature of this material, the MEM enol ether was cleaved to **140a** under protic conditions without further characterisation (*vide infra*).

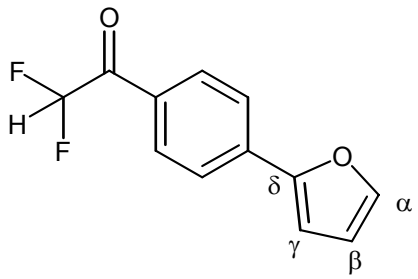
1-[(4-Decen-1'-yl)-phenyl]-2,2-difluoro-ethanone 140a



Acetophenone **140a** was prepared as for **132** using enol acetal **139p** (82 mg, 0.21 mmol) and chlorotrimethylsilane (0.1 ml, 0.78 mmol) in methanol (2 ml). Concentration under reduced pressure afforded a brown oil. Acetone (5 ml) was added and the solution concentrated onto silica to afford a brown powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum) afforded alkyne **140a** as a pale brown oil (46 mg, 78%); 99% by GC; R_f (15% diethyl

ether in light petroleum) 0.70; δ_H (300 MHz, $CDCl_3$) 7.99 (2H, d, ^3J 8.4, ArH), 7.50 (2H, d, ^3J 8.3, ArH), 6.26 (1H, t, $^2J_{HF}$ 53.5, CF_2H), 2.43 (2H, t, ^3J 7.0, $C{\equiv}CCH_2$), 1.61 (2H, tt, ^3J 7.3, 7.3, $C{\equiv}CCH_2CH_2$), 1.49-1.39 (2H, m, $C{\equiv}CCH_2CH_2CH_2$), 1.37-1.23 (8H, envelope, $C{\equiv}C(CH_2)_3(CH_2)_4$), 0.88 (3H, t, ^3J 6.5, CH_3); δ_C (75 MHz, $CDCl_3$) 132.0 (CH), 131.3 (Cq), 129.9 (t, $^3J_{CF}$ 2.0, Cq), 129.5 (t, $^4J_{CF}$ 2.3, CH), 111.3 (t, $^1J_{CF}$ 254.1, CF_2H), 96.3 (C≡C), 80.0 (C≡C), 31.9 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 22.7 (CH_2), 19.6 (CH_2), 14.1 (CH_3), CO too weak to assign; δ_F (282 MHz, $CDCl_3$) -122.0 (d, ^2J 51.1); [HRMS (EI, M) Found: 292.1637; Calc. for $C_{18}H_{22}OF_2$: 292.1639]; *m/z* (EI) 292 (13%, M), 241 (100%, M-CF_2H), 221 (10%), 185 (8%), 157 (8%), 142 (13%), 129 (17%), 115 (17%), 55 (25%), 43 (43%), 41 (63%).

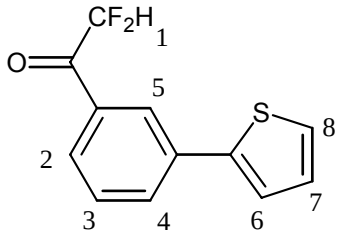
2,2-Difluoro-1-(4-furan-2-yl-phenyl)-ethanone 140b



Chlorotrimethylsilane (0.2 ml, 1.58 mmol) was added dropwise to a solution of enol acetal **139a** (270 mg, 0.87 mmol) in methanol (6 ml) at 0°C. The resulting solution was allowed to warm to ambient temperature, and stirred overnight. Evaporation of the solution afforded crude difluoroketone **140b** as a dark green solid. This material was dissolved in acetone (10 ml) and concentrated onto silica gel to afford a green powder. Purification by flash column chromatography over silica gel (15% diethyl

ether in light petroleum) afforded difluoromethyl ketone **140b** as an amorphous white solid (120 mg, 60%); 100% by HPLC at 225 nm; HPLC t_r (5% EtOAc in hexanes, 3 ml/min) 2.51 min; mp 113-114°C; R_f (15 % diethyl ether in light petroleum) 0.58; ν (nujol mull/cm^{-1}) 1695 w, 1608 w, 1256 w, 1223 w, 1057 w, 1021 w, 906 w, 876 w, 825 w, 746 w, 720 w, 670 w; [Found: C, 64.87; H, 3.75; Calc. for $C_{12}H_8F_2O_2$: C, 64.66; H, 3.63%]; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, d, ^3J 8.5, ArH), 7.87 (2H, d, ^3J 8.5, ArH), 7.70-7.69 (1H, m, H-α), 7.09-7.08 (1H, m, H-γ), 6.84 (1H, t, $^2J_{HF}$ 53.1, CF_2H), 6.59-6.57 (1H, m, H-β); δ_C (75 MHz, CD_3COCD_3) 157.4 (C-δ), 149.5 (C-α), 141.3 (Cq), 135.7 (Cq), 135.1 (CH), 128.8 (CH), 117.6 (C-β), 115.2 (t, $^1J_{CF}$ 248.0, CF_2H), 114.1 (C-γ), CO too weak to assign; δ_F (282 MHz, $CDCl_3$) -121.71 (d, $^2J_{HF}$ 47.4); [HRMS (EI, M) Found: 222.0495; Calc. for $C_{12}H_8F_2O_2$: 222.0492]; *m/z* (EI) 222 (42%, M), 171 (100%, M-CF_2H), 143 (17%, M-$COCF_2H$), 115 (53%), 89 (13%), 63 (12%), 51 (21%), 39 (12%).

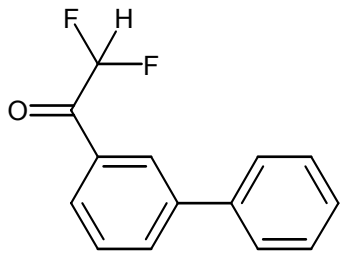
2,2-Difluoro-1-(3-thien-2-yl-phenyl)-ethanone 140c



Thiophene **140c** was prepared as for **140b** using enol acetal **139b** (230 mg, 0.7 mmol) and chlorotrimethylsilane (0.2 ml, 1.56 mmol) in methanol (3 ml). Evaporation of the solution afforded a colourless oil and white needles. Diethyl ether (5 ml) was

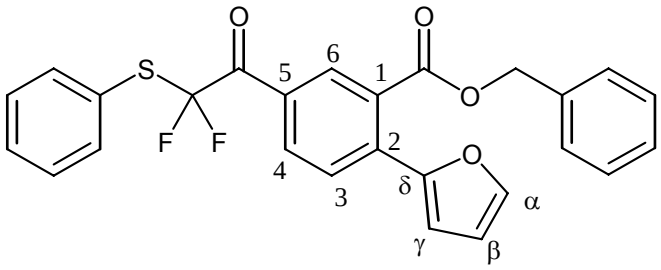
added and the white needles removed by filtration. The filtrate was concentrated under reduced pressure to afford a colourless oil. Acetone was added and the solution concentrated onto silica gel to afford a white powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum $\Rightarrow$ 20% ethyl acetate in light petroleum) afforded difluoromethyl ketone **140c** as a colourless oil (103 mg, 62%); 100% by GC; R_f (20% ethyl acetate in light petroleum) 0.55 (streaks); ν (film/cm^{-1}) 2925 w, 1709 s (C=O), 1600 m, 1580 m, 1482 w, 1442 w, 1422 w, 1345 w, 1299 w, 1275 m, 1247 w, 1232 w, 1205 w, 1136 s, 1067 s, 866 w, 852 w, 792 w, 709 m; δ_H (300 MHz, $CDCl_3$) 8.23 (1H, s, H-5), 7.91 (1H, br. d, ^3J 7.9, H-2 or H-4), 7.84-7.81 (1H, m, H-2 or H-4), 7.48 (1H, t, ^3J 7.9, H-3), 7.34 (1H, d, ^3J 4.4, H-6), 7.30 (1H, d, ^3J 5.1, H-8), 7.08-7.04 (1H, m, H-7), 6.27 (1H, t, $^2J_{HF}$ 53.7, H-1); δ_C (75 MHz, $CDCl_3$) 187.7 (t, $^2J_{CF}$ 25.6, CO), 142.7 (Cq), 135.8 (Cq), 132.4 (t, $^3J_{CF}$ 1.9, Cq), 132.3 (CH), 129.8 (CH), 128.6 (t, $^4J_{CF}$ 2.7, CH), 128.6 (CH), 126.9 (t, $^4J_{CF}$ 2.0, CH), 126.2 (CH), 124.5 (CH), 111.4 (t, $^1J_{CF}$ 253.8 , CF_2H); δ_F (282 MHz, $CDCl_3$) -122.29 (d, $^2J_{HF}$ 53.7); [HRMS (EI, M) Found: 238.0265; Calc. for $C_{12}H_8OSF_2$: 238.0264]; *m/z* (EI) 239 (11%, M+H), 238 (71%, M), 187 (100%, M-CF_2H), 159 (44%, M-HF_2CO), 115 (66%), 79 (8%, HF_2CO).

1-Biphenyl-3-yl-2,2-difluoro-ethanone 140d



Biphenyl ketone **140d** was prepared as for **140b** using enol acetal **139n** (153 mg, 0.48 mmol), chlorotrimethylsilane (0.2 ml, 1.58 mmol) in MeOH (2 ml). Evaporation of the solution afforded a crude brown oil. This material was diluted with acetone and concentrated onto silica gel to afford a brown powder. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum $\Rightarrow$ 20% ethyl acetate in light petroleum) afforded ketone **140d** as a colourless oil (589 mg, 48%); 100% by GC; R_f (20% ethyl acetate in light petroleum) 0.55 (streaks); ν (film/cm^{-1}) 3036, 1711, 1600, 1586, 1481, 1455, 1347, 1319, 1257, 1222, 1138, 1070, 909, 735, 699; δ_H (300 MHz, $CDCl_3$) 8.29 (1H, bd s, ArH), 8.05 (1H, d, ^3J 8.1, ArH), 7.90 (1H, dd, ^3J 7.9, J 0.9, ArH), 7.63-7.58 (3H, envelope, ArH), 7.51-7.38 (3H, envelope, ArH), 6.33 (1H, t, $^2J_{HF}$ 53.5, $COCF_2H$); δ_C (75 MHz, $CDCl_3$) 142.2 (Cq), 139.6 (Cq), 133.5 (CH), 132.0-132.0 (m, Cq), 133.5 (CH), 129.4 (CH), 129.0 (CH), 128.4 (t, $^4J_{CF}$ 2.5 Hz, CH), 128.3 (t, $^4J_{CF}$ 2.1 Hz, CH), 128.1 (CH), 127.2 (CH), 111.3 (t, $^1J_{CF}$ 253.8 Hz, CF_2), CO too weak to assign; δ_F (282 MHz, $CDCl_3$) -122.11 (d, $^2J_{HF}$ 52.6); [HRMS (EI, M) Found: 232.0691; Calc. for $C_{14}H_{10}OF_2$: 232.0700]; *m/z* (EI) 232 (28%, M), 181 (50%, M-CF_2H), 153 (30%, M-$COCF_2H$), 152 (33%, M-1-$COCF_2H$), 51 (74%, CF_2H), 40 (100%).

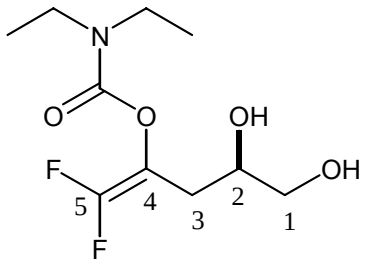
Benzyl 5-[(2,2-difluoro-2-phenylsulfanyl)-acetyl]-2-furan-2'-yl benzenecarboxylate 143



Phenylsulfenyl chloride (40 μl, 0.34 mmol) was added to a solution of furan **139d** (156 mg, 0.34 mmol) in DCM (4 ml) at ambient temperature. After 16 h, the reaction was concentrated under reduced pressure to afford a crude yellow oil. Purification by flash column chromatography over silica gel (30% diethyl ether in light petroleum) afforded ketone **143** as a bright yellow oil (126 mg, 80%); 71% by HPLC at 225 nm; HPLC t_r (20% water in MeCN, 1 ml/min) 11.84 min; minor impurities were observed by ^{19}F, ^{1}H and ^{13}C NMR; R_f (20% ethyl acetate in light petroleum) 0.44 (streaks); ν (film/cm^{-1}) 1734 m, 1730 m, 1700 m, 1696 m, 1600 m, 1499 w, 1474 w, 1454 w, 1441 w, 1372 w, 1306 w, 1265 m, 1239 m, 1136 m, 1095 m, 1034 m, 1012 m, 737 m, 699 m; δ_H (300 MHz, $CDCl_3$) 8.34 (1H, d, ^4J 1.9, H-6), 8.20-8.17 (1H, m, H-4), 7.75 (1H, d, ^3J 8.5, H-3), 7.58-7.55 (2H, m, ArH), 7.48-7.26 (9H, envelope, ArH + H-α), 6.74 (1H, d, ^3J 3.7, H-γ), 6.45 (1H, dd, ^3J 3.7, ^4J 1.9, H-β), 5.36 (2H, s, OCH_2Ph); δ_C (75 MHz, $CDCl_3$) 183.8 (t, $^2J_{CF}$ 2.0, CF_2CO), 168.0 (CO ester), 150.7 (Cq, C-δ), 144.3 (CH, C-α), 136.8 (CH), 135.2 (Cq of benzyl), 134.4 (Cq, C-2), 132.3 (t, $^4J_{CF}$ 2.8, CH, C-4), 131.5 (t, $^4J_{CF}$ 2.8, CH, C-6), 130.7 (CH), 129.4 (CH), 128.7 (CH), 128.7 (CH), 128.5 (CH), 127.4 (CH), 124.5 (t, $^3J_{CF}$ 1.4, Cq of PhS), 123.6 (t, $^1J_{CF}$ 290.5, CF_2), 112.2 (CH, C-γ), 111.3 (CH, C-β), 67.7 (OCH_2Ph), C-1 and C-5 obscured by aryl CH

resonances in δ127-132 range; δ_F (282 MHz, $CDCl_3$) -77.62 (s); [HRMS (ES-TOF, M+Na) Found: 487.0789; Calc. for $C_{26}H_{18}O_4SF_2Na$: 487.0792]; *m/z* (ES-TOF) 519.3 (29%, M+Na+MeOH), 487.2 (100%, M+Na), 465.2 (13%, M+1).

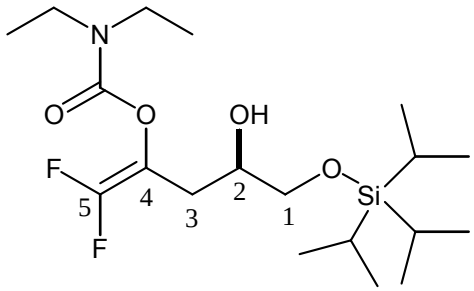
(2*R*)- 4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 156



A solution of AD-mix-β (11.7 g, 1.41 g/mmol) and sodium hydrogencarbonate (1.8 g, 21.4 mmol) in $^tBuOH:H_2O$ (82 ml, 1:1 v/v) was stirred vigorously at ambient temperature until the phases became clear. Diene **99d** (1.82 g, 8.32 mmol) was added in one portion and the slurry stirred vigorously at 0°C until TLC indicated the consumption of starting material. The yellow mixture was quenched with sodium sulfite (12 g) then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (5 ml) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in light petroleum) afforded diol **156** as a colourless oil (1.85 g, 88%); R_f (60% ethyl acetate in light petroleum) 0.25; [Found: C, 47.14; H, 6.77; N, 5.53; Calc. for $C_{10}H_{17}NO_4F_2$: C, 47.43; H, 6.77; N, 5.53%]; ν (film/cm^{-1}) 3600-3100 bd, 1780 m (C=CF_2), 1706 s (C=O), 1476 m, 1429 s,

1382 m, 1291 s, 1239 s, 1217 s, 1158 m, 1115 s, 1047 m, 956 w, 935 w, 785 w, 757 w; δ_H (300 MHz, $CDCl_3$) 3.80-3.72 (1H, m, H-2), 3.65 (1H, dd, ^2J 11.4, ^3J 3.3, H-1a), 3.50 (1H, dd, ^2J 11.4, ^3J 6.6, H-1b), 3.30 (2H, q, ^3J 7.0, CH_2NCH_2), 3.29 (2H, q, ^3J 7.0, CH_2NCH_2), 2.40 (1H, ddd, ^2J 15.1, ^3J 9.9, $^4J_{HF}$ 3.7, H-3a), 2.27-2.18 (1H, m, H-3b), 1.14 (3H, t, ^3J 7.0, (*Me*CH_2)NEt), 1.13 (3H, t, ^3J 7.0, EtNCH_2*Me*); δ_C (75 MHz, $CDCl_3$) 155.6 (dd, $^1J_{CF}$ 289.0, 288.0, C-5), 154.4 (d, $^4J_{CF}$ 2.3, CO), 109.0 (dd, $^2J_{CF}$ 44.7, 16.0, C-4), 67.8 (t, $^4J_{CF}$ 2.8, C-2), 65.8 (C-1), [42.7, 42.1] (CH_2), 31.9 (d, $^3J_{CF}$ 2.8, C-3), [13.9, 13.2] (CH_3); δ_F (282 MHz, $CDCl_3$) -96.40 (1F, dd, ^2J 59.8, $^4J_{HF}$ 5.1), -109.98 (1F, dt, ^2J 59.8, $^4J_{HF}$ 3.7); [HRMS (ES-TOF, M+Na) Found: 276.1034; Calc. for $C_{10}H_{17}NO_4F_2Na$: 276.1023]; *m/z* (CI) 254 (100%, M+H), 100 (20%, $CONEt_2$); *m/z* (ES) 276 (100%, M+Na). Stereochemical assignment is based upon the Sharpless model.[204]

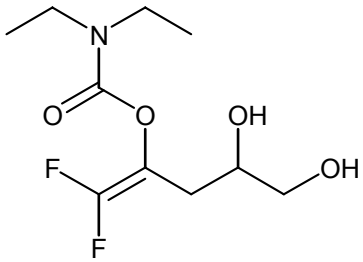
(2*R*)-4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro-1-(tri*iso*propylsilyloxy)-pent-4-en-2-ol 157



Chlorotri*iso*propylsilane (0.22 ml, 1.05 mmol) was added to a solution of diol **156** (266 mg, 1.05 mmol) in DCM (2 ml) containing imidazole (170 mg, 2.50 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 48 h, then diluted with DCM (2 ml). The organic layer was washed consecutively with water (10 ml), a saturated solution of ammonium chloride (10 ml) and brine (10 ml). The organic

extracts were dried and concentrated under reduced pressure to afford alcohol **157** as a colourless oil (430 mg, 100%); 99% by GC; R_f (25% diethyl ether in light petroleum) 0.27; α_D –2.1° (c=18.4, 21°C, MeOH, est. error = ± 0.4°); δ_H (300 MHz, $CDCl_3$) 3.78-3.61 (3H, m, H-1, OH), 3.44 (1H, dd, ^3J 7.0, ^3J 7.0 H-2), 3.35-3.26 (4H, m, CH_2NCH_2), 2.53-2.44 (1H, m, H-3a), 2.37-2.28 (1H, m, H-3b), 1.19-1.01 (27H, m, $(MeCH_2)_2N$), $Si(CHMe_2)_3$); δ_C (75 MHz, $CDCl_3$) 155.4 (t, $^1J_{CF}$ 288, C-5), 153.9 (CO), 109.4 (dd, $^2J_{CF}$ 45.8, 15.8, C-4), 68.3 (t, $^4J_{CF}$ 2.5, C-2), 66.6 (C-1), [42.6, 42.0] (CH_2), 32.1 (d, $^3J_{CF}$ 2.8, C-3), 17.9 (CH_3), [13.9, 13.2] (CH_3), 11.9 (CH); δ_F (282 MHz, $CDCl_3$) -96.91 (1F, dd, ^2J 61.0, $^4J_{HF}$ 3.8), -110.51 (1F, dd, ^2J 61.0, $^4J_{HF}$ 3.8); [HRMS (ES-TOF, M+Na) Found: 432.2344; Calc. for $C_{19}H_{37}NO_4F_2NaSi$: 432.2358]; *m/z* (ES-TOF) 432.4 (100%, M+Na); Chiral HPLC t_r (Chiralcel OD, 10% *iso*propanol in hexane, 1 ml/min) 6.53 min; 95:5 *er*.

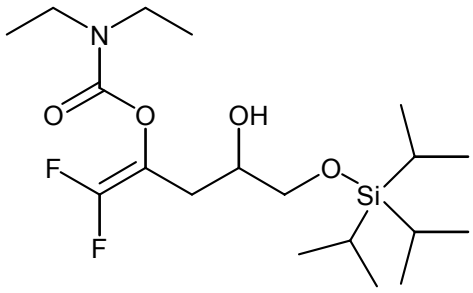
(2*RS*)- 4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro-pent-4-en-1,2-diol 158



A solution of potassium osmate dihydrate (9 mg, 24.5 μmol), potassium ferricyanide (3.03 g, 9.20 mmol), potassium carbonate (1.32 g, 9.54 mmol), quinuclidine (13 mg, 119 μmol) and sodium hydrogencarbonate (260 mg, 3.09 mmol) in *t*BuOH-H_2O (15 ml, 1:1 v/v) was stirred vigourously at ambient temperature until the phases became clear. Diene **99d** (669 mg, 3.05 mmol) was added in one portion and the slurry stirred

vigorously at ambient temperature for 16 h. The yellow mixture was quenched with sodium sulfite (3 g) and then stirred for 30 min to afford a grey solution. The reaction mixture was diluted with DCM (10 ml) and the layers were separated. The aqueous phase was extracted with DCM (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (80% ethyl acetate in light petroleum) afforded diol **158** as a colourless oil (368 mg, 48%); R_f (80% ethyl acetate in light petroleum) 0.38; δ_F (282 MHz, $CDCl_3$) -96.91 (1F, dd, ^2J 61.0, $^4J_{HF}$ 3.8), -110.51 (1F, dd, ^2J 61.0, $^4J_{HF}$ 3.8). This material was taken on without further characterisation.

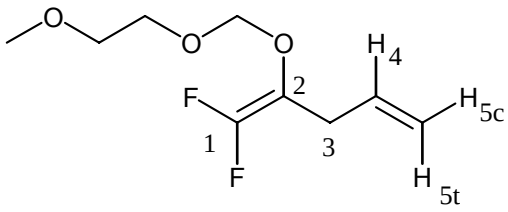
(2*RS*)-4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro-1-(tri*iso*propylsilyloxy)-pent-4-en-2-ol 159



Chlorotri*iso*propylsilane (0.31 ml, 1.45 mmol) was added to a solution of diol **158** (368 mg, 1.45 mmol) in DCM (3 ml) containing imidazole (220 mg, 3.24 mmol) and DMAP (cat.). The mixture was stirred at ambient temperature for 96 h, then diluted with DCM (3 ml). The organic layer was washed consecutively with water (10 ml), a saturated solution of ammonium chloride (10 ml) and brine (10 ml). The organic extracts were dried and concentrated under reduced pressure to afford crude alcohol

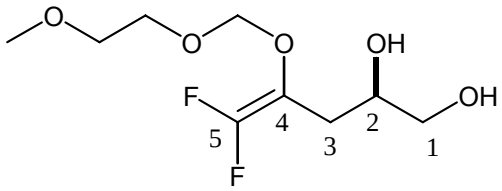
159 as a colourless oil (570 mg, 96%); Chiral HPLC t_r (Chiralcel OD, 20% IPA in hexane, 0.5 ml/min) 6.16 and 6.72 mins; 50:50 *er*.

1,1-Difluoro-2-(2-methoxy-ethoxymethoxy)-penta-1,4-diene 161



1,4-Diene **161** was prepared as for **99d** using palladium(II) acetate (70 mg, 0.31 mmol), CuI (460 mg, 2.43 mmol), triphenylphosphine (320 mg, 1.22 mmol), allyl bromide (1.5 ml, 17.3 mmol) and stannane **118** (6.86 g, 12.15 mmol based on 81% purity) in DMF (10 ml). After 18 h, the usual work-up afforded a yellow oil (3.25 g). Purification by column chromatography over silica gel (20% diethyl ether in hexanes) afforded 1,3-diene **161** as a pale yellow oil (1.48 g, 62%); R_f (20% diethyl ether in hexanes) 0.32; ν (film/ cm^{-1}) 2929 s, 2896 s, 2822 m, 1765 s, 1717 w, 1643 w, 1456 m, 1431 m, 1416 w, 1368 w, 1274 s, 1250 s, 1212 s, 1160 s, 1111 s, 1053 s, 994 s, 974 s, 923 s, 887 w, 851 m, 773 m; δ_H (300 MHz, $CDCl_3$) 5.88-5.71 (1H, m, H-4), 5.21-5.08 (2H, m, H-5c, H-5t), 4.88 (2H, s, OCH_2O), 3.80-3.77 (2H, m, CH_2O), 3.57-3.54 (2H, m, CH_2O), 3.38 (3H, s, OCH_3), 2.97-2.89 (2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 132.8 (C-4), 117.4 (C-5), 94.7-94.6 (m, OCH_2O), 71.5 (CH_2O), [68.1, 68.0] (CH_2O), 59.0 (OCH_3), 30.4 (C-3), C-1 and C-2 too weak to assign due to weak sample; δ_F (282 MHz, $CDCl_3$) -102.50 (1F, dt, ^2J 71.2, $^4J_{HF}$ 2.5), -113.14 (1F, dt, ^2J 70.6, $^4J_{HF}$ 3.8). A satisfactory mass spectrum could not be obained. This material was taken on without further characterisation.

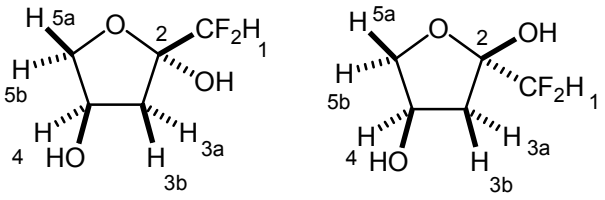
(2*R*)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-pent-4-en-1,2-diol 163



A solution of AD-mix-β (10.00 g, 1.4g/mmol) in *t*BuOH/H_2O (76 ml, 1:1 v/v) was stirred vigourously until the phases became clear. Diene **162** (1.48 g, 6.23 mmol based upon 85% purity, enol carbamate **162** impurity) was added to this solution and the resulting heterogenous mixture stirred vigourously for 21 h. TLC indicated the slow formation of diol **163**, confirmed by ^{19}F NMR. The reaction was quenched with sodium sulfite (11 g) and the reaction stirred for 1 h. DCM (30 ml) was added and the organic layer separated. The aqueous phase extracted with DCM (3 × 30 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil (950 mg). Purification by column chromatography over silica gel (40% ethyl acetate in light petroleum ⇒ 100% ethyl acetate in light petroleum) afforded diol **163** as a colourless oil (145 mg, 10%); R_f (80% ethyl acetate in light petroleum) 0.13; ν (film/cm^{-1}) 3414 bd s (OH), 1767 s, 1709 w, 1643 w, 1457 m, 1368 m, 1274 s, 1241 s, 1202 s, 1113 bd s, 1027 s, 963 s, 889 m, 850 m, 769 w; δ_H (300 MHz, $CDCl_3$) 4.92 (2H, s, OCH_2O), 3.97-3.88 (1H, m, H-2), 3.82-3.78 (2H, m, OCH_2CH_2O), 3.65 (1H, dd, *one half of an ABX*, ^2J 11.2, ^3J 2.9, H-1a), 3.58-3.54 (2H, m, OCH_2CH_2O), 3.50 (1H, dd, *one half of an ABX*, ^2J 11.2, ^3J 6.6, H-1b), 3.39 (3H, s, OCH_3), 3.17-3.02 (1H, bd s, OH), 2.57-2.42 (1H, bd s, OH), 2.37-2.30 (2H, m, H-3); δ_C (75 MHz, $CDCl_3$) 155.2 (dd, $^1J_{CF}$ 287.7, 280.9, C-5), 113.1 (dd, $^2J_{CF}$ 41.3, 14.1, C-4), 95.6 (t, $^4J_{CF}$ 2.8, OCH_2O), 71.6 (CH_2O), 69.3 (dd, $^4J_{CF}$ 3.4, 2.3, C-2), [68.2, 68.2]

(CH_2O), 66.0 (C-1), 59.1 (OCH_3), 30.6 (d, $^3J_{CF}$ 2.8, C-3); δ_F (282 MHz, $CDCl_3$) -100.24 (1F, d, ^2J 68.6), -112.31 (1F, dt, ^2J 68.6, $^4J_{HF}$ 4.4); [HRMS (ES-TOF, M+Na) Found: 265.0865; Calc. for $C_9H_{16}O_5F_2Na$: 265.0864]; *m/z* (ES-TOF) 265.1 (100%, M+Na). Stereochemistry is assigned on the basis of the Sharpless model.[204] Degree of asymmetric induction has not been determined.

1,3-Dideoxy-1,1-difluoro-α-D-*glycero*-pent-2-ulofuranose and 1,3-dideoxy-1,1-difluoro-β-D-*glycero*-pent-2-ulofuranose 155

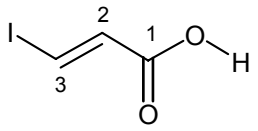


α β

Chlorotrimethylsilane (63 μl, 0.5 mmol) was added dropwise to a solution of diol **163** (145 mg, 0.5 mmol) in methanol (5 ml) at 0°C. The resulting colourless solution was allowed to warm to ambient temperature and stirred for 18 h. The reaction mixture was concentrated under reduced pressure to afford a pale yellow oil. Acetone (5 ml) was added and the solution concentrated onto silica gel to afford a pale yellow powder. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded pentuloses **165** as clear oils (50 mg, 65%, ~1:1 α:β); R_f (60% ethyl acetate in hexanes) 0.31; ν (film/cm^{-1}) 3400 bd s (OH), 2963 m, 2894 m, 2520 bd s (OD), 1704 w, 1471 w, 1437 m, 1372 w, 1076 s; δ_H (300 MHz, CD_3OD) 5.68 (0.5H, t, $^2J_{HF}$ 55.9, H-1α), 5.59 (0.5H, t, $^2J_{HF}$ 56.3, H-1β), 4.58-4.50 (0.5H, m, H-4α), 4.44-4.37 (0.5H, m, H-4β), 4.11 (0.5H, dd, ^2J 9.4, ^3J 4.8, H-5bα), 3.96-3.93 (1H, m, envelope,

H-5aβ, H-5bβ), 3.75 (0.5H, dd, ^{2}J 9.3, ^{3}J 3.1, H-5aα), 2.43-2.36 (0.5H, m, H-3bβ), 2.17-2.11 (1H, m, envelope, H-3aα, H-3bα), 1.92-1.85 (0.5H, m, H-3aβ); δ_C (126 MHz, CD_3OD) 115.4 (t, $^{1}J_{CF}$ 246.0, C-1, α and β), 104.8-104.2 (m, C-2, α and β), 76.8 (C-5β), 76.0 (C-5α), 71.2 (C-4, α or β), 71.2 (C-4, α or β), 42.6 (C-3α), 41.1 (C-3β); δ_F (282 MHz, CD_3OD) -130.22 (dd, ^{2}J 283.7, $^{3}J_{HF}$ 56.1, α isomer), -134.01 (dd, ^{2}J 283.7, $^{3}J_{HF}$ 55.8, α isomer), -132.10 (apparent d, 55.9 Hz separation, highly distorted ABX, β isomer)(1.05:1 α:β after 24 h in CD_3OD; 1.35:1 α:β after 2 months in CD_3OD); *m/z* (CI) 308 (52%, 2M or 2M-H_2O+NH_4), 290 (28%, 2M-H_2O), 194 (29%), 172 (81%, M+NH_4), 154 (100%, M).

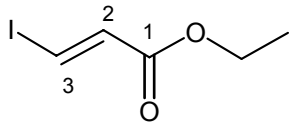
(*E*)-3-Iodoacrylic acid 178



A mixture of propiolic acid (18 ml, 3 × 6 ml, 292 mmol) and aqueous HI (66 ml of a 57% w/w (7 M) aqueous solution, 3 × 22 ml, 462 mmol) was heated in three foil-wrapped Ace® tubes at 95°C for 21 h. The resulting mixtures were allowed to cool to ambient temperature to afford a suspension of acid **178** (as large white crystals) in excess aqueous HI. The pressure was released (CARE), then the mixtures were diluted with water (5 ml) and filtered under vacuum, using water to wash out the product from the tube. A final washing of the suspended product with light petroleum (20 ml) followed by drying afforded iodoacid **178** as large white needles (54.32 g, 94%); m.p.147-149°C (lit. 147-148°C, 144-147°C);[213a] [Found: C, 18.33; H, 1.36;

Calc. for $C_3H_3O_2I$; C, 18.20; H, 1.53%]; δ_H (300 MHz, $CDCl_3$) 10.54-8.66 (1H, bd s, OH), 8.08 (1H, d, ^3J 14.7, H-2), 6.89 (1H, d, ^3J 14.7, H-3). Spectral data were in agreement with those reported both by Takeuchi.[213a]

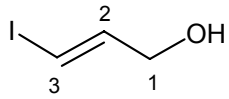
(*E*)-Ethyl 3-iodoacrylate 179



Sulfuric acid (9.0 ml of a 98% aqueous solution) was added to a solution of iodoacid **178** (33.2 g, 168 mmol) in absolute ethanol (200 ml) to afford a colourless solution. This was then heated under reflux, with yellowing, for 23 h before being cooled to ambient temperature. A saturated aqueous solution of sodium bicarbonate (150 ml) was added, then the pH was adjusted to 7.4 by the addition (CARE) of solid sodium bicarbonate (until loss of effervescence). The ethanol was removed under reduced pressure and the residue diluted with ethyl acetate (40 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 $\times$ 150 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude ester **179** as a yellow oil. Filtration through a pad of silica using diethyl ether as eluant afforded an orange oil (28.3 g), after evaporation of solvents. Further purification by distillation under reduced pressure afforded iodoester **179** as a pale yellow oil (24.8 g, 65%); b.p 65°C/~10 mmHg (lit. 74-76°C/9 Torr);[213a] R_f (15% diethyl ether in hexanes) 0.61; ν (film/cm^{-1}) 3070 w, 2982 m, 1722 s, 1593 s, 1465 w, 1446 w, 1391 w, 1368 m, 1298 s, 1259 s, 1216 s, 1146 s, 1034 s, 949 s; δ_H (300 MHz, $CDCl_3$) 7.85 (1H, d, ^3J 14.7, H-3), 6.84 (1H, d, ^3J 14.7, H-2), 4.17 (2H, q, ^3J 7.4,

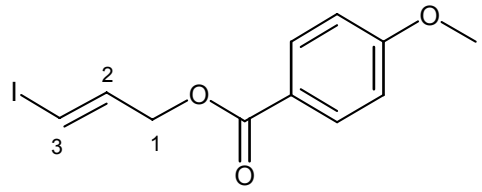
C*H*$_2$CH$_3$), 1.26 (3H, t, ^3J 7.4, CH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 164.2 (C-1), 136.6 (C-2), 99.4 (C-3), 61.0 (CH_2), 14.2 (CH_3). Spectral data were in agreement with those reported by Takeuchi.[213a]

(*E*)-3-Iodoprop-2-en-1-ol 180



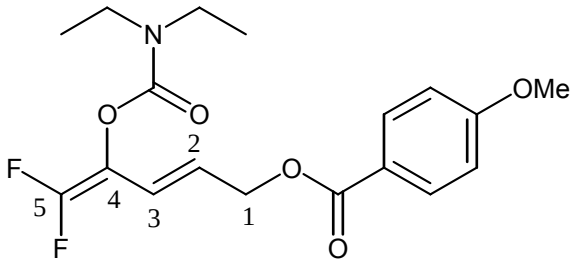
Di*iso*butylaluminium hydride (8.84 ml of a 1 M solution in hexanes, 8.84 mmol) was added dropwise to a solution of iodoacrylate **179** (1.00 g, 4.42 mmol) in dry DCM (10 ml) at –75°C under an atmosphere of nitrogen. The addition was controlled so that the temperature did not exceed –70°C. The pale yellow solution was stirred for 45 min at –75°C and then allowed to warm to 0°C. The mixture was quenched at this temperature with methanol (10 ml), methanol/water (20 ml, 3:1 v/v) and water (10 ml) with the formation of a white emulsion. DCM (30 ml) was added followed by Rochelle's salt (30 ml of a 10% aqueous solution) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 20 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a runny pale yellow oil (0.76 g). Purification by column chromatography over silica gel (60% diethyl ether in light petroleum) afforded iodoalcohol **180** as a colourless oil (410 mg, 50%); R_f (60% diethyl ether in light petroleum) 0.40; δ_H (300 MHz, $CDCl_3$) 6.69 (1H, dt, ^3J 14.3, 5.5, H-2), 6.39 (1H, d, ^3J 14.7, H-3), 4.09 (2H, dd, ^3J 5.2, 1.8, H-1), 1.71 (1H, s, OH); δ_C (75 MHz, $CDCl_3$) 144.8 (C-2), 78.1 (C-3), 65.1 (C-1); *m/z* (EI) 184 (32%, M), 127 (20%, I), 57 (100%, M-I), 39 (17%).

(*E*)-3-Iodoprop-2-enyl 4-methoxybenzenecarboxylate 181



4-Anisoyl chloride (2.02 g, 11.84 mmol) was added to a solution of iodoalcohol **180** (2.00 g, 10.88 mmol), pyridine (0.9 ml, 11.0 mmol) and 4-(dimethylamino)pyridine (78 mg, 0.64 mmol) in DCM (20 ml) at 0°C. The resulting solution was allowed to warm to ambient temperature and then stirred for 18 h. The reaction was quenched with water (10 ml), followed by extraction of the aqueous phase with DCM (3 × 15 ml). The combined organic extracts were washed with 1.0 M HCl (20 ml), before being dried and concentrated under reduced pressure to afford a crude pale yellow oil. Purification by column chromatography over silica gel (10% diethyl ether in light petroleum) afforded iodoester **181** as a colourless oil (3.36 g, 97%); 93% by GC; 98% by HPLC at 225 nm; HPLC t_r (10% water in MeCN, 1 ml/min) 4.44 min; R_f (10% diethyl ether in light petroleum) 0.24; ν (film/cm^{-1}) 1714 s (C=O), 1607 s (C=C), 1512 m, 1371 w, 1317 m, 1257 s, 1169 s, 1102 m, 1030 m, 847 m, 770 m; δ_H (300 MHz, $CDCl_3$) 7.99 (2H, d, ^3J 8.8, ArH), 6.91 (2H, d, ^3J 8.8, ArH), 6.74 (1H, dt, ^3J 14.7, 5.9, H-2), 6.55 (1H, dt, ^3J, 14.7, ^4J 1.4, H-3), 4.70 (2H, dd, ^3J 5.9, ^4J 1.3, H-1), 3.85 (3H, s, ArO*Me*); δ_C (75 MHz, $CDCl_3$) 165.7 (CO), 163.6 (C_q-OMe), 140.0 (C-2), 131.8 (Ar*C*H), 122.1 (C_q-CO), 113.7 (Ar*C*H), 80.8 (C-3), 65.9 (C-1), 55.5 (OCH_3); [HRMS (ES-TOF, M+Na) Found: 340.9646; Calc. for $C_{11}H_{11}O_3INa$: 340.9651]; *m/z* (ES-TOF) 341.0 (100%, M+Na).

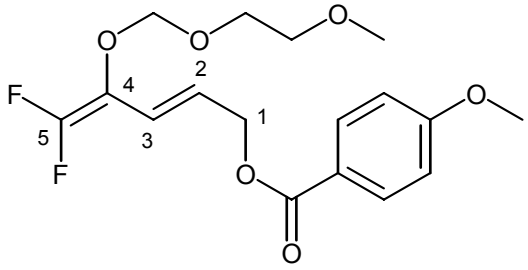
(*E*)-[(4-(*N,N*-Diethylcarbamoyloxy)-5,5-difluoro)-penta-2,4-dienyl] 4-methoxybenzenecarboxylate 182



Ester **182** was prepared as for 95a using *tris*(dibenzylideneacetone)dipalladium(0)-chloroform adduct (23 mg, 22 μmol), triphenylphosphine (58 mg, 0.22 mmol), CuI (26 mg, 0.14 mmol), iodoalkene **181** (359 mg, 1.1 mmol) and stannane **81** (520 mg, 1.11 mmol). Following the usual work-up, a crude brown oil was isolated. Purification by column chromatography over silica gel (15% diethyl ether in light petroleum ⇒ 20% ethyl acetate in light petroleum) afforded pentadienyl ester **182** as a pale orange oil (355 mg, 83%); R_f (20% ethyl acetate in light petroleum) 0.35; ν (film/cm^{-1}) 1734 bd s, 1606 m, 1511 m, 1421 m, 1381 w, 1251 s, 1168 m, 1097 m, 1031 m, 955 w, 847 w, 770 w; δ_H (300 MHz, $CDCl_3$) 8.03-7.98 (2H, m, ArH), 6.94-6.89 (2H, m, ArH), 6.38 (1H, ddt, ^3J 15.5, ^4J 1.5, $^4J_{HF}$ 2.4, H-3), 5.84 (1H, dt, ^3J 15.5, 6.1, H-2), 4.86 (2H, dd, ^3J 6.1, ^4J 1.5, H-1) 3.86 (3H, s, OCH_3), 3.42-3.32 (4H, two overlapping q, ^3J 7.0, CH_2NCH_2), 1.23-1.15 (6H, two overlapping t, ^3J 7.0, $N(CH_2Me)_2$); δ_C (75 MHz, $CDCl_3$) 165.7 (CO), 163.3 (Cq-OMe), 154.2 (dd, $^1J_{CF}$ 294.4, 292.2, C-5), 152.1 (t, $^4J_{CF}$ 2.2, CO), 131.5 (CH), 123.0 (dd, $^3J_{CF}$ 11.9, 4.5, C-3), 122.1 (Cq), 120.1 (d, $^4J_{CF}$ 4.5, C-2), 113.5 (CH), 111.6 (dd, $^2J_{CF}$ 40.1, 18.7, C-4), 63.9 (C-1), 55.2 (OCH_3), [42.4, 41.8] (CH_2), [13.9, 13.0] (CH_3); δ_F (282 MHz, $CDCl_3$) -94.32 (1F, d, ^2J 39.4), -104.59 (1F, dd, ^2J 39.4, $^3J_{HF}$ 2.5); [HRMS (ES-TOF, M+Na) Found: 392.1289; Calc. for

$C_{18}H_{21}NO_5F_2Na$: 392.1285]; *m/z* (EI) 369 (27%, M), 269 (11%, M-ODEC), 218 (8%, M-$OCOC_6H_4OMe$), 152 (5%), 135 (58%, $MeOC_6H_4CO$), 100 (100%, $CONEt_2$), 72 (68%, H_2NEt_2).

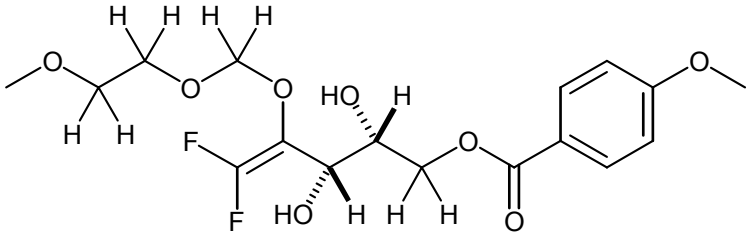
(*E*)-[(5,5-Difluoro-4-(2-methoxy-ethoxymethoxy))-penta-2,4-dienyl] 4-methoxy-benzenecarboxylate 190



A flask containing palladium(II) acetate (28 mg, 0.13 mmol), copper(I) iodide (199 mg, 1.04 mmol) and triphenylphosphine (136 mg, 0.52 mmol) was evacuated and the vacuum released to a nitrogen inlet. The procedure was repeated twice. Dry, degassed DMF (5 ml) was added and the resulting dark solution warmed to 30°C. Iodoalkene **181** (1.59 g, 5.0 mmol) was added as a solution in DMF (1 ml). The reaction mixture was warmed to 50°C. Stannane **118** (2.76 g, 6.0 mmol) was added at 40°C as a solution in DMF (1 ml). The resulting solution was heated for 3 h at 50°C and monitored by TLC. Upon consumption of the starting material, the solution was diluted with diethyl ether (20 ml), then transferred to a conical flask. An aqueous solution of KF (20 ml of a 0.97 M solution) was added and the resulting mixture stirred rapidly for 1 h. The precipitated solid (Bu_3SnF) was filtered under vacuum and washed with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were

dried and concentrated under reduced pressure to afford an orange oil, containing a red sediment ([$(PPh_3)_2PdI_2$]). Purification by column chromatography over alumina (Brockmann 1, pH 9-11, 10% ethyl acetate in hexanes) afforded pentadienyl ester **190** as a pale yellow oil (730 mg, 41%); R_f (20% ethyl acetate in hexanes) 0.32; ν (film/cm^{-1}) 1716 s, 1697 s, 1606 s, 1511 s, 1257 bd s, 1168, 910, 848; δ_H (300 MHz, $CDCl_3$) 7.97 (2H, d, ^3J 8.8, ArH), 6.91 (2H, d, ^3J 8.8, ArH), 6.24 (1H, br. d, ^3J 15.6, H-3), 6.03 (1H, dt, ^3J 15.6, 6.0, H-2), 4.91 (2H, s, OCH_2O), 4.84 (2H, br. d, ^3J 6.3, H-1), 3.82 (3H, s, OCH_3), 3.84-3.81 (2H, m, OCH_2CH_2O), 3.55-3.51 (2H, m, OCH_2CH_2O), 3.35 (3H, s, CH_2OMe); δ_C (75 MHz, $CDCl_3$) 165.9 (CO), 163.5 (C_q-OMe), 155.3 (dd, $^1J_{CF}$ 295.0, 293.9, C-5), 131.7 (ArCH), 123.8 (dd, $^3J_{CF}$ 11.9, 4.5, C-3), 122.4 (C_q-CO), 121.3 (d, $^4J_{CF}$ 5.1, C-2), 115.2 (dd, $^2J_{CF}$ 35.6, 17.5, C-4), 113.6 (ArCH), 96.4 (t, $^4J_{HF}$ 2.8, OCH_2O), 71.6 (OCH_2), 68.7 (OCH_2), 64.2 (C-1), 59.0 (CH_2OMe), 55.4 ($ArOCH_3$); δ_F (282 MHz, $CDCl_3$) -97.03 (1F, d, ^2J 45.8), -105.68 (1F, dd, ^2J 45.8, $^3J_{HF}$ 4.0); [HRMS (ES-TOF, M+Na) Found: 381.1134; Calc. for $C_{17}H_{20}O_6F_2Na$: 381.1126]; *m/z* (ES-TOF) 381.0 (100%, M+Na). This material is unstable (neat) and has a lifetime of *ca.* 24 hours even in a refrigerated (-5°C) environment and should ideally be used immediately after preparation or stored as a solution in CH_2Cl_2 under a positive nitrogen atmosphere.

(2*R*,3*S*)-[(5,5-Difluoro-2,3-dihydroxy-4-(2-methoxy-ethoxymethoxy)-pent-4-enyl] 4-methoxybenzenecarboxylate 192



Method A (pH control): A three-necked flask was charged with potassium osmate dihydrate (0.11 g, 0.30 mmol), potassium carbonate (6.25 g, 45.2 mmol), potassium ferricyanide (14.88 g, 45.2 mmol) and $(DHQD)_2PHAL$ (0.47 g, 0.60 mmol). The mixture was homogenised by the addition of *t*BuOH/H_2O (200 ml, 1:1 v/v) with rapid stirring at ambient temperature. Diene **190** (5.39 g, 15.03 mmol) was added dropwise as a solution in *t*BuOH/H_2O (10 ml, 1:1 v/v). The resulting orange solution was stirred at ambient temperature and the progress of the reaction monitored by TLC and pH measurements made using a pH probe. Aqueous sodium hydroxide (1 M) was added *via* syringe in order to maintain the pH in the 11.0-12.0 range at all times. pH-Monitoring was continued until a constant pH measurement was recorded over a period of 30 min, with confirmation by TLC (*ca.* 1-3 h). Sodium sulfite (21 g) was then added and the solution stirred rapidly for 1 h. The *t*BuOH was removed under reduced pressure and the mixture diluted with ethyl acetate (20 ml). The phases were separated and the aqueous phase extracted with ethyl acetate (6 x 200 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a pale yellow oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded diol **192** as a colourless oil (3.16 g, 54%);

98% by HPLC at 225 nm; HPLC t_r (40% water in MeCN; 1ml/min) 3.52 min; R_f (60% ethyl acetate in hexanes) 0.18; (film/cm^{-1}) 3430 bd s, 1754 m, 1694 m, 1608 m, 1514 w; δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, ^3J 8.9, ArH), 6.88 (2H, d, ^3J 8.9, ArH), 5.00 (1H, d, *one half of an AB*, ^3J 6.5, H-a), 4.87 (1H, d, *one half of an AB*, ^3J 6.5, H-a), 4.42 (1H, dd, *one half of an ABX*, ^2J 12.0, ^3J 3.9, H-1), 4.35-4.30 (1H, m, H-3), 4.27 (1H, dd, *one half of an ABX*, ^2J 11.9, ^3J 5.2, H-1'), 4.13-4.07 (1H, m, H-2), 3.95-3.89 (2H, envelope, m + *one half of an ABXY*, OH + H-b), 3.83 (3H, s, OMe), 3.77 (1H, ddd, *one half of an ABXY*, ^2J 10.9, ^3J 4.8, 2.9, H-b'), 3.58-3.54 (2H, m, H-c, H-c'), 3.38 (3H, s, ArOCH_3), 3.28-3.24 (1H, bd s, OH); δ_C (100 MHz, $CDCl_3$) 166.3 (CO), 163.51 (C_q-OMe), 155.1 (dd, $^1J_{CF}$ 292.8, 287.7, C-5), 131.7 (C_{meta}-OMe), 122.1 (C_q-CO), 116.0 (dd, $^2J_{CF}$ 36.6, 12.2, C-4), 113.6 (C_{ortho}-OMe), 98.2 (OCH_2O), 71.3 (CH_2OMe), 70.8 (C-2), 68.7 (CH_2CH_2OMe), 67.6 (C-3), 64.9 (C-1), 59.0 (CH_2O*Me*), 55.4 (ArO*Me*); δ_F (282 MHz, $CDCl_3$) -97.32 (1F, d, ^2J 59.5), -107.93 (1F, dd, ^2J 59.5, $^4J_{HF}$ 2.5); [HRMS (ES-TOF, M+Na) Found: 415.1178; Calc. for $C_{17}H_{22}O_8F_2Na$: 415.1180]; *m/z* (ES-TOF) 415.1 (100%, M+Na). See **Appendix XXVII** for HSQC.

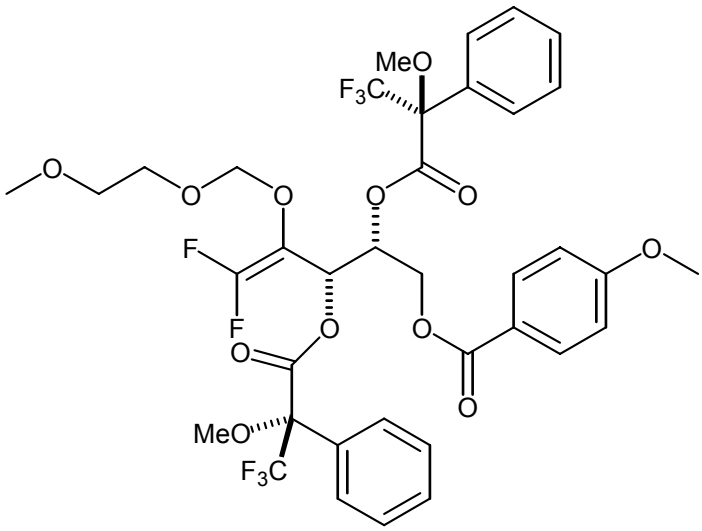
Method B (without pH control): As above except that the pH was not monitored and no base was added. Methanesulfonamide was also added (one equivalent) at the start of the reaction. After nine days at ambient temperature, the reaction was worked up in a similar manner, except that the combined organic extracts were washed in triplicate with ice-cold 2 M KOH in order to remove methanesulfonamide as the water-soluble potassium salt. Baseline material was removed by filtration through a plug of silica gel using 100% ethyl acetate. The crude diol was purified by semi-

preparative HPLC (40% water in MeCN; 1ml/min) to afford a pure sample as a colourless oil.

(Rac)-diol 192

Racemic diol **192** was prepared as for chiral diol **192** using potassium osmate dihydrate (10 mg, 28 μmol), potassium ferricyanide (1.36 g, 4.14 mmol), potassium carbonate (0.57 g, 4.14 mmol), quinuclidine (6 mg, 55 μmol), diene **190** (494 mg, 1.38 mmol) in *t*BuOH-H_2O (18 ml, 1:1 v/v). Sodium hydroxide (1 ml aliquots of a 1.0 M aqueous solution) was added intermittently to keep the pH of the reaction mixture above 11.0 for as long a period as possible. After 22 hours, sodium sulfite (2 g) was added and the reaction stirred for 1 h. *t*BuOH was removed under reduced pressure then ethyl acetate (20 ml) was added. The organic phase was separated and the aqueous phase extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a brown oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded racemic diol **192** as a colourless oil (34 mg, 6%); 95% by HPLC at 254 nm; HPLC t_r (40% water in MeCN, 1 ml/min) 3.52 min; R_f (60% ethyl acetate in hexanes) 0.18; δ_F (282 MHz, $CDCl_3$) -97.15 (1F, d, ^2J 58.5), -107.68 (1F, dd, ^2J 58.5, $^4J_{HF}$ 3.2). This material was further purified by semi-preparative HPLC (40% water in MeCN, 1 ml/min). Chiral HPLC (Chiralcel OD, 10% IPA in hexane, 1 ml/min, 225 nm) gave a single peak (t_r 25.43 min).

(2*R*,3*S*)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-2,3-*bis*-(2*S*)-[(3,3,3-trifluoro-2-methoxy-2-phenyl-propionyloxy)]-pent-4-enyl 4-methoxybenzenecarboxylate 195



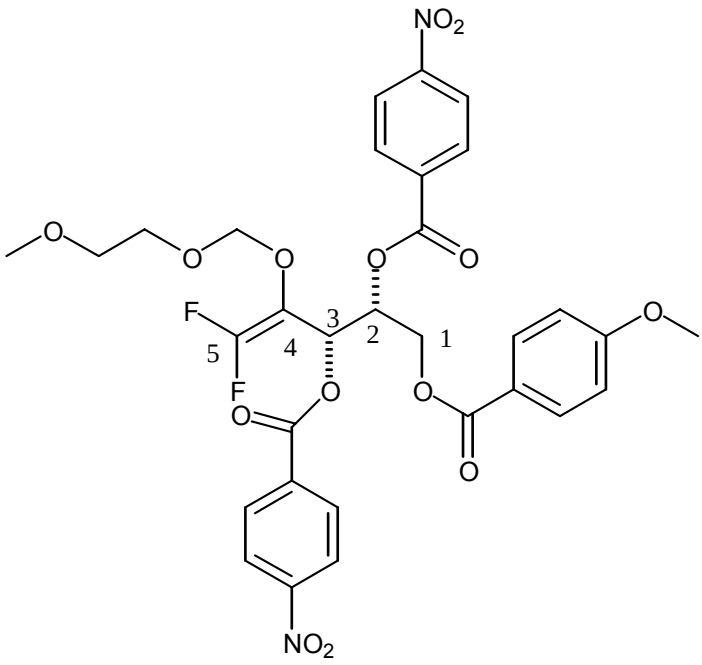
(*R*)-(-)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 μl, 100 mg/100 μl DCM, 55 μmol) was added to a solution of analytically pure chiral diol **192** (6.0 mg, 15.3 μmol), 2,6-lutidine (20 μl) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 ml) at 0°C. The solution was warmed to ambient temperature and stirred for 4 h and monitored by TLC. Diol **192** was consumed within 1 h, with a concomitant build up of monoester. *Bis*-esterification was complete within a further 3 h. The reaction was diluted with diethyl ether (3 ml), then poured into a saturated aqueous solution of sodium bicarbonate (5 ml). The phases were separated and the aqueous phase extracted with diethyl ether (2 × 3 ml) and ethyl acetate (2 × 3 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude *bis*-Mosher ester **195** as a colourless oil containing a brown sediment; δ_F (282 MHz, $CDCl_3$, 4096 scans, 512K data points) -71.23 (3F, s), -71.71 (3F, s), -92.38 (1F, d, ^2J

47.7), -101.96 (1F, d, ^2J 47.7); [HRMS (ES-TOF, M+Na) Found: 847.1977; Calc. for $C_{37}H_{36}O_{12}F_8Na$: 847.1977]; R_f (20% ethyl acetate in hexanes) 0.17; Estimated *de* > 99.5%.

Bis-MTPA ester 195 of (rac)-diol 192

(*R*)-(-)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride (14 μl of a 100 mg/100 μl DCM, 55 μmol) was added to a solution of analytically pure racemic diol **192** (7.9 mg, 20.2 μmol), triethylamine (23 μl) and 4-(dimethylamino)pyridine (one crystal) in DCM (1 ml) at 0°C. The solution was warmed to ambient temperature and stirred for 4 h. TLC indicated the presence of products resulting from *mono*- and *bis*-esterifcation. More triethylamine (10 μl) and acid chloride (10 μl) was added and the reaction stirred for a further 2 h. TLC indicated the formation of a single product. The reaction was diluted with diethyl ether (3 ml), then poured into a saturated aqueous solution of sodium bicarbonate (5 ml). The phases were separated and the aqueous phase extracted with ethyl actetate (2 × 3 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford crude *bis*-Mosher ester **195** as a 1:1 mixture of two diastereoisomers; δ_F (282 MHz, $CDCl_3$, 32 scans) -71.22 (3F, s, 2R,3S diastereoisomer), -71.71 (3F, s, 2R,3S diastereoisomer), -71.79 (3F, s, 2S,3R diastereoisomer), -71.86 (3F, s, 2S,3R diastereoisomer), -92.32 (1F, d, ^2J 47.0, 2S,3R diastereoisomer), -92.35 (1F, d, ^2J 48.3, 2R,3S diastereoisomer), -101.81 (1F, d, ^2J 47.0, 2S,3R diastereoisomer), -101.95 (1F, d, ^2J 48.3); R_f (40% ethyl acetate in hexanes) 0.75; *de* 0%.

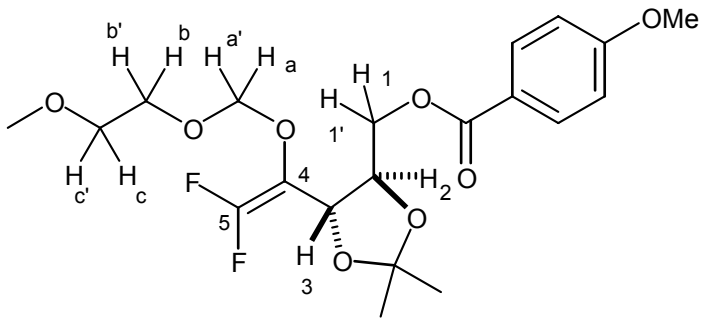
(2*R*,3*S*)-5,5-Difluoro-4-(2-methoxy-ethoxymethoxy)-2,3-*bis*-(*para*-nitrobenzoyl-oxy)-pent-4-enyl 4-methoxybenzenecarboxylate 198



p-Nitrobenzoyl chloride (13 mg, 73 μmol) was added to a solution of diol **192** (13 mg, 33 μmol), 2,6-lutidine (40 μl, 0.34 mmol) and DMAP (1 crystal) in DCM (5 ml) at ambient temperature. The resulting solution was stirred with monitoring by TLC. After 2 h, TLC indicated the presence of both diester and triester, with no further change after a further 1 h. More *p*-nitrobenzoyl chloride (6 crystals) was added and the resulting solution allowed to stir for a further 4 h (7 h total), affording a single spot by TLC. Water (5 ml) was added and the phases separated. The aqueous phase was extracted with DCM (3 × 5 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford an amorphous yellow solid. Purification by column chromatgraphy over silica gel (40% ethyl acetate in hexanes) afford triester **198** as a colourless oil (22 mg, 96%); R_f (40% ethyl acetate in

hexanes) 0.36; δ_H (300 MHz, $CDCl_3$) 8.25-8.18 (4H, envelope, ArH), 8.13-8.08 (4H, envelope, ArH), 8.00-7.95 (2H, m, ArH), 6.96-6.91 (2H, m, ArH), 6.26 (1H, dt, ^3J 9.2, $^4J_{HF}$ 2.2, H-3), 6.06 (1H, ddd, ^3J 9.2, 4.1, 2.8, H-2), 5.10-5.08 (1H, m, *one half of an AB*, OC*H*H'O), 5.04-5.02 (1H, m, *one half of an AB*, OCH*H*'O), 4.88 (1H, dd, *one half of an AMX*, ^2J 12.7, ^3J 2.8, H-1), 4.53 (1H, dd, *one half of an AMX*, ^2J 12.7, ^3J 4.1, H-1'), 3.92-3.78 (2H, m, CH_2O), 3.87 (3H, s, $ArOCH_3$), 3.52-3.48 (2H, m, CH_2O), 3.32 (3H, s, CH_2OCH_3); δ_C (75 MHz, $CDCl_3$) 165.6 (CO of *p*MBz), 163.8 (CO of *p*NBz), 163.8 (CO of *p*NBz), 163.3 (Cq-OMe), 156.3 (dd, $^1J_{CF}$ 295.7, 291.9, CF_2), 150.8 (Cq-NO_2), 150.8 (Cq-NO_2), 134.3 (Cq-CO of *p*NBz), 134.2 (Cq-CO of *p*NBz), 131.7 (CH of *p*NBz), 131.7 (CH of *p*NBz), 130.8 (CH of *p*MBz), 123.7 (CH of *p*NBz), 123.7 (CH of *p*NBz), 121.4 (Cq-CO of *p*MBz), 113.9 (CH of *p*MBz), 110.9 (dd, $^2J_{CF}$ 36.5, 16.9, *C*=CF_2), 98.1-98.1 (m, OCH_2O), 71.5 (dd, $^3J_{CF}$ 3.2, 2.0, C-2), 71.4 (CH_2O), 69.7 (dd, $^3J_{CF}$ 4.9, 2.3, C-3), [68.9, 68.9] (CH_2O), 62.0 (C-1), 59.0 (CH_2OCH_3), 55.5 ($ArOCH_3$); δ_F (282 MHz, $CDCl_3$) -93.90 (1F, d, ^2J 46.8), -102.04 (1F, d, ^2J 46.8); [HRMS (ES-TOF, M+Na) Found: 713.1414; Calc. for $C_{31}H_{28}N_2O_{14}F_2Na$: 713.1406]; *m/z* (ES-TOF) 713.3885 (100%, M+Na). Due to the non-crystalline nature of this material, further characterisation was not pursued.

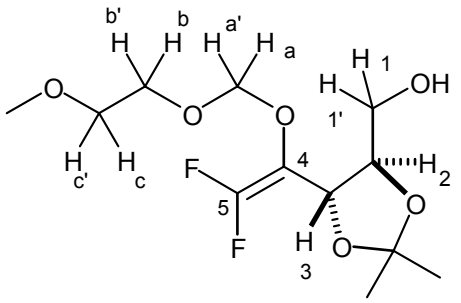
(2*R*,3*S*)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 199



Anhydrous copper(II) sulfate (2.57 g, 16.1 mmol) was added to a solution of diol **192** (3.16 g, 8.05 mmol) in acetone (100 ml) followed by a catalytic amount of *p*TSA (few crystals). The mixture was stirred at ambient temperature for 42 h, then quenched with brine (50ml). The residual copper(II) sulfate was removed by filtration and washed with acetone (30 ml). The acetone was removed under reduced pressure, then the mixture diluted with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 $\times$ 30 ml). The combined organic extracts were dried and concentrated under reduced presssure to afford the crude acetonide **199** as a pale green oil. Purification by chromatography over alumina (20% ethyl acetate in hexanes) afforded acetonide **199** as a colourless oil (2.38 g, 68%); 99% by HPLC at 225/254/275 nm; HPLC t_r (20% water in MeCN; 1 ml/min) 5.19 min; R_f (20% ethyl acetate in hexanes) 0.44; ν (film/cm^{-1}) 2988 m, 2936 m, 1756 s, 1716 s, 1608 s, 1582 m, 1513 m, 1456 m, 1383 m, 1373 m, 1258 bd s, 1169 s, 1030 s, 951 s, 849 m, 770 m; δ_H (300 MHz, $CDCl_3$) 7.98 (2H, d, ^3J 8.8, ArH), 6.91 (2H, d, ^3J 8.8, ArH), 5.08 (1H, d, *one half of an AB*, ^2J 5.9, H-a), 5.00 (1H, d, *one half of an AB*, ^2J 5.9, H-a'), 4.62-4.34 (4H, envelope, H-3, H-2, H-1), 3.95-3.88 (1H,

m, *one half of an ABXY*, H-b), 3.86 (3H, s, CH_2OMe), 3.80-3.73 (1H, m, *one half of an ABXY*, H-b'), 3.58-3.55 (2H, m, H-c, H-c'), 3.38 (3H, s, ArO*Me*), 1.45 (3H, s, Me), 1.42 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 165.6 (CO), 163.5 (C_q-OMe), 156.3 (dd, $^1J_{CF}$ 293.4, 289.3, C-5), 131.6 (Ar*C*H), 121.9 (C_q-CO), 113.6 (Ar*C*H), 110.6 (dd, $^2J_{CF}$ 33.8, 14.9, C-4), 110.0 (C_qMe_2), 98.4 (t, $^4J_{CF}$ 3.4, C-a), 74.5 (t, $^4J_{CF}$ 2.6, C-2), 74.0 (dd, $^3J_{CF}$ 4.3, 2.0, C-3), 71.4 (C-c), 68.5 (d, $^6J_{CF}$ 1.7, C-b), 62.9 (C-1), 58.9 (CH_2OMe), 55.3 (ArO*Me*), 26.8 (Me), 26.5 (Me); δ_F (282 MHz, $CDCl_3$) -93.61 (1F, d, ^2J 54.8), -107.09 (1F, dd, ^2J 55.5, $^4J_{HF}$ 3.0); [HRMS (ES-TOF, M+Na) Found: 455.1481; Calc. for $C_{20}H_{26}O_8F_2Na$: 455.1493]; *m/z* (ES-TOF) 455.1 (100%, M+Na).

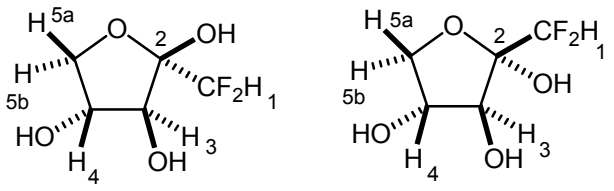
(2*R*,3*S*)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2,2-dimethyl-[1,3]dioxalan-4-yl)-methanol 200



A solution of ester **199** (2.38 g, 5.5 mmol) in THF/H_2O (100 ml, 3:1 v/v) was cooled to 0°C. Hydrogen peroxide (2.6 ml of a 30% w/w aqueous solution (8.8 M), 23 mmol) was added followed by lithium hydroxide monohydrate (0.51 g, 12 mmol). The resulting cloudy solution was stirred for 140 h at ambient temperature and the progress monitored by TLC. Upon completion, the reaction was quenched with sodium sulfite (2.5 g) and the resulting solution stirred rapidly for 1 h. The THF was

removed under reduced pressure, then the mixture diluted with ethyl acetate (20 ml). The organic layer was separated and the aqueous phase extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were dried and concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography over alumina (Brockmann 1, pH 9-11, gradient: 40-100% ethyl acetate in hexanes) afforded alcohol **200** as a clear oil (1.00 g, 61%); 96% by HPLC at 245 nm; HPLC t_r (Luna 5μ silica (2) 250 mm × 4.6 mm; 100% DCM; 1ml/min) 13.59 min; R_f (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; ν (film/cm^{-1}) 3468 bd s (OH), 1755 s ($C=CF_2$), 1456 w, 1373 m, 1291 m, 1247 s; $[\alpha]_D$ +80.79° (c=11.63, acetone, 20°C, est. error = ±0.01°); [Found: C, 48.26; H, 6.93; Calc. for $C_{12}H_{20}O_6F_2$: C, 48.32; H, 6.76%]; δ_H (300 MHz, $CDCl_3$) 5.03 (1H, d, *one half of an AB*, ^3J 5.9, H-a), 4.96 (1H, d, *one half of an AB*, ^3J 5.9, H-a'), 4.56 (1H, ddd, ^3J 8.9, $^4J_{HF}$ 3.7, 2.4, H-3), 4.17 (1H, dt, ^3J 8.9, 3.5, H-2), 3.92-3.85 (1H, m, *one half of an ABXY*, H-b), 3.80 (1H, dd, ^3J 12.9, 3.5, H-1), 3.77-3.53 (2H, envelope, m + *one half of an ABXY*, H-1', H-b'), 3.55 (2H, dd, ^3J 5.7, 3.9, H-c, H-c'), 3.36 (3H, *s*, O*Me*), 2.32-2.23 (1H, bd s, O*H*), 2.14 (6H, *s*, C*Me*$_2$); δ_C (75 MHz, $CDCl_3$) 156.5 (dd, $^1J_{CF}$ 293.3, 289.9, C-5), 110.9 (dd, $^2J_{CF}$ 33.6, 14.1, C-4), 109.7 (*C*Me_2), 98.5 (dd, $^4J_{CF}$ 4.0, 2.8, C-a), 77.0 (C-2), 72.8 (dd, $^3J_{CF}$ 4.2, 2.3, C-3), 71.6 (C-c), 68.6 (d, $^6J_{CF}$ 1.7, C-b), 60.6 (C-1), 59.1 (OCH_3), 27.0 (CH_3), 26.7 (CH_3); δ_F (282 MHz, $CDCl_3$) -93.65 (1F, d, ^2J 56.6), -107.43 (1F, dd, ^2J 56.6, $^3J_{HF}$ 3.8); [HRMS (ES-TOF, M+Na) Found: 321.1134; Calc. for $C_{12}H_{20}O_6F_2Na$: 321.1126]; *m/z* (ES-TOF) 321.1 (100%, M+Na).

1-Deoxy-1,1-difluoro-α-D-xylulofuranose and 1-deoxy-1,1-difluoro-β-D-xylulofuranose 173

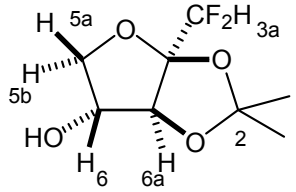


α β

A flask containing alcohol **200** (323 mg, 1.09 mmol) was evacuated and the vacuum released to a nitrogen atmosphere. Methanol (10 ml) was added and the resulting colourless solution cooled to 0°C. Chlorotrimethylsilane (160 μl, 1.26 mmol) was added in one portion and the resulting colourless solution stirred at ambient temperature for 23 h. After consumption of starting material, the reaction was concentrated to afford a pale yellow oil. Purification by flash column chromatography over silica gel (80% ethyl acetate in hexanes) afforded pentuloses **173** as a clear oil (163 mg, 88%, ~3:1 α:β); R_f (80% ethyl acetate in hexanes) 0.32; $[\alpha]_D$ = -27.66° (c = 14.2, acetone, 20°C, est. error = ±0.6°, α:β = ~3:1), lit (-18.9°, c=0.95, acetone, 25°C);[211] [Found: C, 31.65; H, 5.39; Calc. for $C_5H_8O_4F_2.H_2O$: C, 31.92; H, 5.36%]; ν (film/cm^{-1}) 3402 bd s (OH), 2514 bd s (OD), 1470 m, 1401 m, 1347 m, 1204 m, 1078 s; δ_H (300 MHz, CD_3OD) 5.85 (0.23H, dd, $^2J_{HF}$ 55.9, 54.2, H-1β), 5.72 (0.77H, t, $^2J_{HF}$ 55.5, H-1α), 4.30-4.23 (1H, envelope, H-4α, H-5aβ), 4.19-4.12 (1H, envelope, H-5aα, H-4β), 4.08-4.06 (0.23H, m, H-3β), 4.06 (0.77H, bd d, ^3J 4.8, H-3α), 3.94 (0.23H, ddd, ^2J 9.2, ^3J 3.7, ^4J 1.5, H-5bβ), 3.62 (0.77H, dd, ^2J 9.0, ^3J 5.0, H-5bα); δ_C (100 MHz, CD_3OD) 115.2 (t, $^1J_{CF}$ 247.0, C-1α), 114.6 (dd, $^1J_{CF}$ 246.0, 243.0, C-1β), 103.9 (dd, $^2J_{CF}$ 26.2, 20.3, C-2β), 101.3 (t, $^2J_{CF}$ 24.6, C-2α), 82.6 (d, $^3J_{CF}$ 1.8, C-3β), 78.0 (d,

$^4J_{CF}$ 1.8, C-4β), 77.6 (C-3α), 77.0 (C-4α), 75.1 (C-5β), 71.9 (C-5α); δ_F (282 MHz, CD_3OD) -132.09 (0.23F, dd, *one half of an ABX*, ^2J 291.5, $^3J_{HF}$ 54.05, β isomer), -133.41 (0.77F, dd, *one half of a highly distorted ABX*, ^2J 286.1, $^3J_{HF}$ 54.7, α isomer), -134.94 (0.77F, dd, *one half of a highly distorted ABX*, ^2J 286.1, $^3J_{HF}$ 55.95, α isomer), -140.42 (0.23F, dd, *one half of an ABX*, ^2J 291.5, $^3J_{HF}$ 55.95, β isomer)(3.3:1 α:β, CD_3OD); δ_F (282 MHz, D_2O) -132.07 (0.25F, dd, ^2J 293.3, $^3J_{HF}$ 53.4, β isomer), -133.76 (0.75F, dd, ^2J 288.6, $^3J_{HF}$ 54.8, α isomer), -135.15 (0.75F, dd, ^2J 288.6, $^3J_{HF}$ 54.8, α isomer), -139.77 (0.25F, dd, ^2J 293.4, $^3J_{HF}$ 55.4, β isomer)(3:1 α:β, D_2O); *m/z* (CI) 171 (100%, M+1), 153 (8%, M+1-H_2O). NMR data is in agreement with those reported by Bouvet.[211]

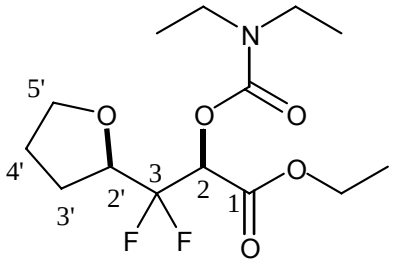
(3a*R*,6*R*,6a*S*)-3*a*-Difluoromethyl-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]-dioxol-6-ol 201



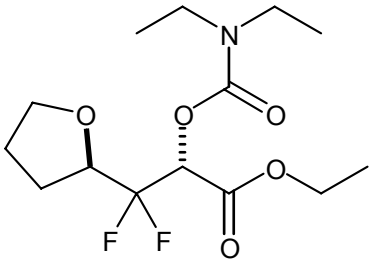
Hydrochloric acid (5 drops of a 12 M soln) was added to a solution of alcohol **200** (30.5 mg, 102 μmol) in THF (5 ml). The resulting solution was stirred at ambient temperature for 23 h. Sodium bicarbonate (1 microspatula) was added followed by direct concentration of the reaction mixture. The concentrate was taken up in acetone (5 ml) and anhydrous copper(II) sulfate (2 microspatulas) and *p*TSA (1 microspatula) were added consecutively. The resulting heterogenous mixture was stirred for 66 h and monitored by TLC. Brine (5 ml) was added and the acetone removed under

reduced pressure. Ethyl acetate (10 ml) was added and the organic layer separated. The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic extracts dried and concentrated under reduced pressure. Purification by column chromatography over silica gel (40% ethyl acetate in hexanes) afforded acetonide **201** as a white solid (14 mg, 66%); mp 77-80°C; [Found: C, 45.87; H, 5.73; Calc. for $C_8H_{12}F_2O_4$: C, 45.72; H, 5.75%]; R_f (40% ethyl acetate in hexanes) 0.33; UV (254 nm) inactive; δ_H (300 MHz, $CDCl_3$) 5.87 (1H, t, $^2J_{HF}$ 55.5, H-3a), 4.62 (1H, s, H-6a), 4.32-4.27 (1H, m, H-6), 4.25 (1H, dd, ^2J 9.9, ^3J 2.9, H-5b), 4.03 (1H, d, ^2J 9.9, H-5a), 1.97 (1H, dd, *J* 8.5, 2.9 Hz, OH), 1.52 (3H, s, H-2), 1.38 (3H, s, H-2'); δ_F (282 MHz, $CDCl_3$) -128.99 (1F, dd, *one half of a highly distorted ABX*, ^2J 287.5, $^2J_{HF}$ 55.9), -130.23 (1F, ddd, *one half of a highly distorted ABXY*, ^2J 287.4, $^2J_{HF}$ 54.7, $^4J_{HF}$ 2.5); *m/z* (CI) 211 (100%, M+1), 194 (6%), 178 (29%), 151 (8%), 133 (6%), 116 (6%), 107 (10%), 59 (7%), 47 (9%), 45 (9%). There was an insufficient amount of material to obtain a ^{13}C NMR.

Ethyl (*syn*) 2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2'-yl)-propionate 202 and ethyl (*anti*) 2-(*N*,*N*-diethylcarbamoyloxy)-3,3-difluoro-3-(tetrahydrofuran-2'-yl)-propionate 203



(*syn*) **202**

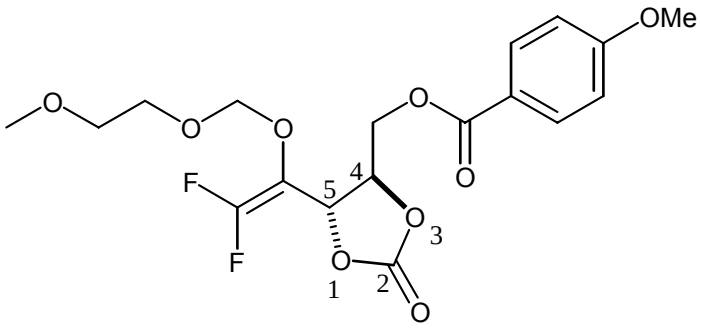


(*anti*) **203**

A flask containing AIBN (1.5 mg, 9.1 μmol) and BPO (1.5 mg, 6.2 μmol) was pump-purged with nitrogen. Alkenoate **94** (52 mg, 0.21 mmol) was added as a solution in THF (3 ml). The resulting solution was heated to reflux and stirred for 16 h. The resulting mixture was cooled to ambient temperature and quenched with a saturated aqueous solution of sodium sulfite (3 ml). DCM (5 ml) was added and the organic phase separated. The aqueous phase was extracted with DCM (3 × 5 ml) and the combined organic extracts dried and concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography over silica gel (30% ethyl acetate in light petroleum ⇒ 40% ethyl acetate in light petroleum) afforded an inseparable mixture of *syn* and *anti* diastereoisomers **202** and **203** as a colourless oil (56 mg, 82%); 90% by GC; R_f (30% ethyl acetate in light petroleum) 0.43; δ_H (300 MHz, $CDCl_3$) 5.44 (0.58H, dd, $^3J_{HF}$ 14.7, 7.4, H-2), 5.31 (0.42H, dd, 21.2, 4.6, H-2), 4.42-4.16 (3H, m, envelope, H-2', O*C*H_2CH$_3$), 3.89-3.78 (2H, m, envelope, H-5'), 3.38-3.21 (4H, m, envelope, CH_2NCH_2), 2.21-1.81 (4H, m, envelope, H-3', H-4'), 1.31-1.09 (9H, m, envelope, C*H*$_3$CH$_2$NCH$_2$C*H*$_3$, OCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$)

165.9-165.6 (m, CO ester, both diastereoisomers), 153.8 (Cq, CO carbamate, major), 153.7 (Cq, CO carbamate, minor), 123.2-116.0 (m, Cq, CF_2 major and minor), 76.3 (dd, $^2J_{CF}$ 32.2, 31.9, CH, C-2 major), 76.1 (dd, $^2J_{CF}$ 33.3, 23.2, CH, C-2 minor), 71.6 (dd, $^2J_{CF}$ 29.4, 26.0, CH, C-2' major), 71.3 (dd, $^2J_{CF}$ 36.7, 24.3, CH, C-2' minor), 69.6 (CH_2, C-5' major), 69.6 (CH_2, C-5' minor), 61.9 (CH_2, CO_2CH_2Me major), 61.8 (CH_2, CO_2CH_2Me minor), 42.4 (CH_2N), 42.3 (CH_2N), 41.7 (CH_2, major and minor), 25.8 (CH_2, C-4' minor), 25.7 (CH_2, C-4' major), 24.9 (dd, 20.1, 4.2, C-3' major and minor), 14.0 (CH_3, $CO_2CH_2CH_3$ minor), 13.9 (CH_3, $CO_2CH_2CH_3$ major), 13.9 (NCH_2CH_3 major and minor), 13.3 (NCH_2CH_3 major and minor); δ_F (282 MHz, $CDCl_3$) major diastereoisomer (58%) -113.61 (1F, ddd, ^2J 261.0, $^3J_{HF}$ 14.6, 3.8), -121.15 (1F, ddd, ^2J 261.0, $^3J_{HF}$ 22.3, 7.7) minor diastereoisomer (42%) -116.91 (dd, ^2J 261.3, $^3J_{HF}$ 21.6), -123.11 (1F, ddd, ^2J 261.0, $^3J_{HF}$ 22.2, 3.8); [HRMS (ES-TOF, M+Na) Found: 346.1436; Calc. for $C_{14}H_{23}N\,O_5F_2Na$: 346.1442]; *m/z* (ES-TOF) 346.2 (100%, M+Na).

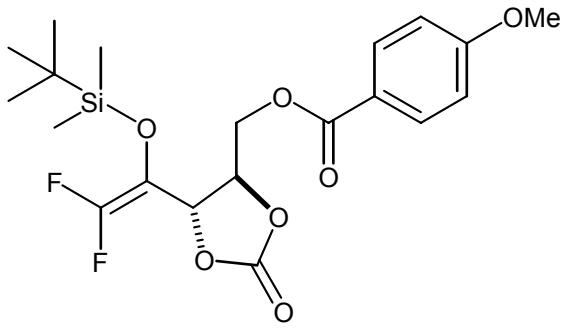
(2*R*,3*S*)-(5-(2,2-Difluoro-1-(2-methoxy-ethoxymethoxy)-vinyl)-2-oxo-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 214



Triphosgene (25 mg, 84 μmol) was added to a solution of diol **192** (33 mg, 84 μmol) in DCM (5 ml) containing 2,6-lutidine (20 μl, 168 μmol) at ambient temperature. The solution was heated at reflux for 20 h, with monitoring by TLC. The reaction mixture was allowed to cool to ambient temperature, then quenched with methanol (5 ml) and water (5 ml) in order to destroy excess phosgene. Extractive work-up with DCM (3 × 5 ml), followed by drying and concentration under reduced pressure afforded crude **214** as a brown oil. Purification by column chromatography over silica gel (60% ethyl acetate in hexanes) afforded carbonate **214** as a colourless oil (23 mg, 66%); R_f (60% ethyl acetate in hexanes) 0.67; δ_H (300 MHz, $CDCl_3$) 7.90 (2H, d, ^3J 8.8, ArH), 6.88 (2H, d, ^3J 8.8, ArH), 5.24-5.20 (1H, m, H-5), 5.05-4.94 (3H, envelope, OCH_2O and H-4), 4.53 (1H, dd, *one half of an ABX*, ^2J 12.6, ^3J 3.1, C*H*H'O*p*MBz), 4.44 (1H, dd, *one half of an ABX*, ^2J 12.6, ^3J 3.3, CH*H*'O*p*MBz), 3.87-3.71 (2H, m, CH_2O), 3.80 (3H, s, $ArOCH_3$), 3.57-3.49 (2H, m, CH_2O), 3.32 (3H, s, CH_2OCH_3); δ_C (75 MHz, $CDCl_3$) 165.3 (CO ester), 163.8 (Cq-OMe), 155.4 (dd, $^1J_{CF}$ 292.2, 296.8, CF_2), 153.4 (C-2), 131.7 (ArCH), 120.8 (Cq-CO), 113.8 (ArCH), 111.4 (dd, $^2J_{CF}$ 34.6, 16.1, *C*=CF_2), 98.6 (dd, $^4J_{CF}$ 4.6, 1.9, OCH_2O), 75.4 (t, $^4J_{CF}$ 2.3, C-4), 73.5 (dd, $^3J_{CF}$ 5.7,

2.0, C-5), 71.3 (CH_2O), [69.0, 69.0] (CH_2O), 62.5 (CH_2O*p*MBz), 58.8 (ArOCH_3), 55.3 (CH_2OCH_3); δ_F (282 MHz, $CDCl_3$) -91.28 (1F, dd, ^2J 50.9, $^4J_{HF}$ 2.5), -104.89 (1F, dd, ^2J 50.9, $^4J_{HF}$ 2.5); *m/z* (ES-TOF) 441.4 (47%, M+Na), 397.4 (100%, M+Na-CO_2). This material decomposed before full characterisation could be achieved.

Attempted preparation of (2*R*,3*S*)-(5-(2,2-difluoro-1-(*tert*-butyldimethylsilyloxy)-vinyl)-2-oxo-[1,3]dioxalan-4-yl)-methyl 4-methoxybenzenecarboxylate 215



tert-Butyldimethylsilyl triflate (12.6 μl, 55 μmol) was added dropwsie to a solution of carbonate **214** (23 mg, 55 μmol) and 2,6-lutidine (6.4 μl, 55 μmol) in THF (3 ml) at 0°C under a nitrogen atmosphere. After 18 h, TLC indicated the formation of a less polar material. Concentration under reduced pressure and analysis by ^{19}F NMR indicated an 86:14 mixture of silyl difluoroenol ether **215** and carbonate **214**. Attempted purification by flash column chromatography (40% ethyl acetate in light petroleum) failed to afford any of the desired product silyl difluoroenol ether **215**.

Crude data for **215**; R_f (60% ethyl acetate in light petroleum) 0.65; δ_F (282 MHz, $CDCl_3$) -99.71 (1F, dd, ^2J 71.2, $^4J_{HF}$ 2.5), -114.24 (1F, dd, ^2J 71.2, $^4J_{HF}$ 2.5). Chemical

shifts are in agreement for silyl difluoroenol ethers, according to the work of Haworth.[189]

Chapter Five

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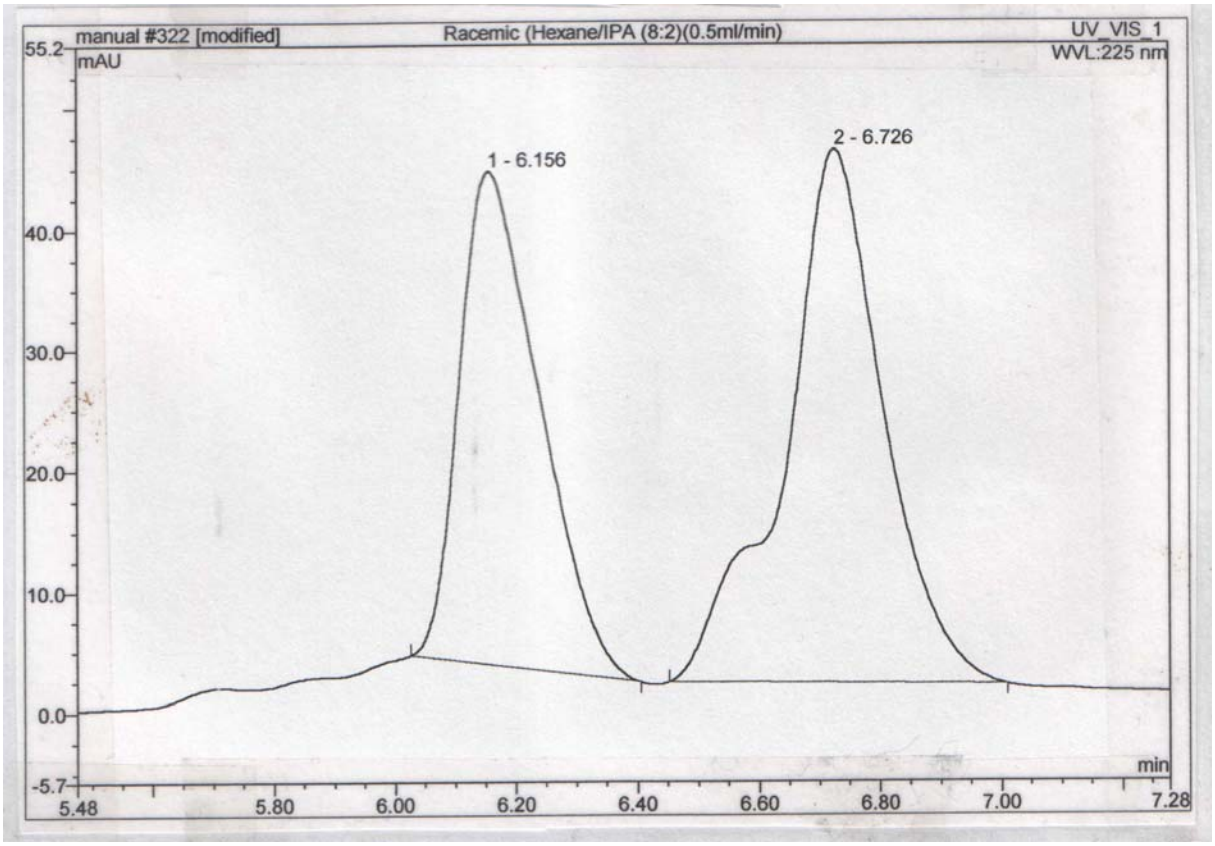
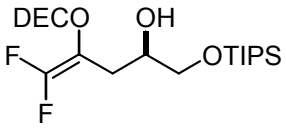
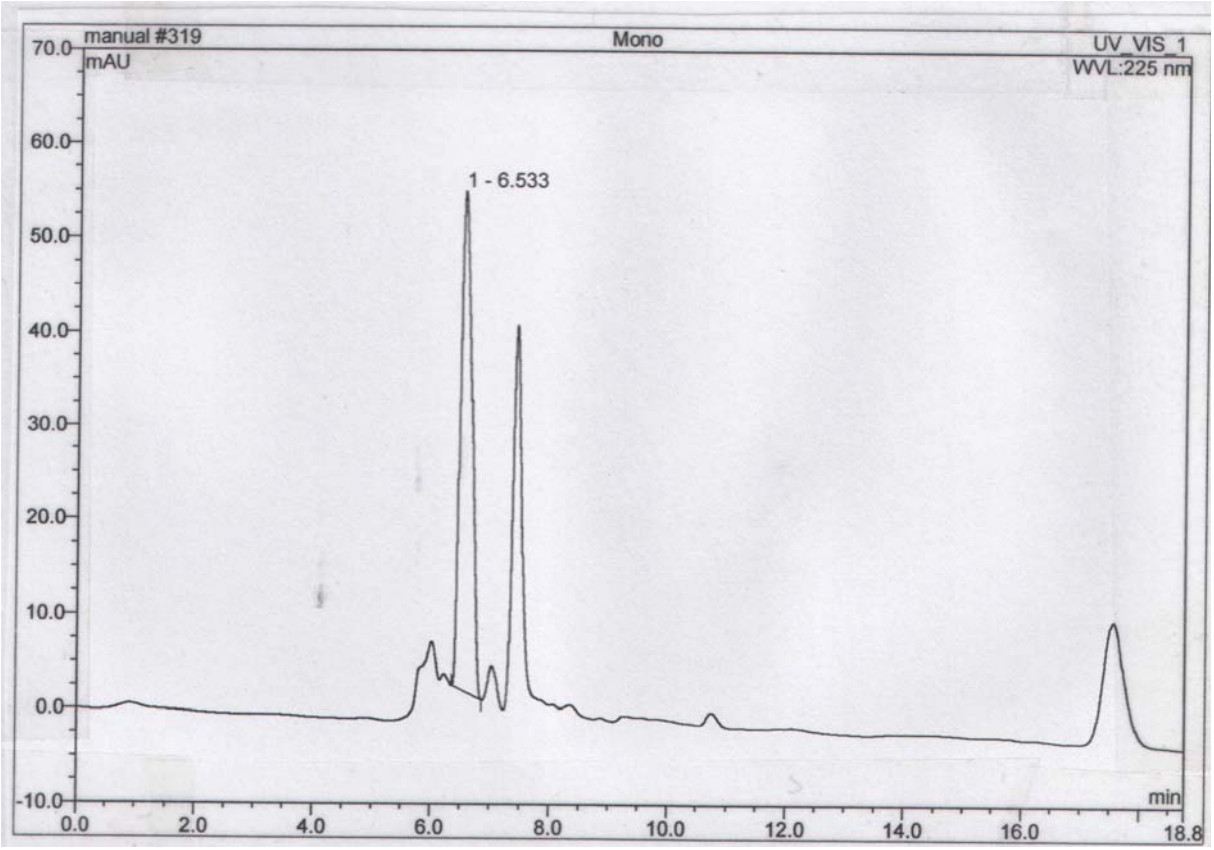
Chapter Six

Appendices

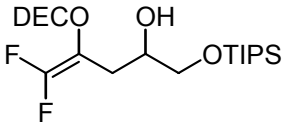


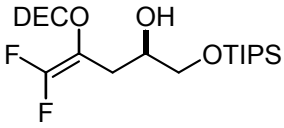
Appendix I: Chiral HPLC trace of racemic alcohol **159** with shoulder impurity

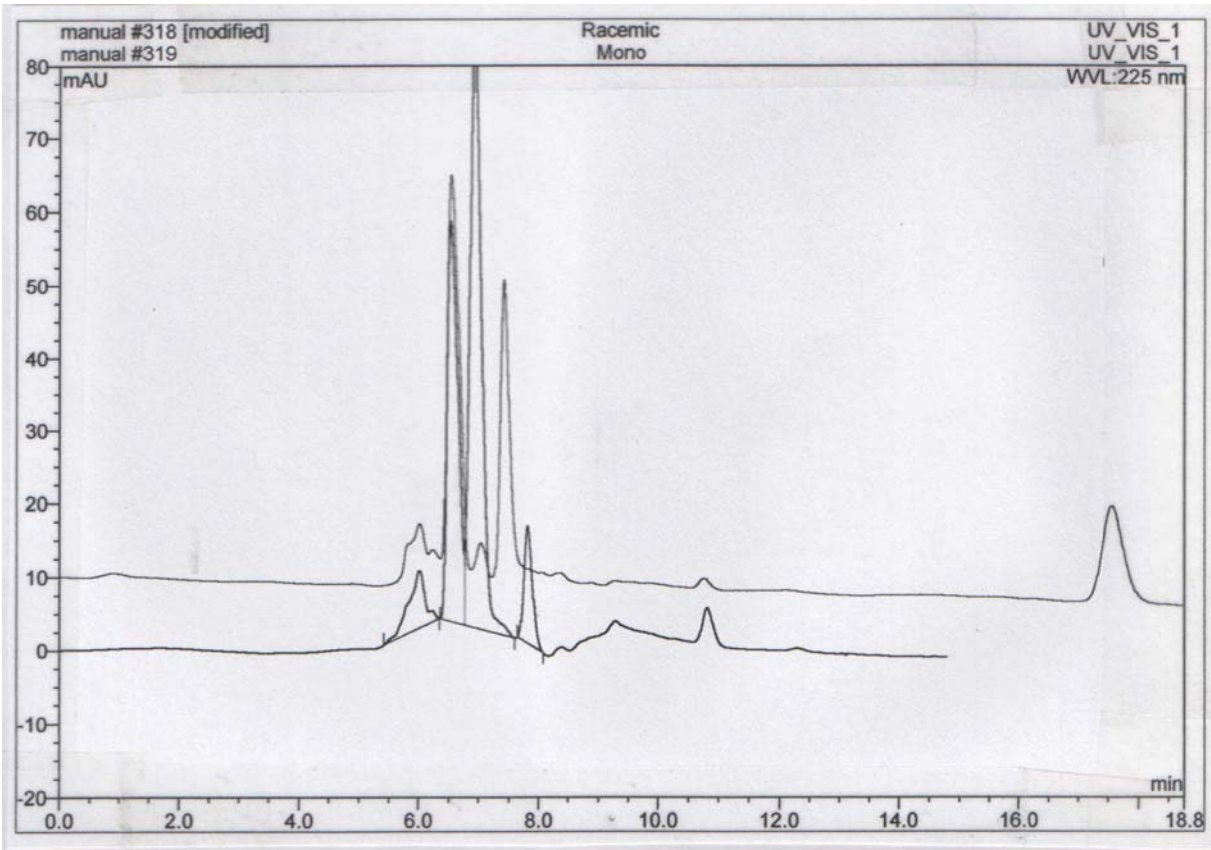




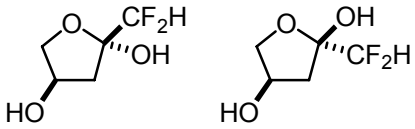
Appendix II: Chiral HPLC trace of chiral alcohol **157** with ketone impurity





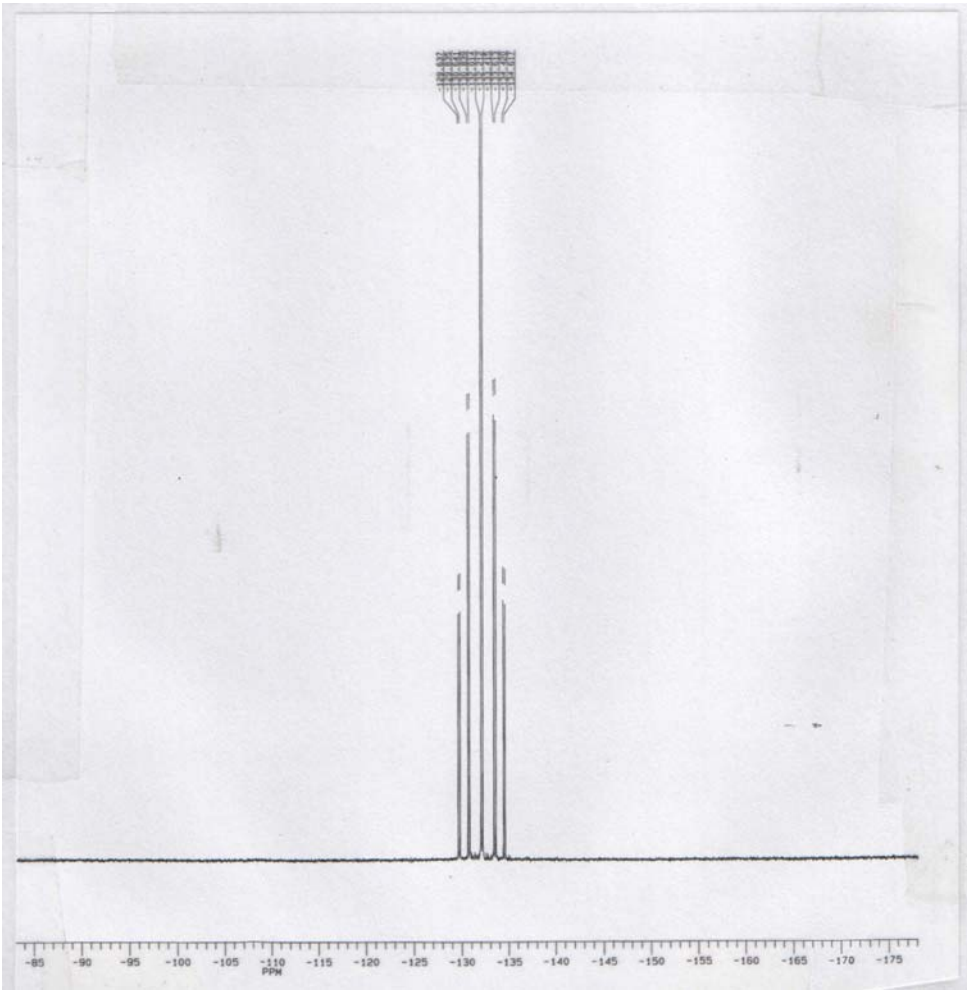


Appendix III: Overlay of Chiral HPLC traces of chiral alcohol **157** and racemic alcohol **159**

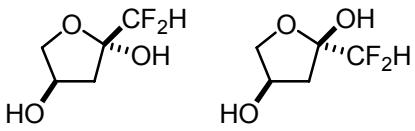


α β

major minor

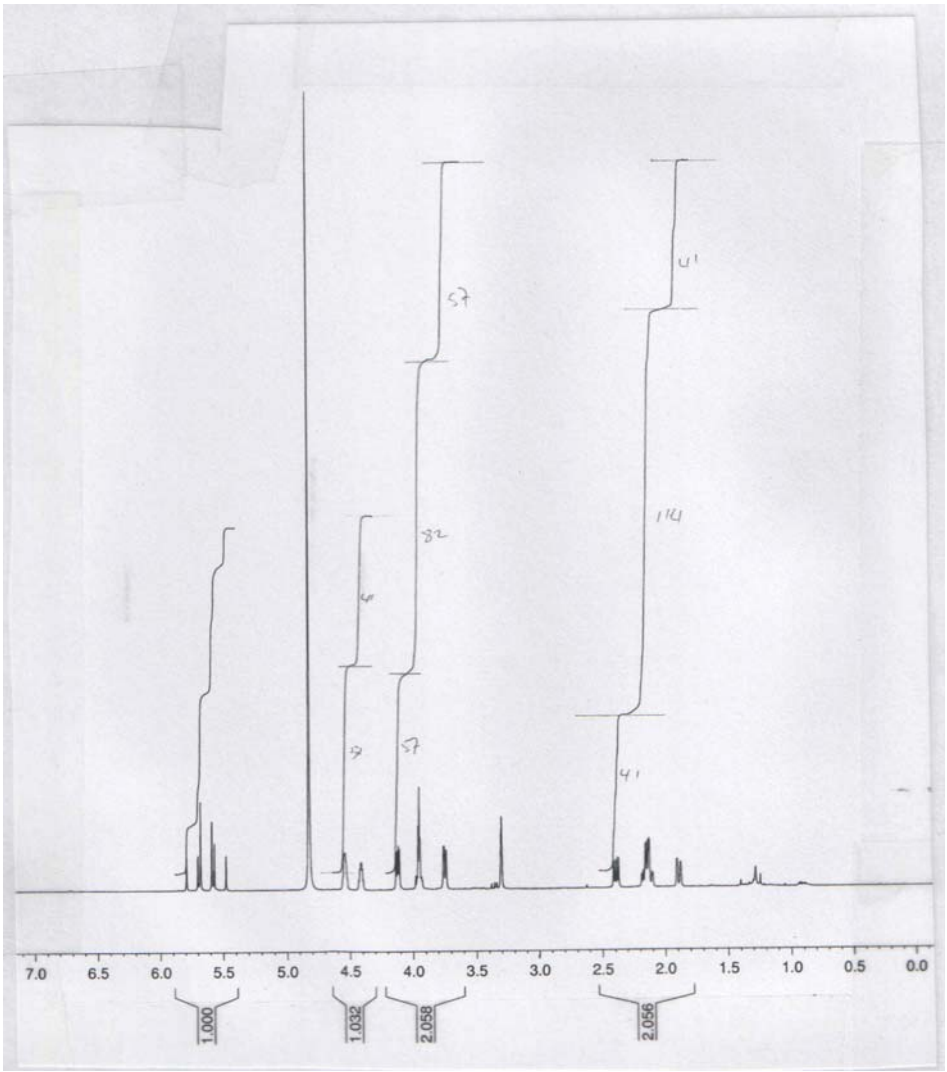


Appendix IV: ^{19}F of sugar **155** (282 MHz, CD_3OD)

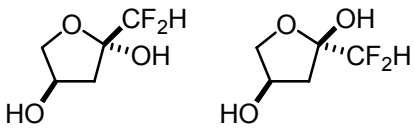


α major

β minor

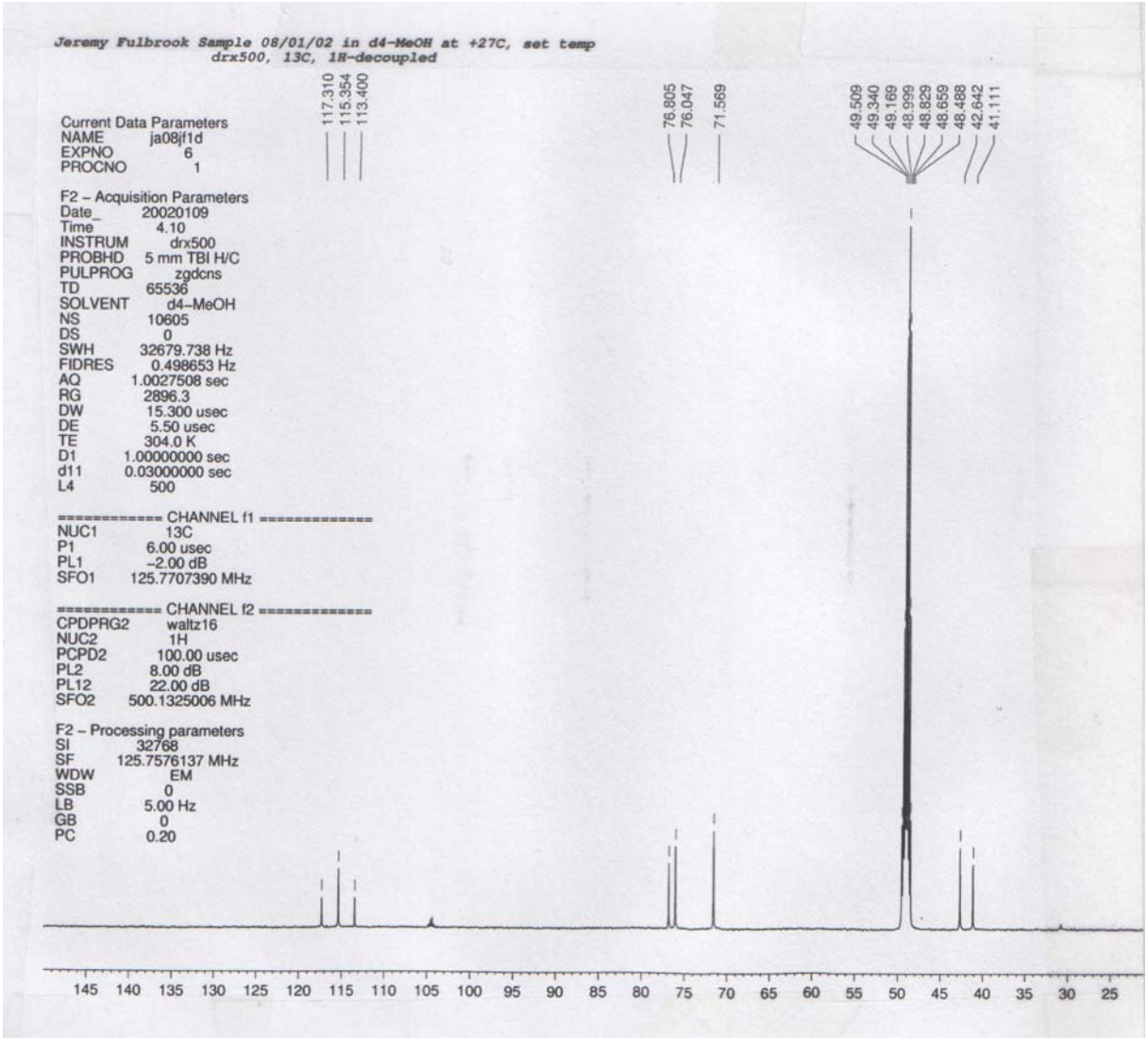


Appendix V: ^{1}H of sugar **155** (500 MHz, CD_3OD)

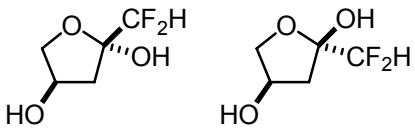


α major

β minor

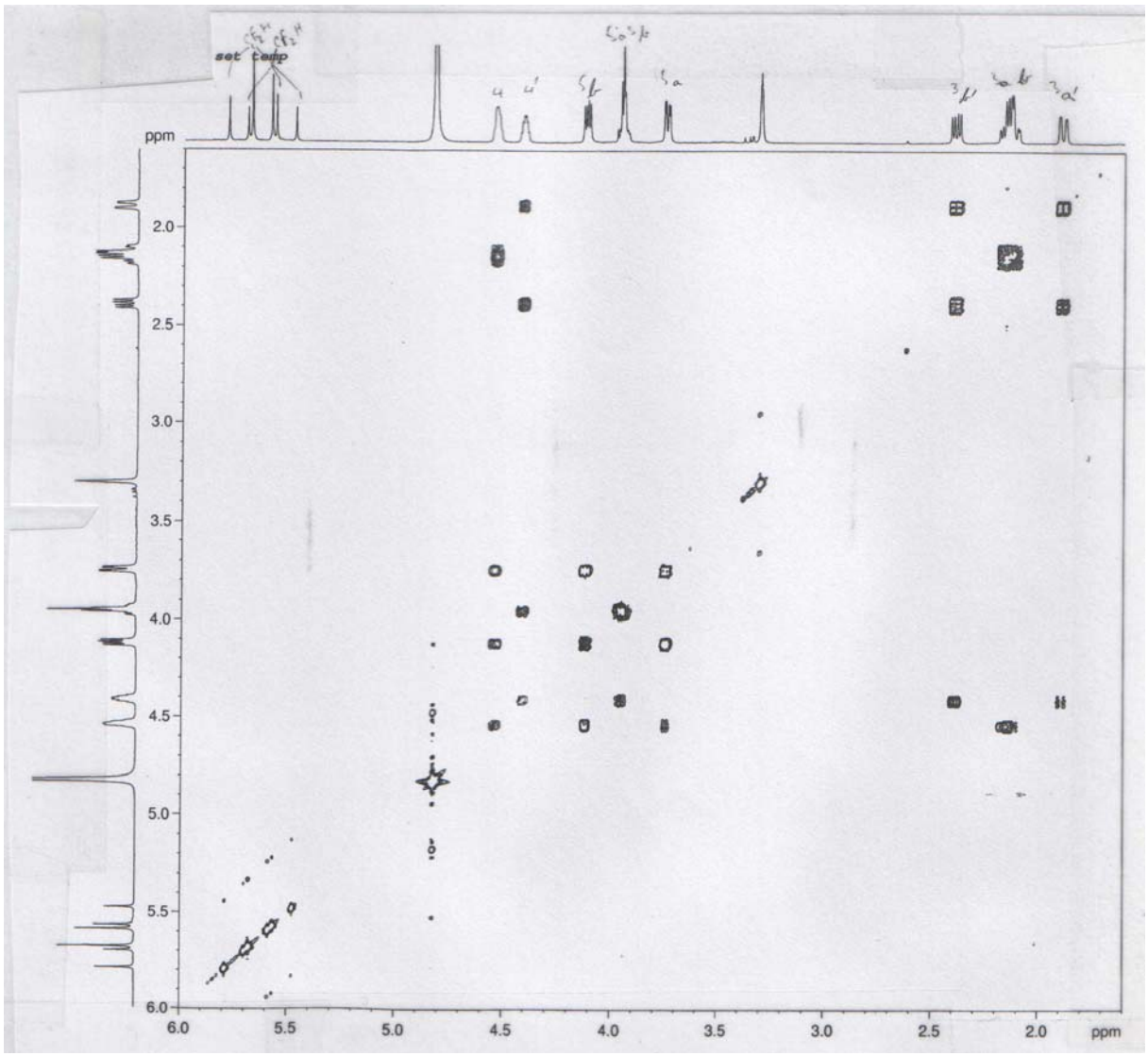


Appendix VI: ^{13}C of sugar **155** (126 MHz, CD_3OD)

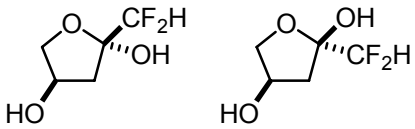


α β

major minor

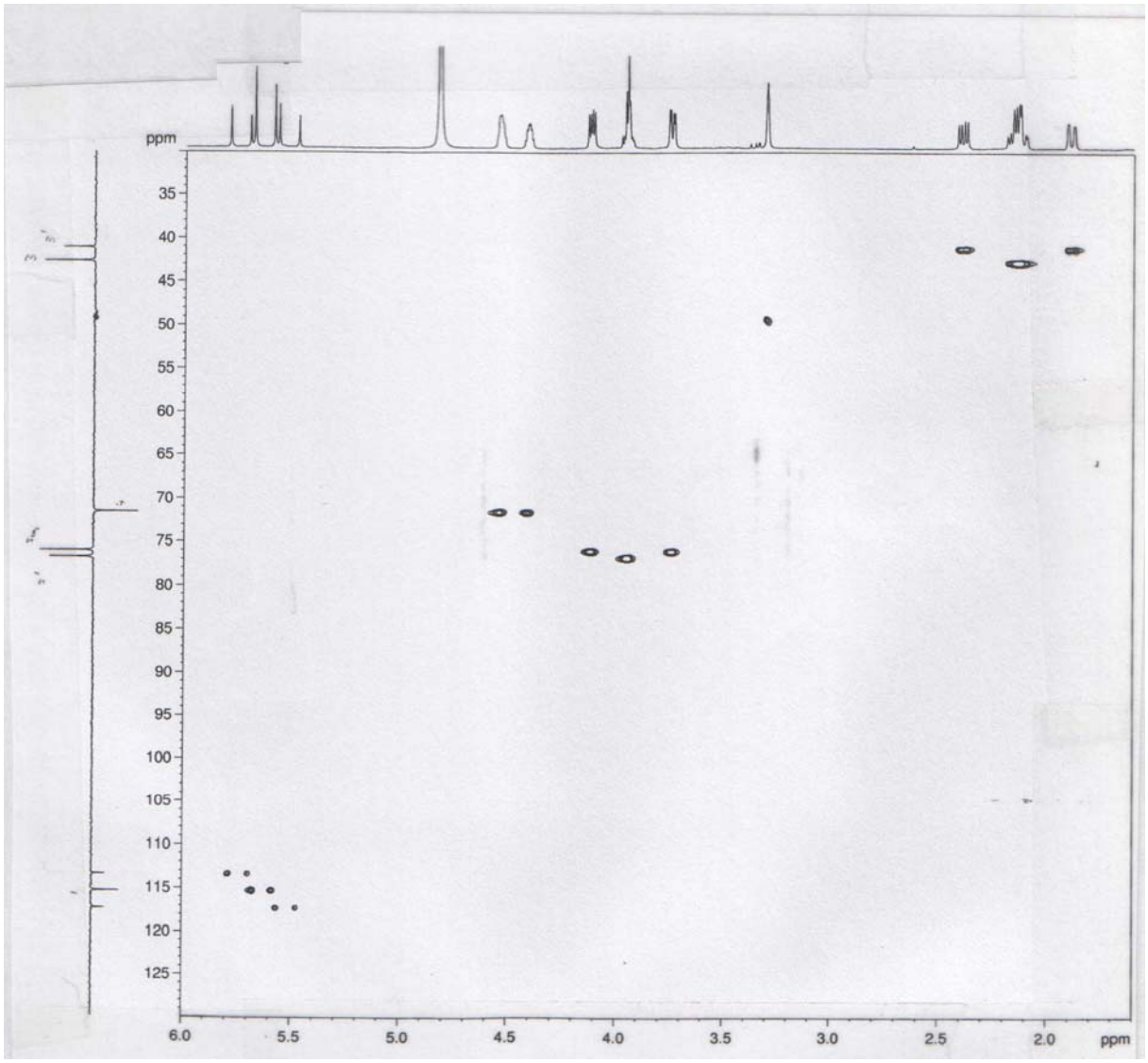


Appendix VII: COSY90 of sugar **155** (500 MHz, CD_3OD)

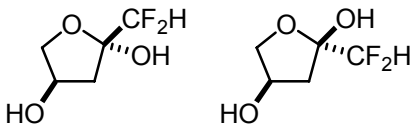


α β

major minor

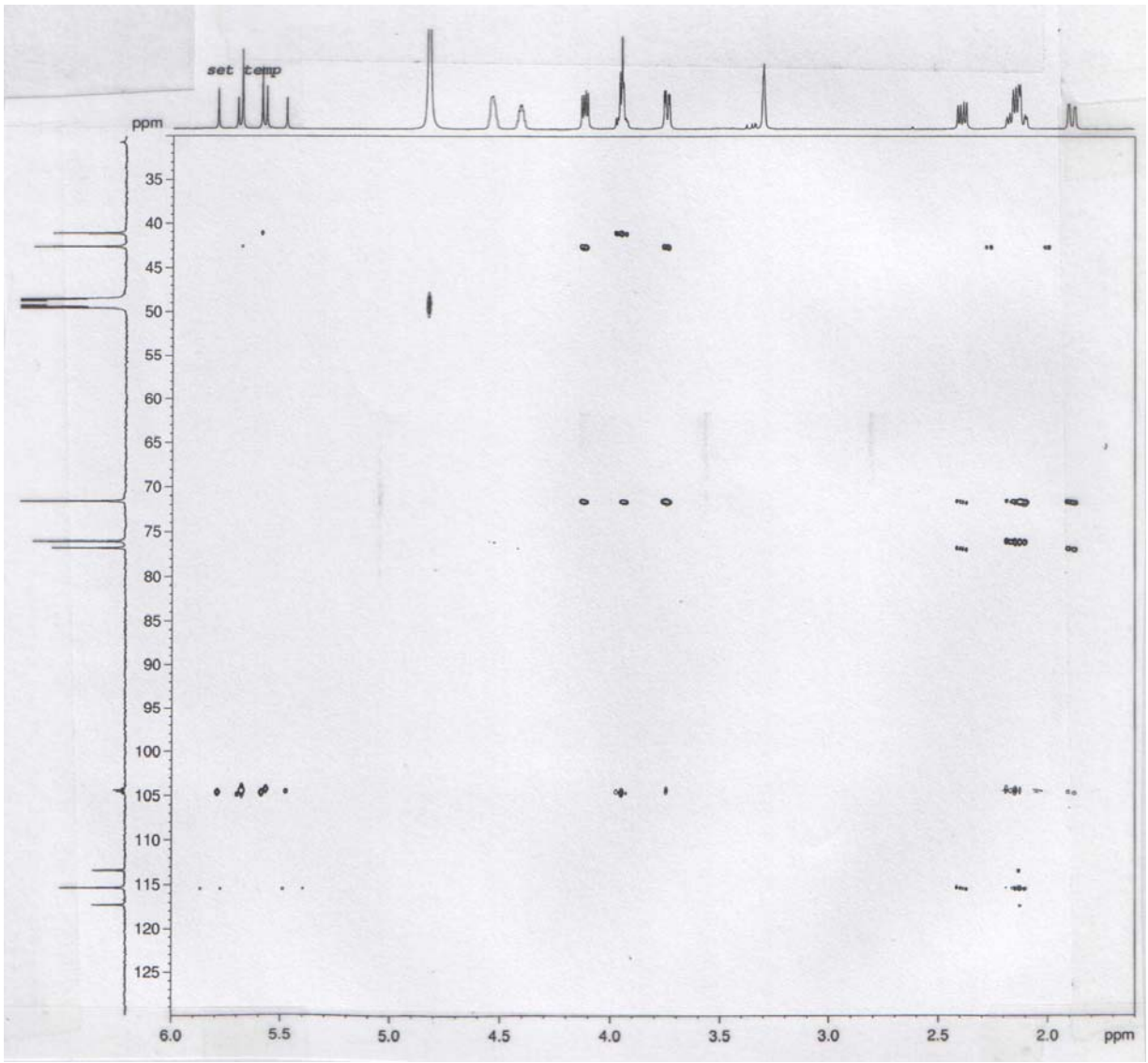


Appendix VIII: HSQC of sugar **155** (500/126 MHz, CD_3OD)

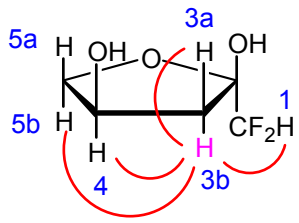


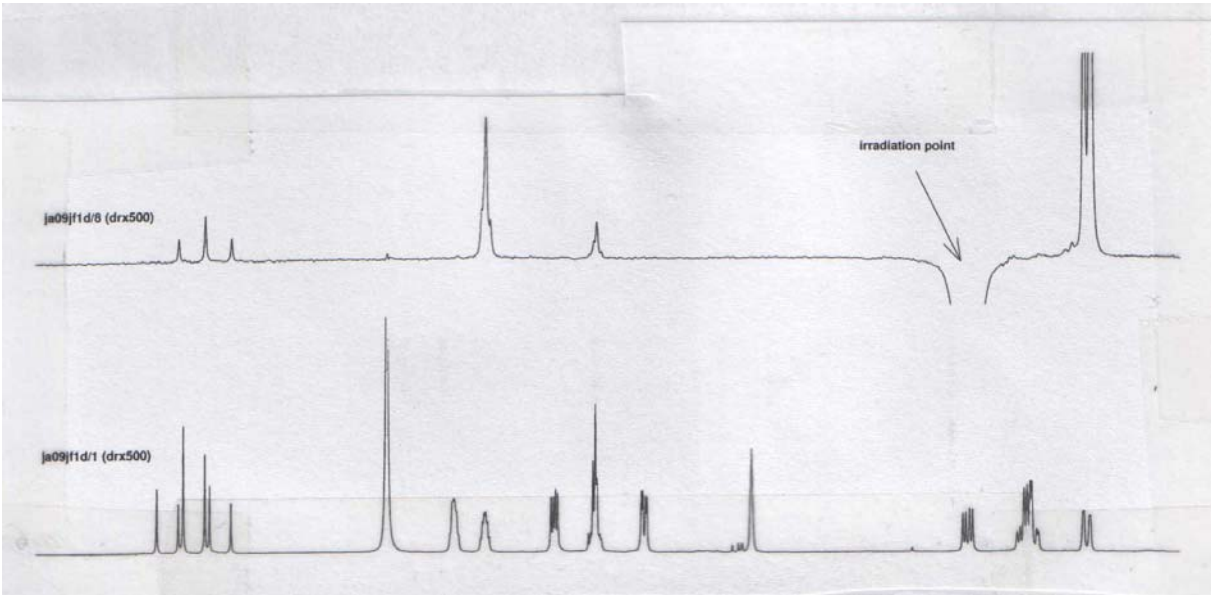
α major

β minor

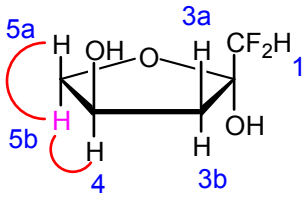


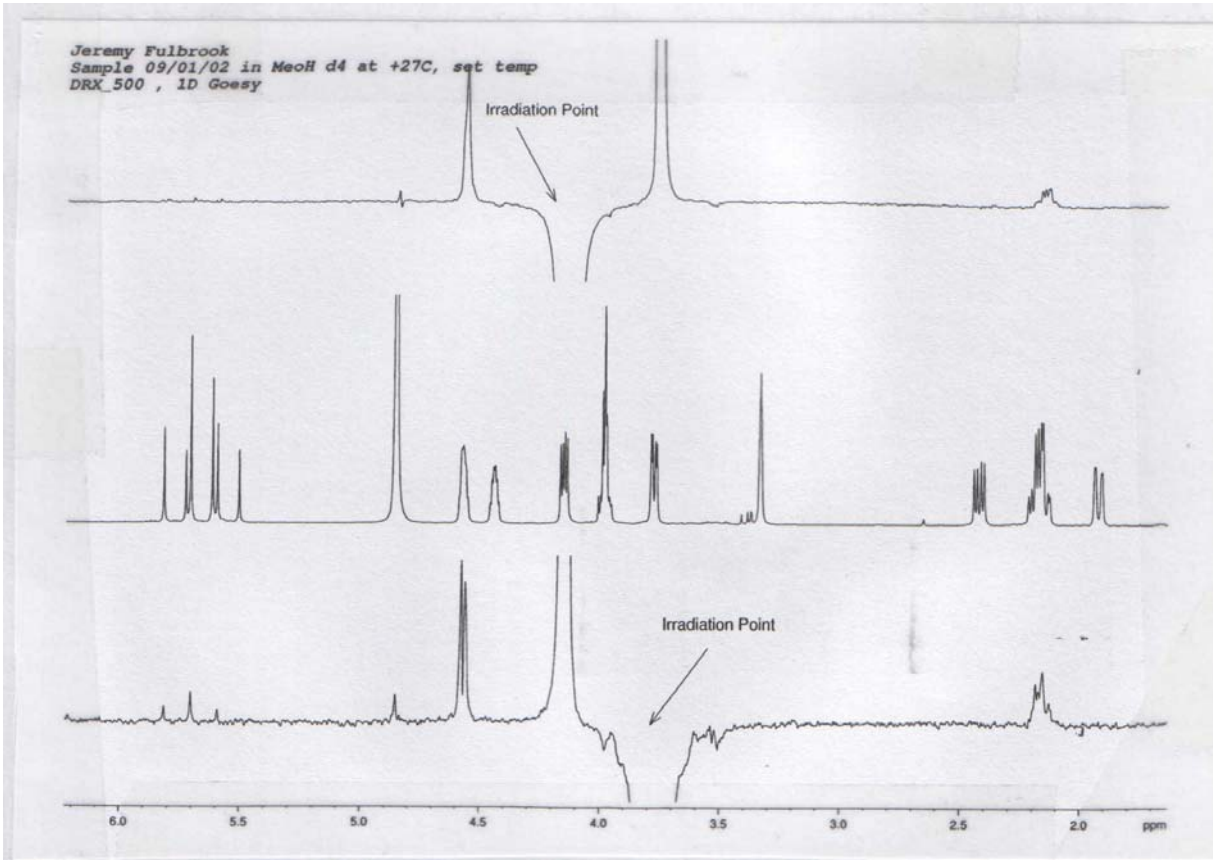
Appendix IX: HMBC of sugar **155** (500/126 MHz, CD_3OD)

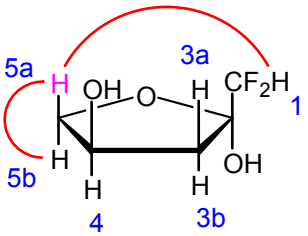




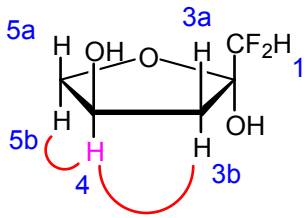
Appendix X: Partial 1D-GOESY spectrum of sugar **155** (500 MHz, CD_3OD)

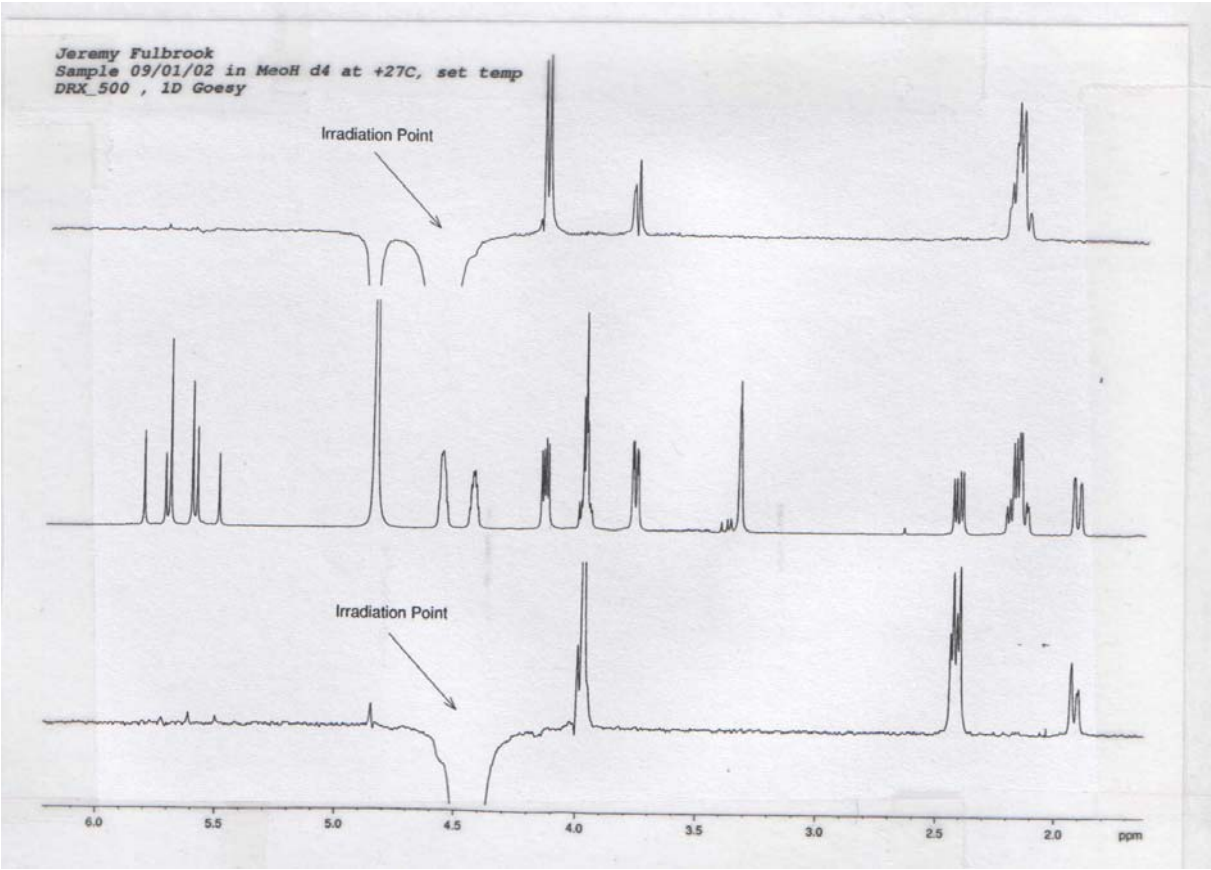


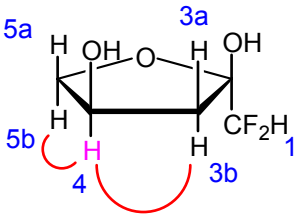




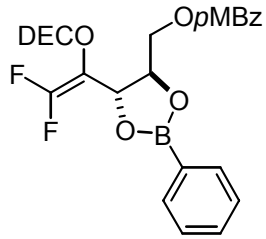
Appendix XI: Partial 1D-GOESY spectrum of sugar **155** (500 MHz, CD_3OD)

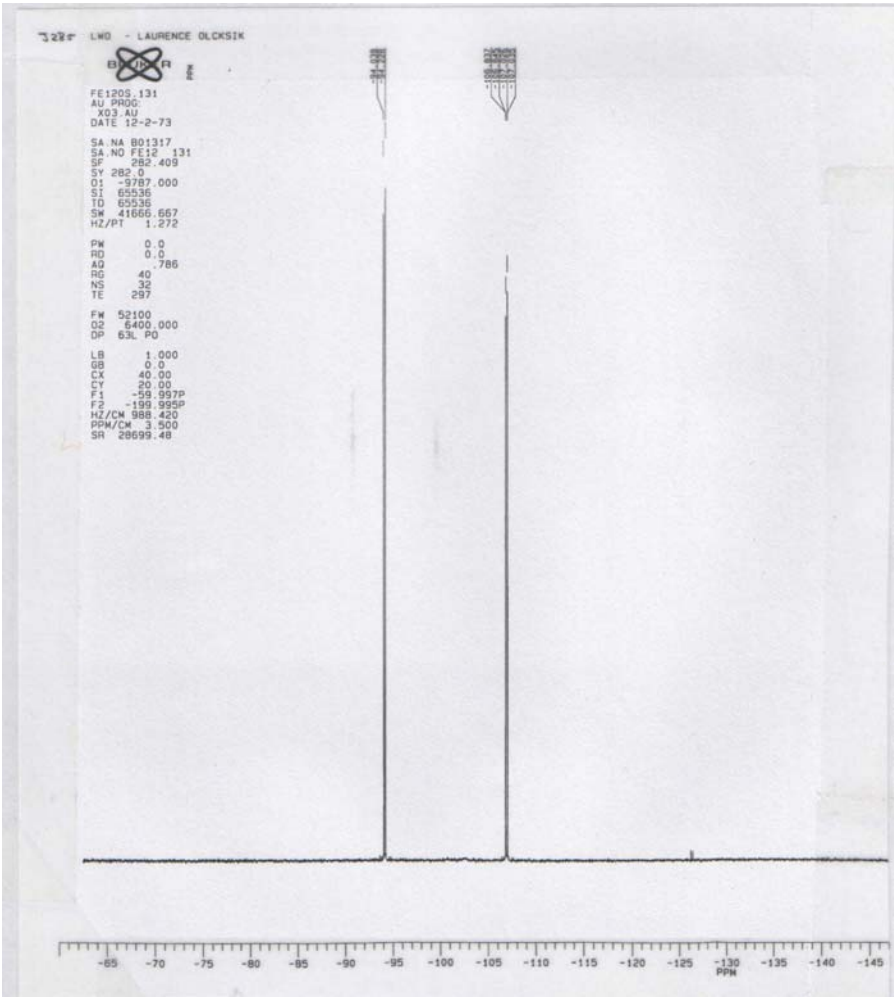




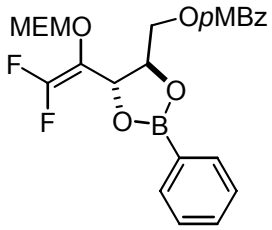


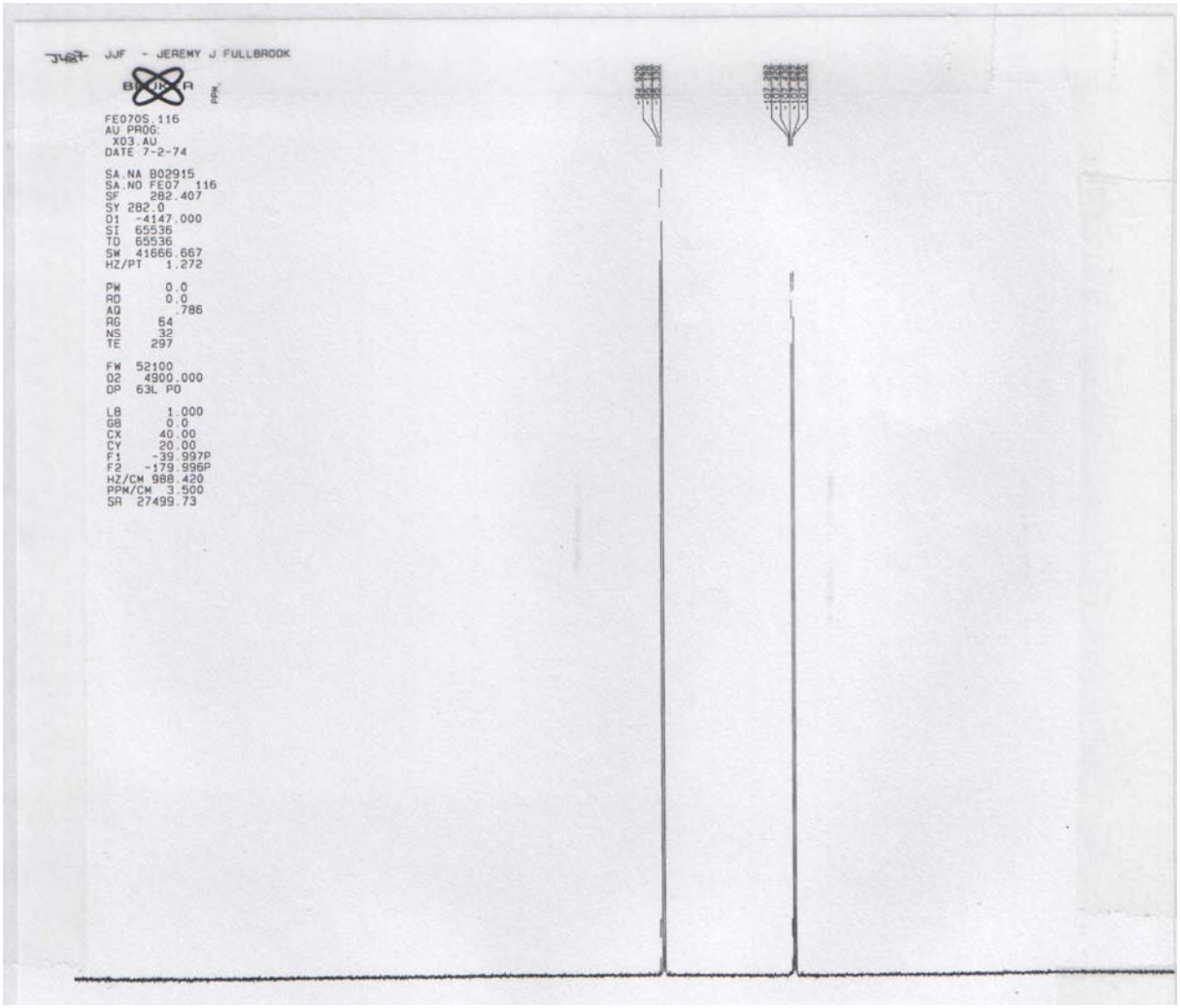
Appendix XII: Partial 1D-GOESY spectrum of sugar **155** (500 MHz, CD_3OD)



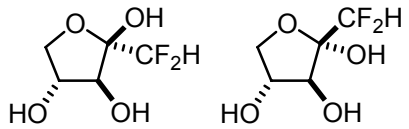


Appendix XIII: Crude ^{19}F of racemic boronate ester **189** (282 MHz, $CDCl_3$)



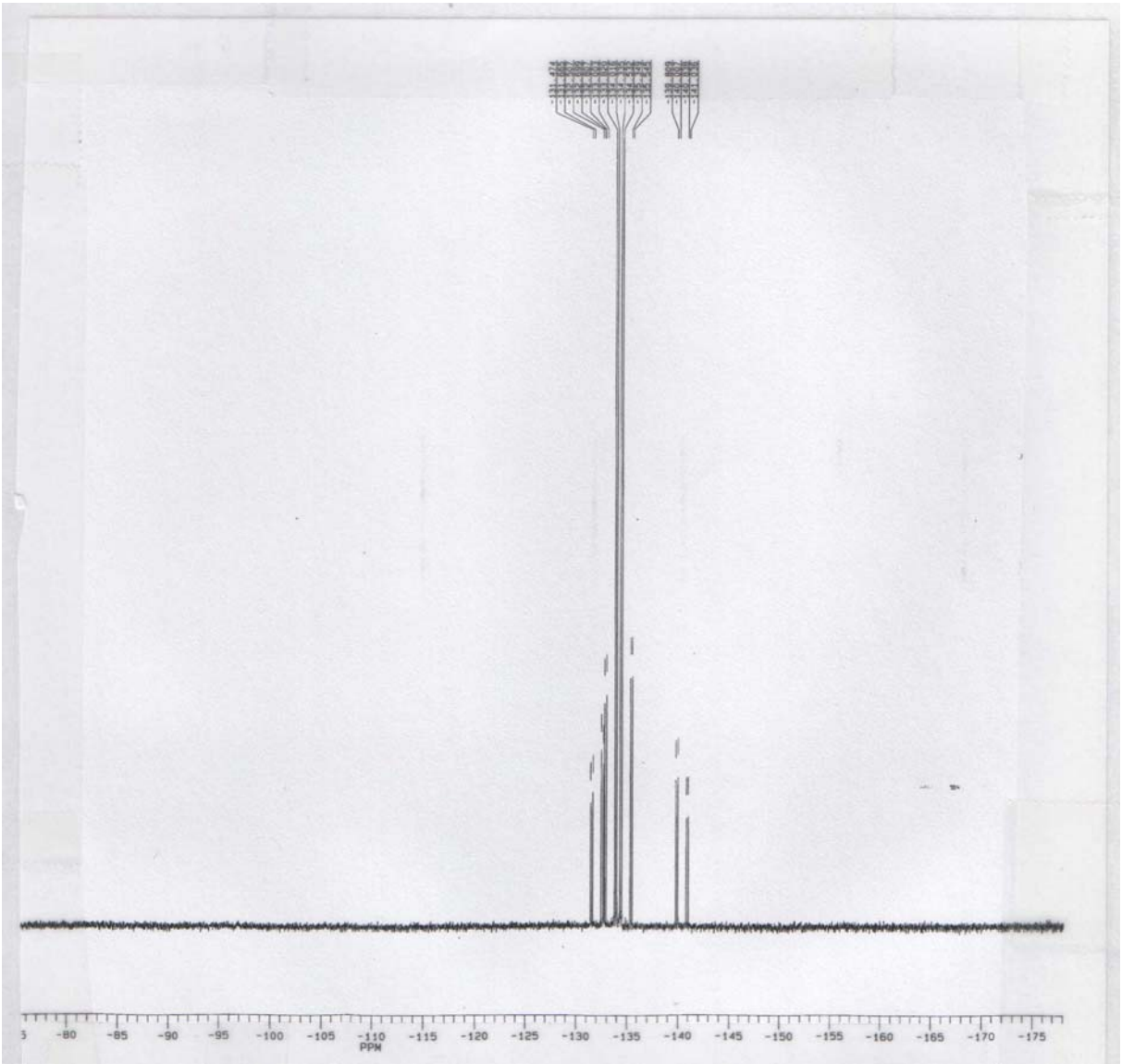


Appendix XIV: Crude ^{19}F of racemic boronate ester **197** (282 MHz, $CDCl_3$)

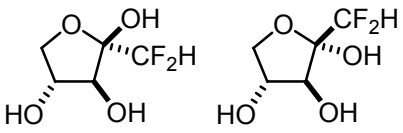


α β

major minor

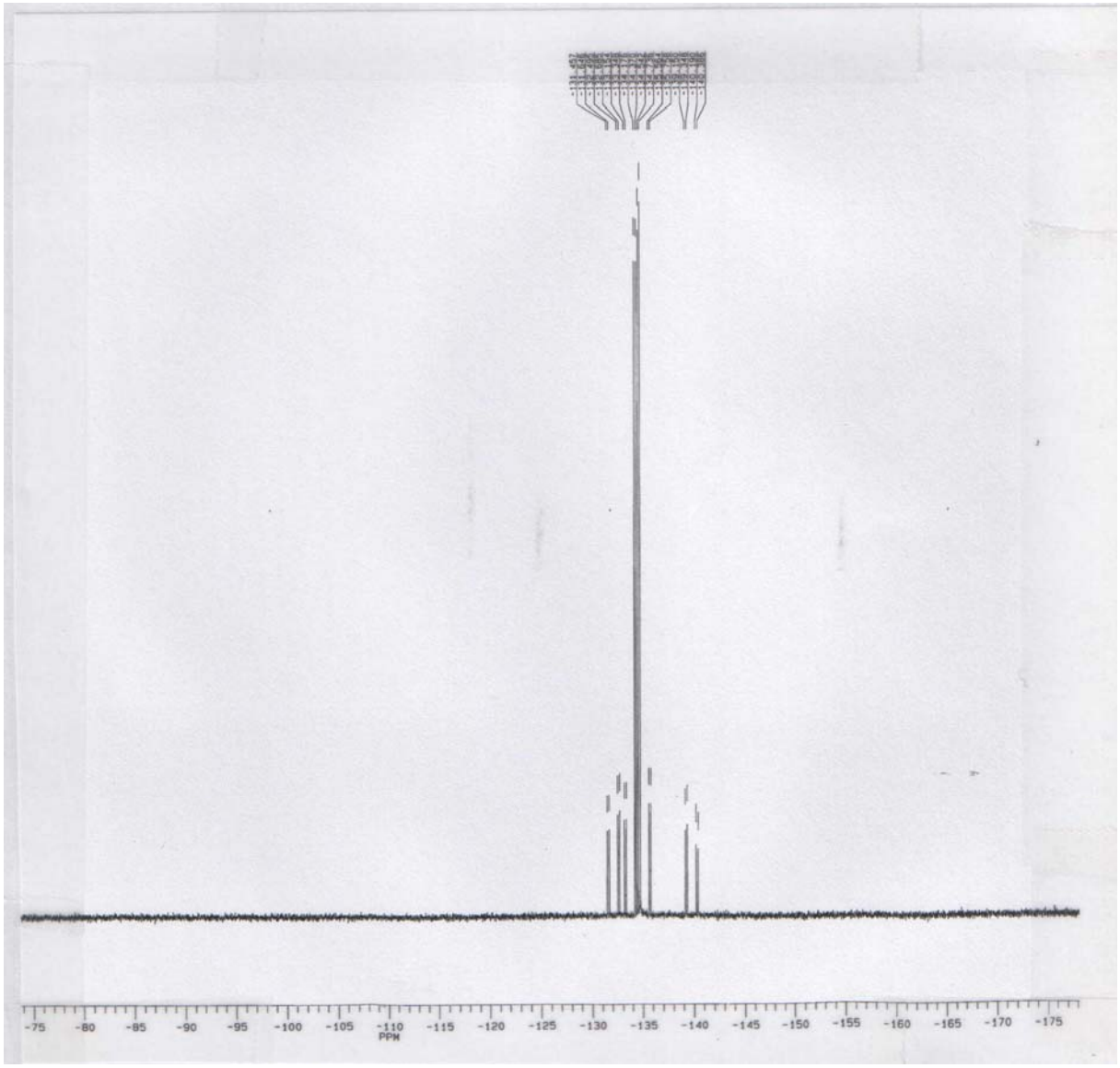


Appendix XV: ^{19}F NMR of **173** (282 MHz, CD_3OD)

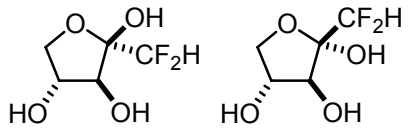


α β

major minor

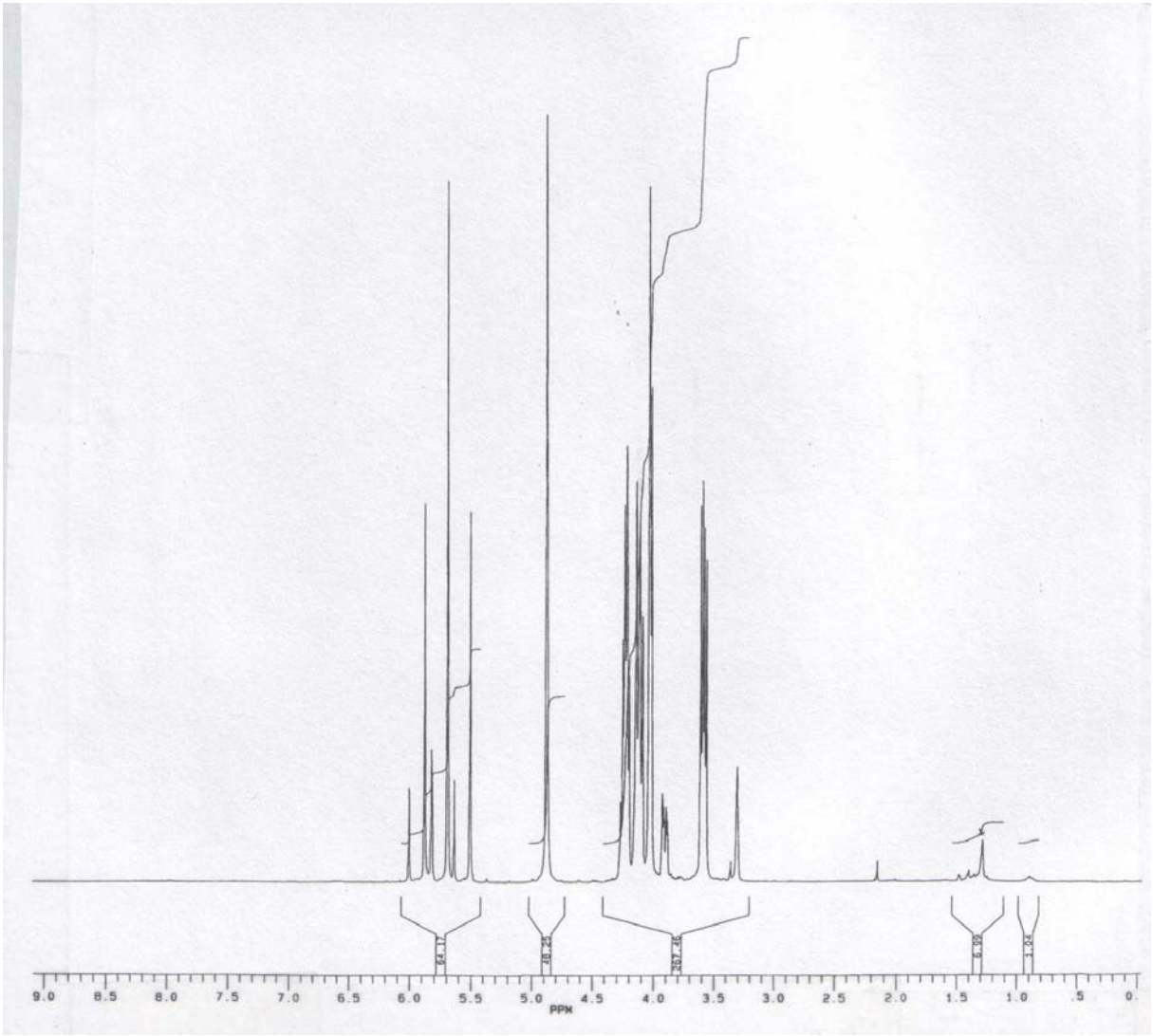


Appendix XVI: ^{19}F NMR of **173** (282 MHz, D_2O)

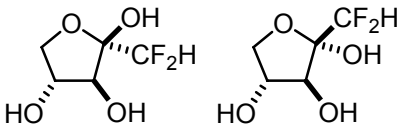


α β

major minor

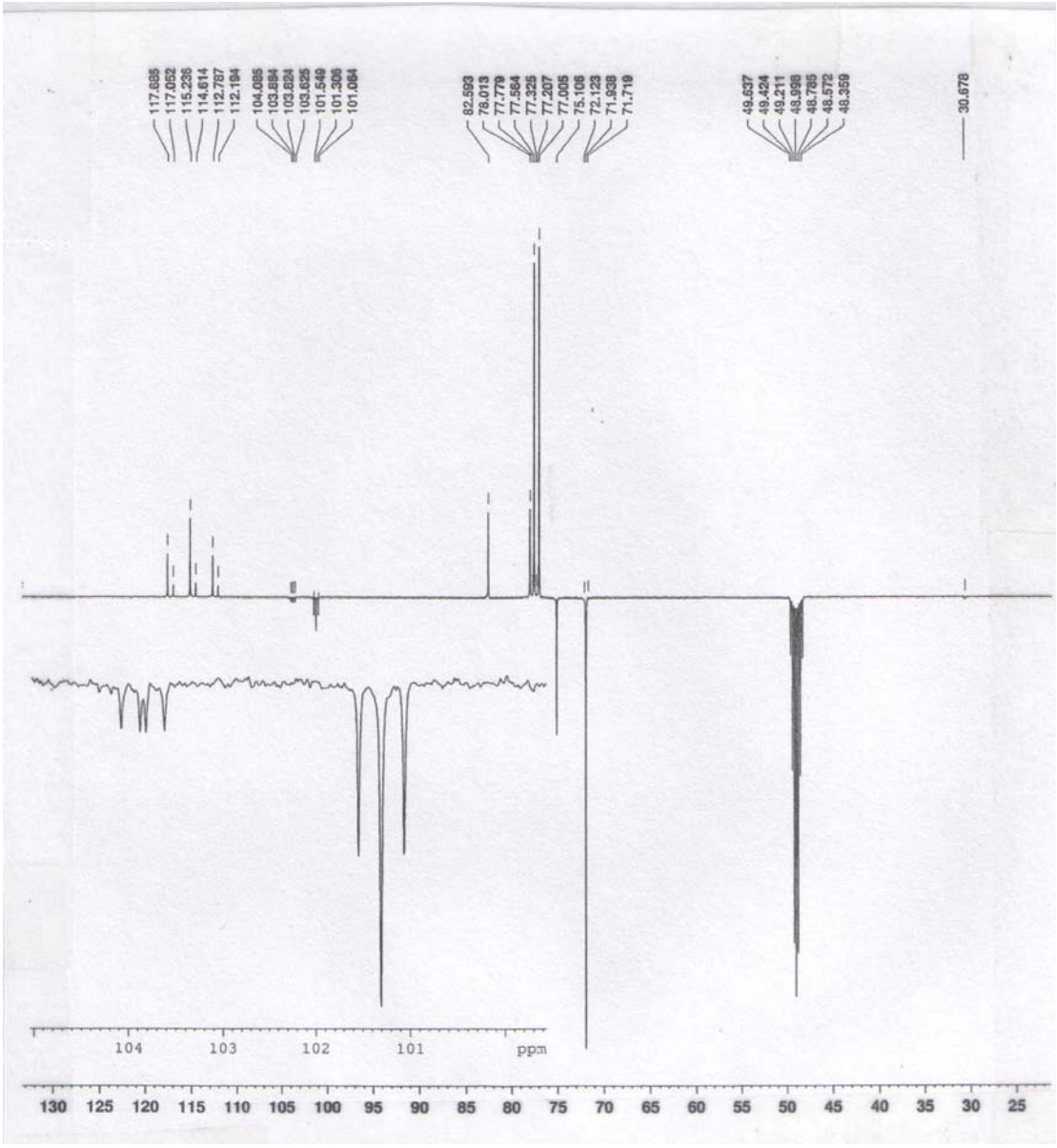


Appendix XVII: ^{1}H NMR of **173** (300 MHz, CD_3OD)

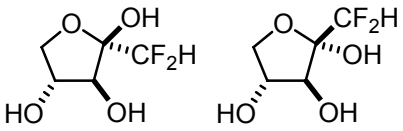


α β

major minor

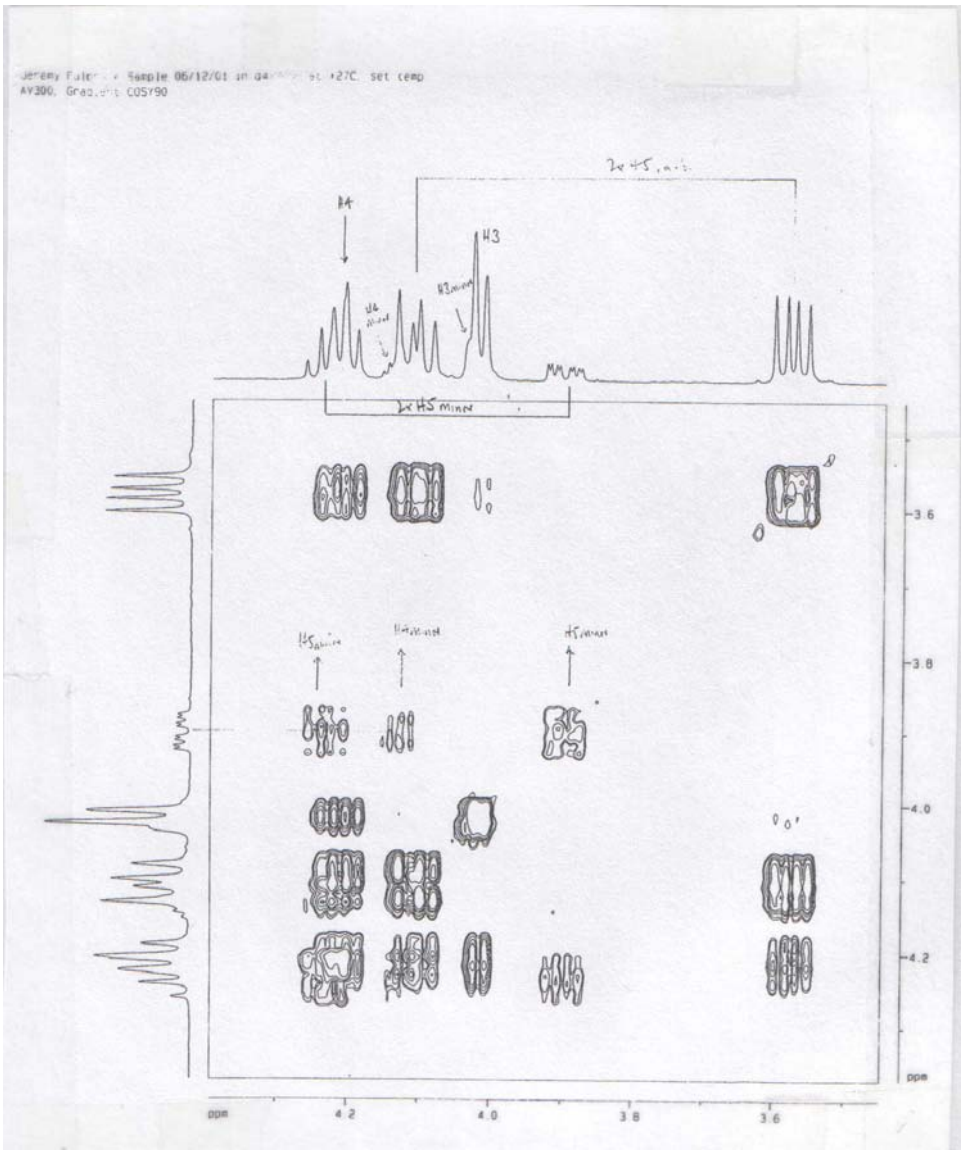


Appendix XVIII: ^{13}C NMR of **173** (100 MHz, CD_3OD)

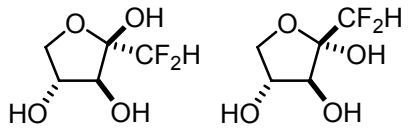


α β

major minor

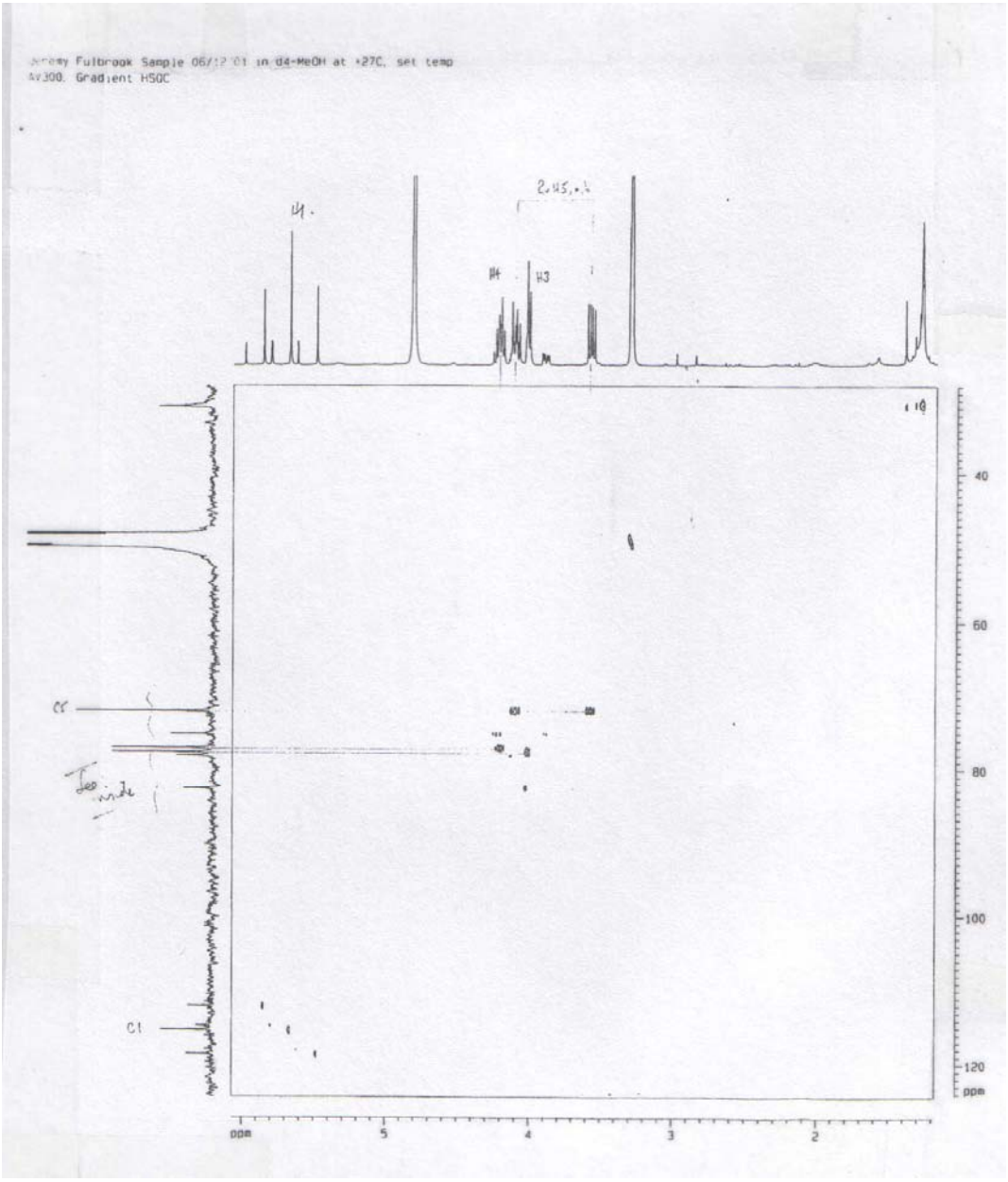


Appendix XIX: COSY90 of **173** (300 MHz, CD_3OD)

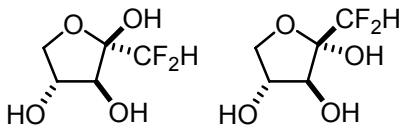


α β

major minor

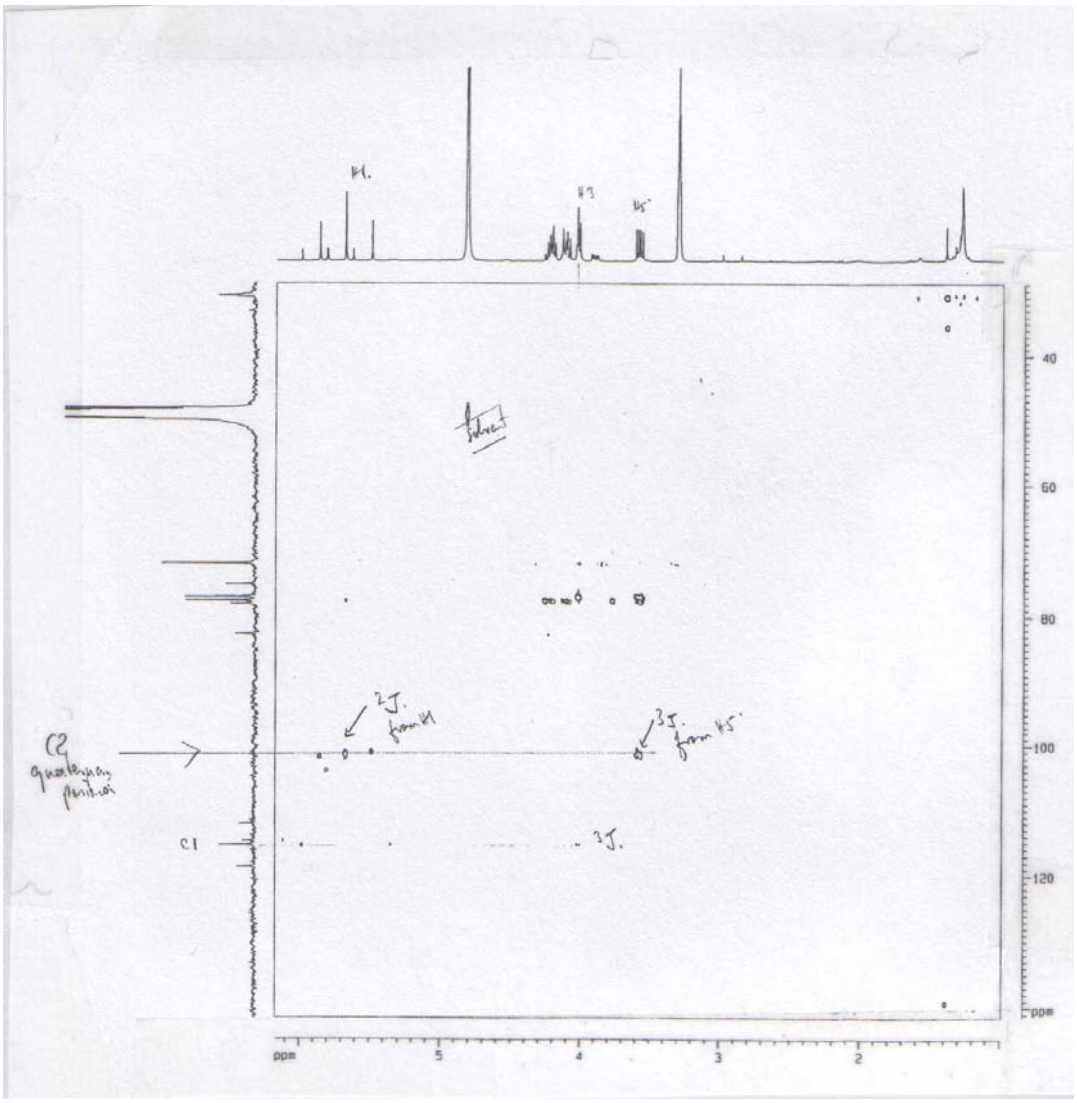


Appendix XX: HSQC of **173** (75/300 MHz, CD_3OD)

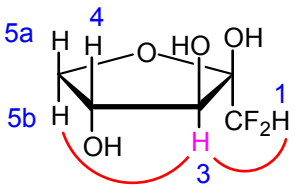


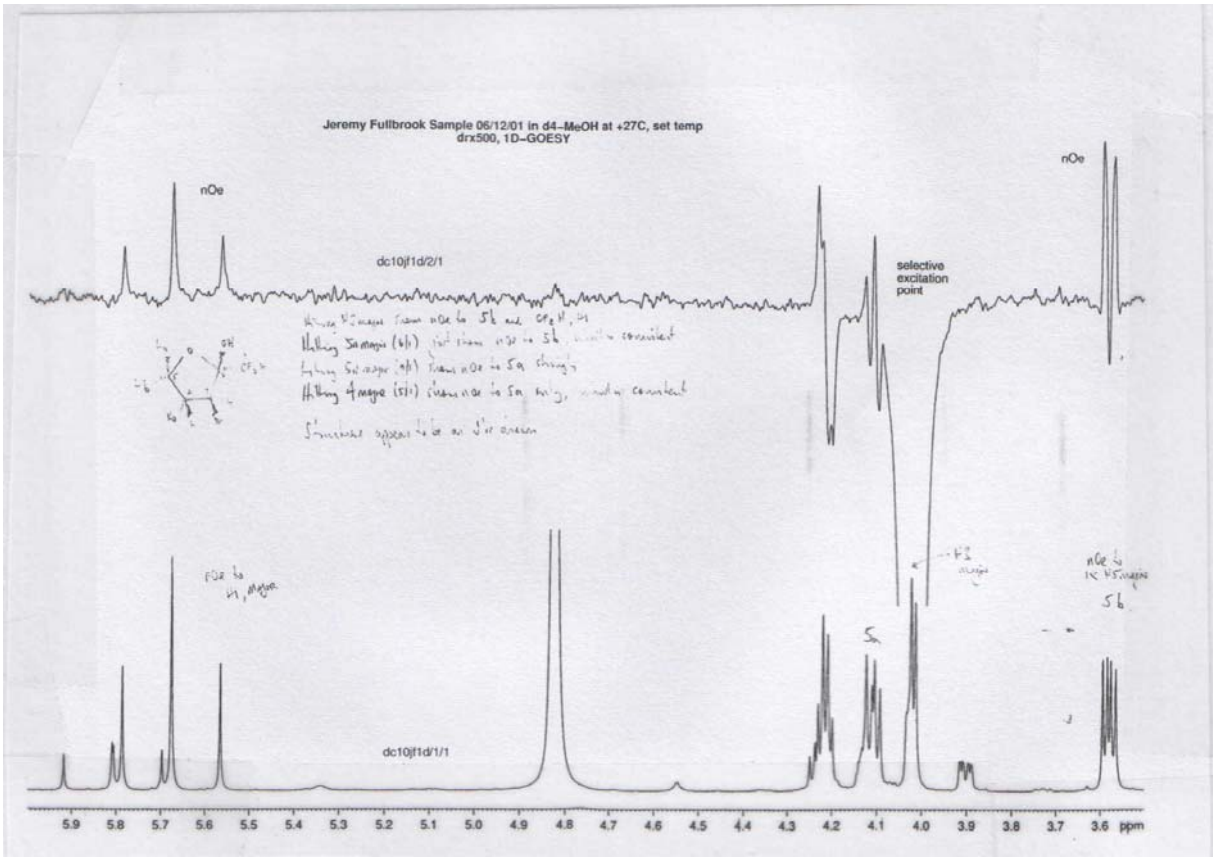
α β

major minor

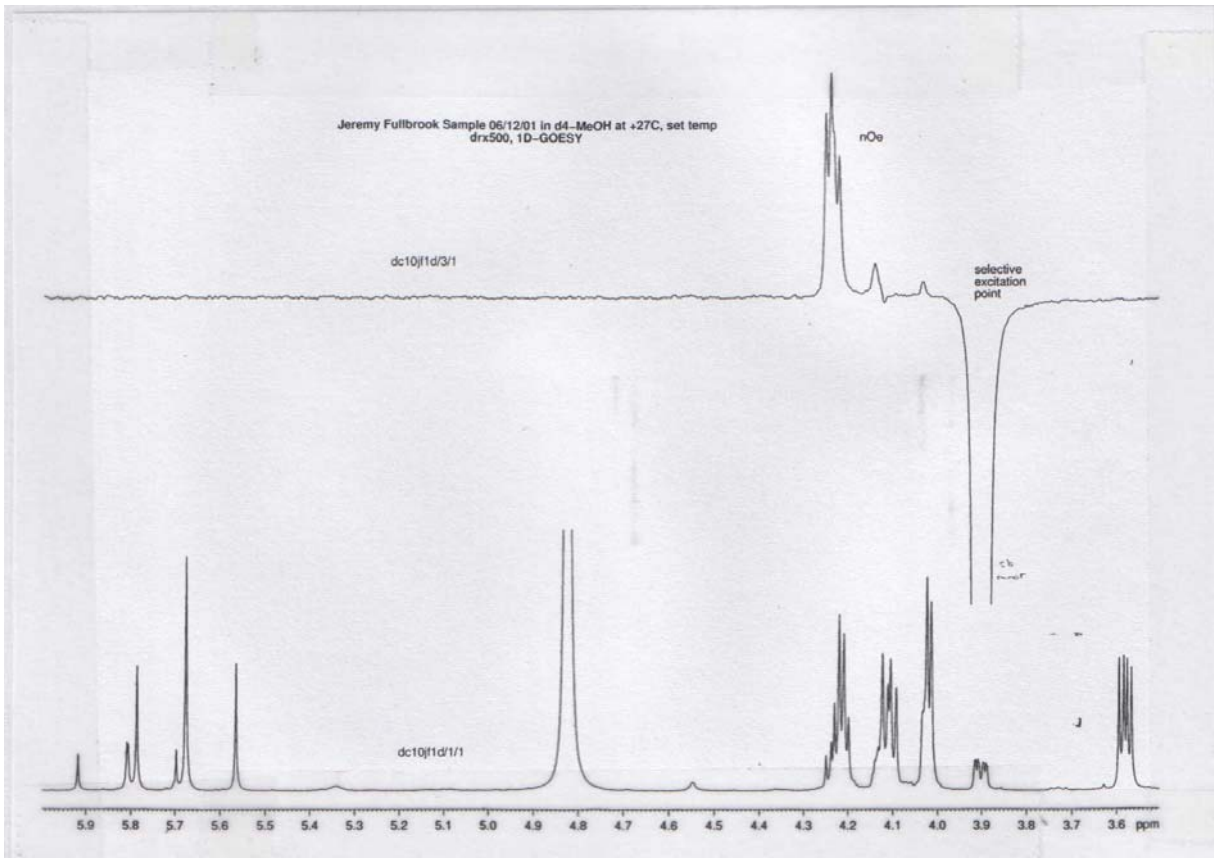


Appendix XXI: HMBC of **173** (75/300 MHz, CD_3OD)

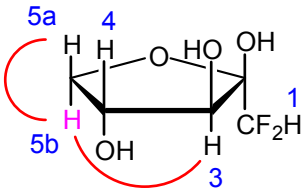


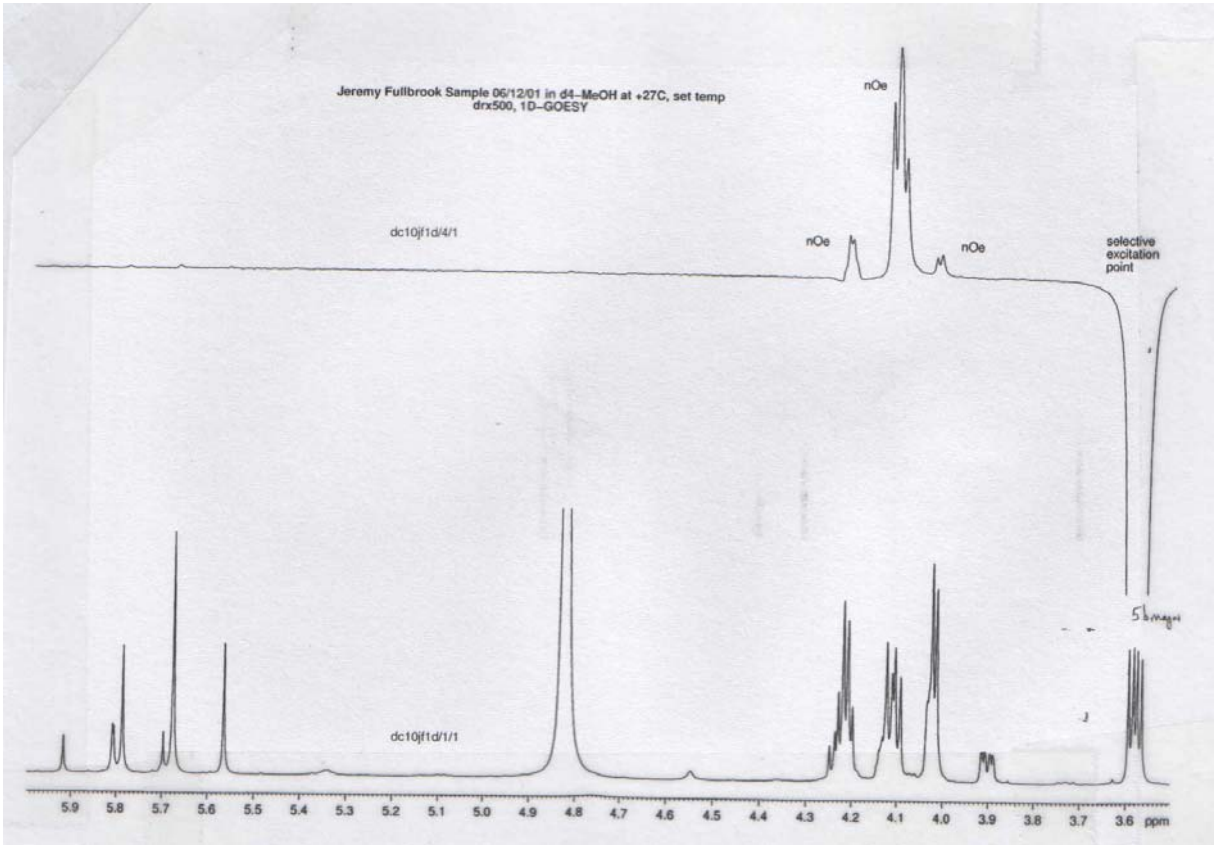


Appendix XXII: Partial 1D-GOESY of **173** (500 MHz, CD_3OD)

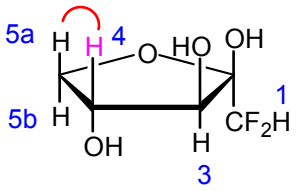


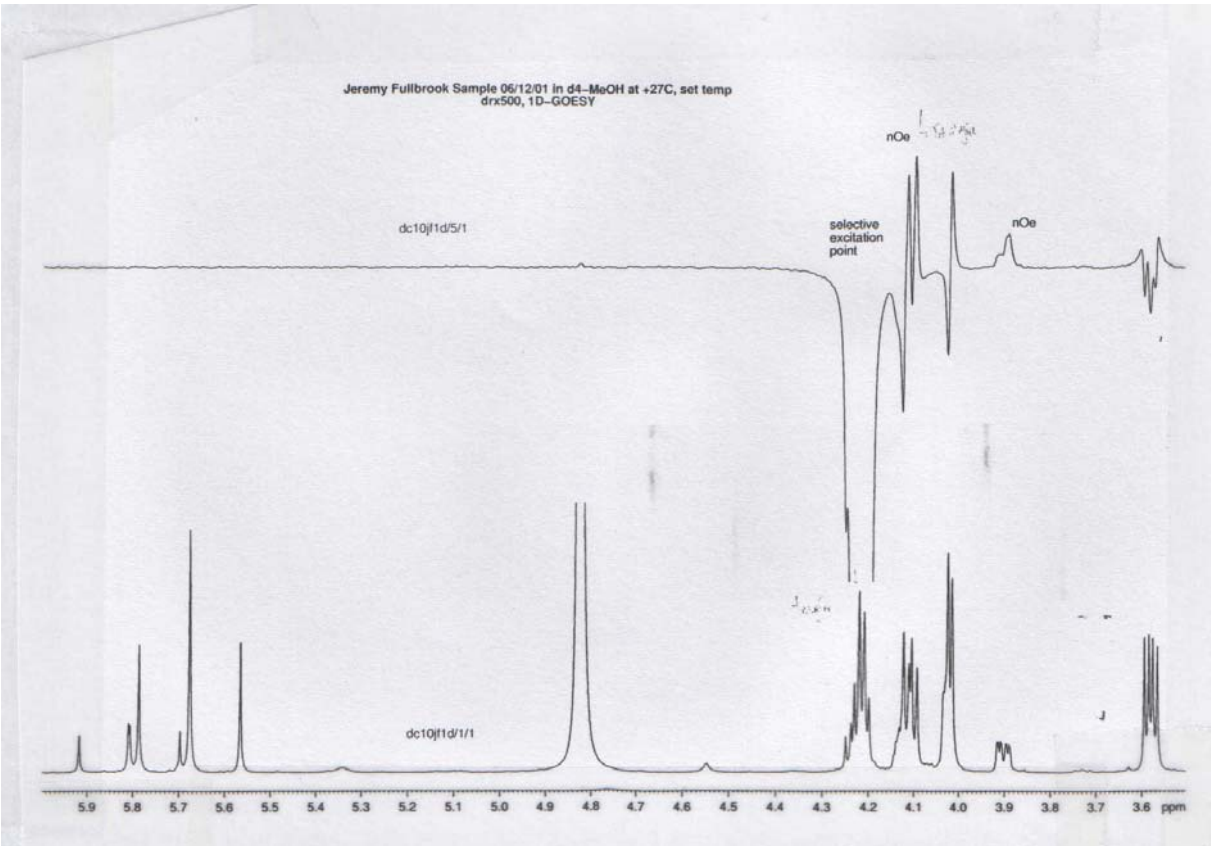
Appendix XXIII: Partial 1D-GOESY of **173** (500 MHz, CD_3OD)



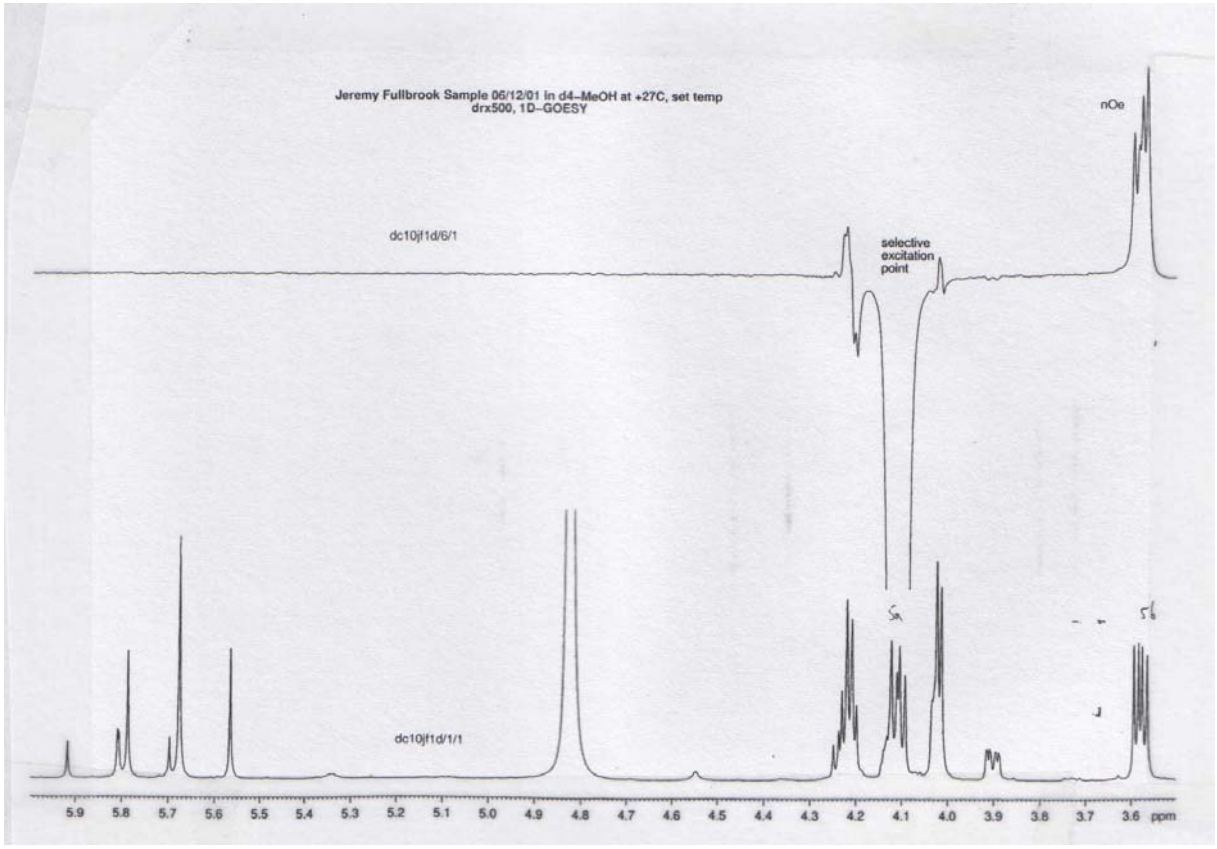


Appendix XXIV: Partial 1D-GOESY of **173** (500 MHz, CD_3OD)

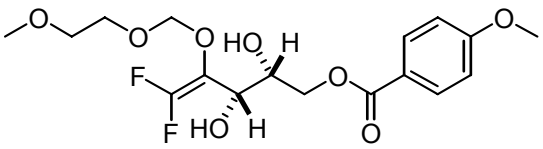


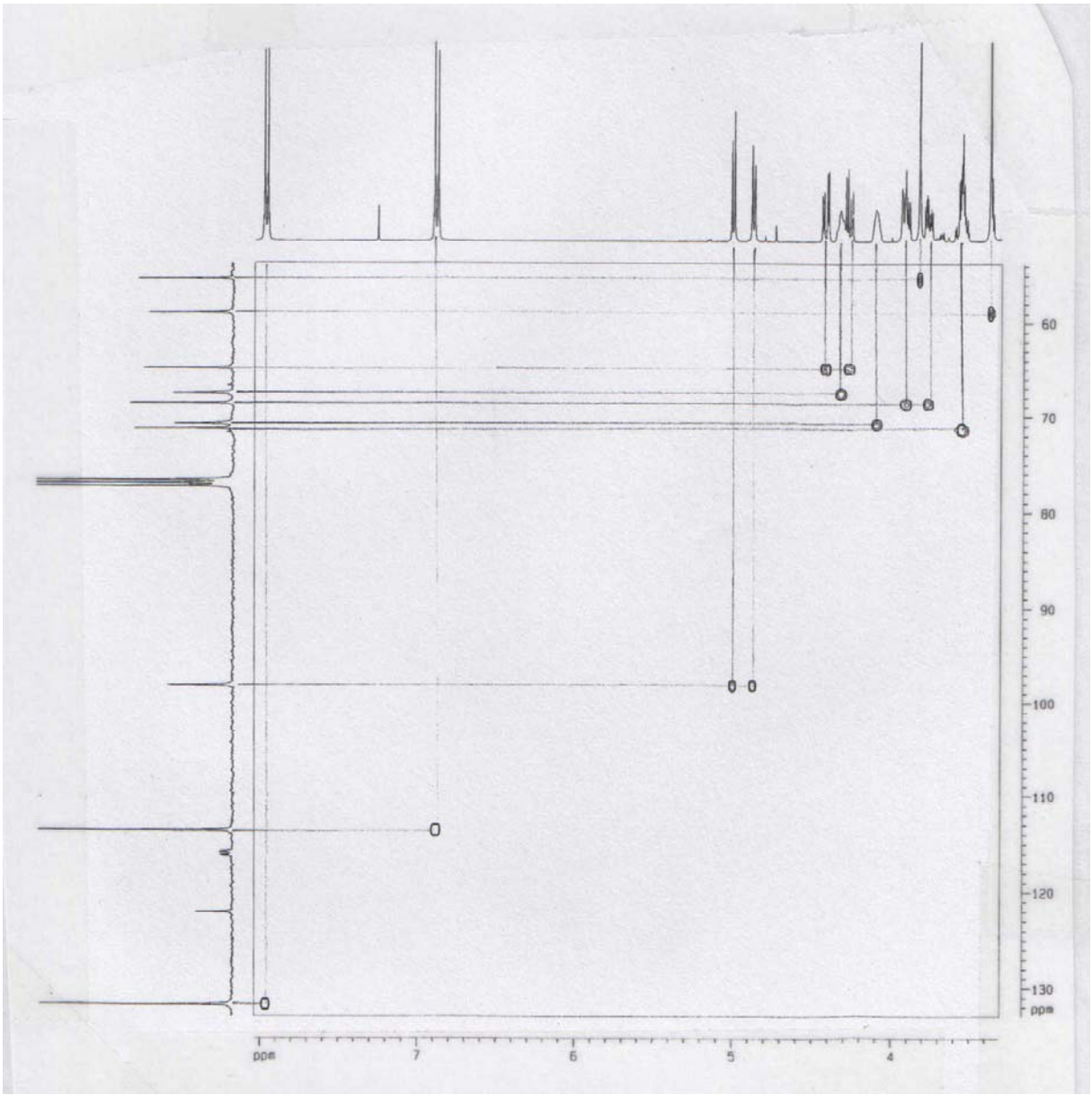


Appendix XXV: Partial 1D-GOESY of **173** (500 MHz, CD_3OD)



Appendix XXVI: Partial 1D-GOESY of **173** (500 MHz, CD_3OD)





Appendix XXVII: HSQC of diol **192** (400 MHz, $CDCl_3$)