UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

School Of Chemistry

The Enantioselective Synthesis of α,α′,β,β′-Tetrafluoroethylidene Substituted Carbohydrates

By

A. James Boydell

Thesis for the Degree of Doctor of Philosophy

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ABSTRACT

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The Enatioselective Synthesis of α,α′,β,β′-Tetrafluoroethylidene Substituted Carbohydrates

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The syntheses of a number of tetrafluoroethylidene substituted carbohydrates are disclosed. From a commercially available fluorinated building block chirality is introduced by way of an asymmetric dihydroxylation (AD). We also disclose the beginnings of work towards the synthesis of fluorinated chiral ligands designed for use in this AD.

The chiral 1,2-diol obtained from the AD is selectively protected at either the primary or seconday alcohol to form the central intermediate our our syntheses. The functionalisation and subsequent cyclisation of these compounds are disclosed. To synthesise compounds with the tetrafluoroethylidene unit proximal to the anomeric centre we utilised a novel halogen-lithium exchange/cyclisation procedure. This reaction is shown to have wide scope being used to synthesise hexoses and pentoses in both their pyranose and hexose forms.

The intermediate is also shown to take part in a radical addition/atom transfer/nucleophilic cyclisation sequence to form tetrafluoroethylidene substituted carbohydrates where the fluorinated substituent is remote from the anomeric centre.

We also disclose the synthesis of a tetrafluoroethylidene substituted nucleoside and glycal.

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2.0 THE SHARPLESS AD OF 4-BROMO-3,3,4,4-TETRAFLUOROBUT-1-ENE ..... - 2 -

PREFACE

The research described in this thesis was carried out under the supervision of Dr B. Linclau at the University of Southampton between October 2002 and October 2005. No part of this thesis has been previously submitted for a degree. All work is my own unless otherwise stated.

ACKNOWLEDGEMENTS

Firstly I must thank Bruno for all his advice, patience, help and enthusiasm.

Secondly thanks must go to my family. My Mother and Father who fostered my interest in science and attempted, somewhat vainly, to instill me with a work ethic. They both have my love and respect. My brothers are a constant I would not do without. They are the only people who would get away with explaining this work as "basically he's spent the last 3 years cooking and then not eating what he makes!".

My friends who have been a respite from the lab, or companions in it. Rich and Helen, who still manage to make me smile whenever we overindulge in nostalagia, normally while overindulging in general. To Phil (the master of carol singing), Rob (the only black belt who'll let you tickle him), Henry (he who usefully maps dragon locations whilst wearing funky trousers), Helen (the most polite swearing I have ever heard), Benedetta (the loudest, and only, Italian swearing I have heard), and Leo (the donkey) – you were a pleasure to work with and made the lab a pleasant pastime rather than a labour. So much so I'm still not convinced we could actually call it work.

I must thank Joan Street and Dr Neil Wells for running the NMR service. Research without them would be near to impossible. Dr John Langley and Julie Herniman also deserve recognition for the impeccably run MS service; they have proved invaluable. I should also thank Ann and Karl for running the store, always smiling no matter how idiotic people are.

Lastly I must thank Marlies for her time, inexhaustable patience, love and support. She has made the last 7 years a pleasure. Hopefully, she can now have her boyfriend back in the evenings and weekends. He looks forward to it.

ABBREVIATIONS

Ac	Acetyl
AIBN	Azo-*bis*(isobutyronitrile)
aq	Aqueous
Bn	Benzyl
br.	Broad
Bu	Butyl
BVE	Benzyl vinyl ether
C	Celsius
Celite	Celite 545®
CI	Chemical ionisation
cm	Centimetre
Cp	Cyclopentadienyl
d (time)	days
d (NMR)	Doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
dm	Decimetre
DMA	Dimethylacetamide
DMF	Dimethylformamide
ee	Enantiomeric excess
EI	Electron ionisation
Et	Ethyl
Ether	Diethyl ether
EVE	Ethyl vinyl ether
FT	Fourier transform
h	Hour
HMPA	Hexamethylphosphoramide

HRMS	High resolution mass spectroscopy
Hz	Hertz
IPF	Internal polyfluoroalkyl fragment
IR	Infrared
m	Multiplet
m	Moderate
M	Molar (mol dm^{-3})
m.p.	Melting point
Me	Methyl
MHz	Megahertz
min	Minute
mmol	Millimoles
mol	Moles
Nap	2- naphthylmethyl
NMR	Nuclear magnetic resonance
Petrol	Petroleum ether 40-60
Ph	Phenyl
Piv	Pivaloyl
q	Quartet
RT	Room temperature
s (NMR)	Singlet
s (IR)	Strong
t	*Tert*, tertiary
t	Triplet
TBDMS	*t*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

1.0 INTRODUCTION

1.1 CARBOHYDRATES

Carbohydrates, the most prevalent natural products, are produced in massive quantities (4×10^{14} kg) each year. They are a family of compounds that comprise the monosaccharide, oligo- and polysaccharides. The term "carbohydrate" also applies to compounds derived from monosaccharides by reduction of the anomeric carbonyl group (alditols), oxidation of one or more of the terminal hydroxyls, or replacement of one or more hydroxyl groups with a hydrogen, amino, thiol or other heteroatomic functional group.[1,2]

The importance of carbohydrates is evidenced by their myriad roles in biological systems. They are the main source of energy on most cells, often as food storage polymers (e.g. starch). Polysaccharides play vital roles as structural materials – cellulose, pectin and xylan determine the structure of plants and chitin forms the exoskeleton of insects, crabs and lobsters. As well as these structural and energetic roles carbohydrates are involved a wide range of processes including:[3] cell-cell recognition, fertilization, embryogenesis, neuronal development, as blood group antigens,[4] hormone activities, proliferation of cells, tissue organisation, viral and bacterial infection and tumour cell metastasis.[5]

1.1.1 Configuration and Naming of Monosaccharides[6,7]

Carbohydrate was a term coined to describe the family of compounds with the molecular formula $C_x(H_2O)_y$. This definition of the term is now too narrow to be strictly applied as many structures do not conform to the proscribed formula but are classified as carbohydrates by virtue of their chemical properties.[8]

Monosaccharides are monomeric, chiral, polyhydroxylated carbonyl compounds which commonly exist in a cyclic hemi-acetal form. Monosaccharides can be divided into two

main groups according to whether their acyclic form possesses an aldehyde (aldoses) or a ketone (ketoses). These are then further subdivided according to the number of carbon atoms in the monomeric chain into pentoses (5 carbons), hexoses (6 carbons), heptoses *et cetera*. To demonstrate the naming conventions, and as an insight into monosaccharide configuration we shall consider the most common monosaccharide; D-glucose (**1.01**).

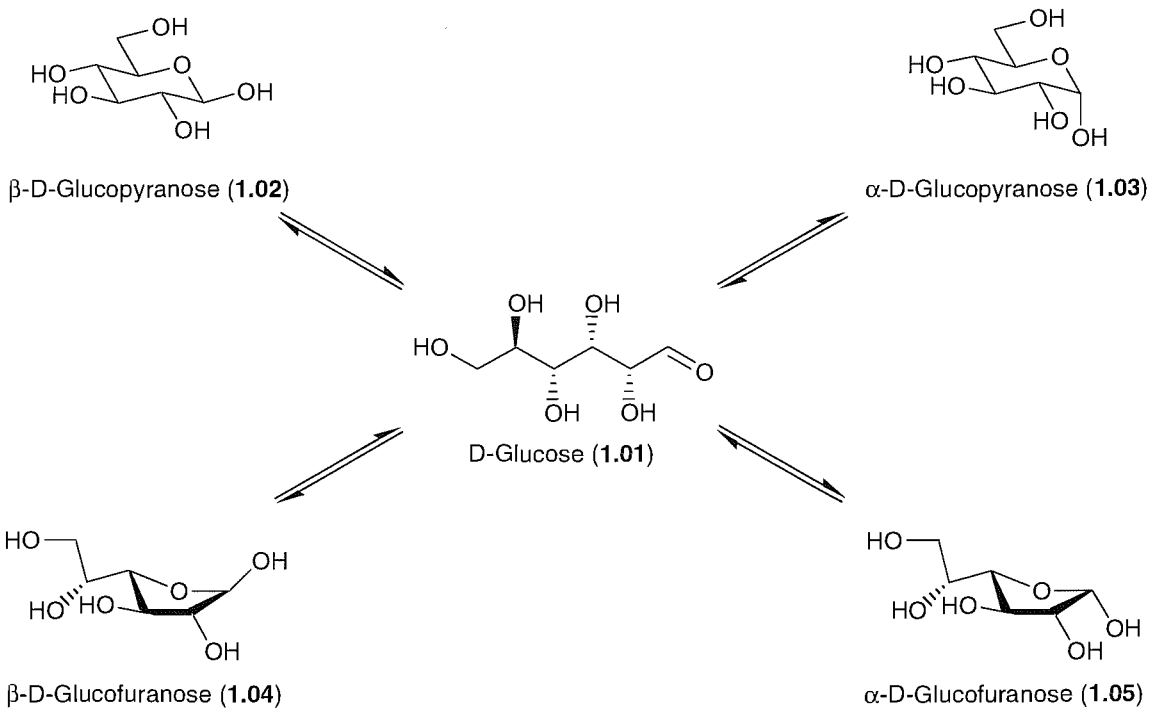
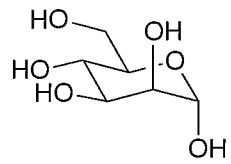


Figure 1

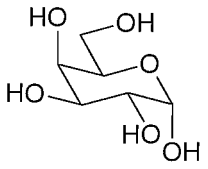
The linear form of **1.01** is energetically unfavourable compared to its cyclic form. Ring closure by nucleophilic attack of the hydroxyl group on C-4 (O-4) or C-5 (O-5) on the carbonyl carbon atom gives rise to several hemi-acetal structures. Attack by O-4 gives rise to the glucofuranoses **1.04** and **1.05**. Attack by the O-5 results in two glucopyranoses **1.02** and **1.03**. In general, the six-membered pyranose forms are favoured over the five membered furanose forms, with both of these cyclic forms much favoured over the straight chain ketone or aldehyde forms. The distribution of these forms at equilibrium differs considerably between aldoses; a direct consequence of differences in the anomeric and steric effects of particular monosaccharides. This cyclic hemi-acetal formation also

forms a new stereogenic centre and therefore the cyclisation can form either of two diastereomeric hemi-acetals, known as anomers.

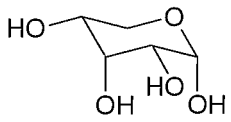
Whilst D-glucose is the most abundant monosaccharide it is far from the only naturally occurring monomeric carbohydrate; others of interest– both aldoses and ketoses are shown in Figure 2.



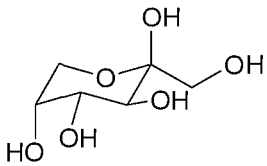
α-D-Mannopyranose (**1.06**)



α-D-Galactofuranose (**1.07**)



α-D-Ribopyranose (**1.08**)



α-D-Fructopyranose (**1.09**)

Figure 2

1.1.2 The Anomeric Effect[9-13]

With such a wide variety of conformers possible for each monosaccharide a method with which to assess their particular stabilities is necessary. Generally, the stability can be explained in terms of purely steric factors. A basic rule for cyclohexane derivatives is that an equatorial orientation is preferred for large substituents. The electronegative substituent at the anomeric centre of a pyranoside, however, prefers an axial position.

The tendency of an electronegative substituent to adopt an axial orientation at the anomeric centre was first described by Edwards[14] and named "the anomeric effect" by

Lemieux[15,16]. Initially this effect was explained by destabilizing dipole-dipole interactions, largest in the β-anomer (**1.10**) which is therefore disfavoured (Figure 3).[17]

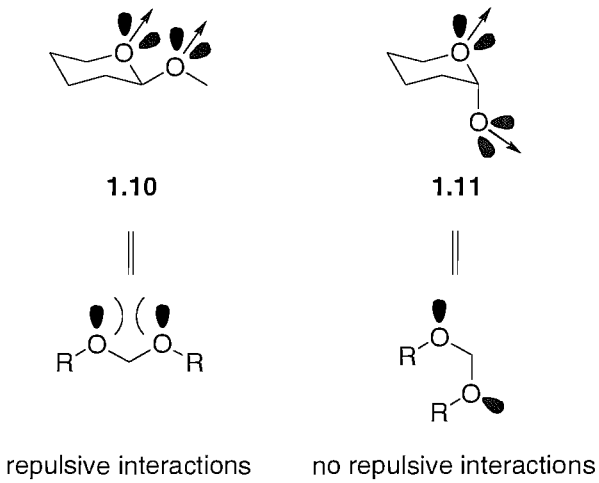


Figure 3

However, this model does not explain an observed difference in bond lengths in axially substituted pyrans. When an electronegative substituent exists in the favoured axial conformation the C-X bond (where X is the electron withdrawing substituent) is significantly shortened and the adjacent C-O bond is shortened.[18] This effect is not observed when the substituent occupies an equatorial position. To account for these effects, an alternative explanation for the anomeric effect has been proposed. In this model, the axial conformation (**1.13**) is stabilised by delocalisation of an electron pair of the oxygen atom to the antiperiplanar C-X anti-bonding orbital (Figure 4).[19,20]

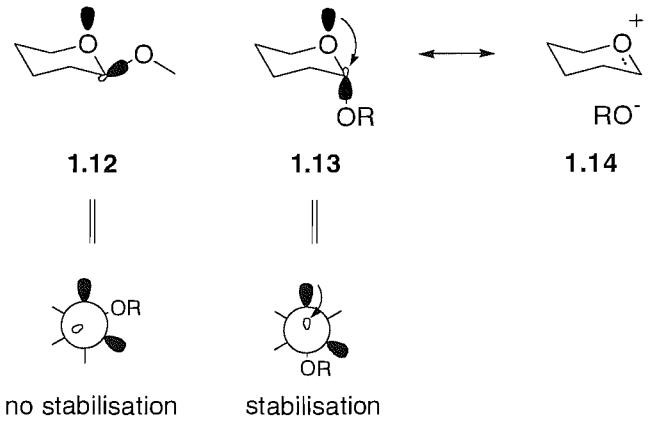


Figure 4

1.2 FLUORINE AND FLUOROALKYL CHEMISTRY

Fluorine plays a key role in recent pharmaceutical, agrochemical and material sciences.[21,22] As the incorporation of fluorine and/or fluorine containing groups into a molecule often drastically alters the chemical, physical and biological properties of the compound,[23-26] it is thought that synthesis of desired fluorinated compounds should lead to the invention of novel agents.[27]

While the effects of fluorinated substituents on reactive intermediates (carbocations, carbanions, carbenes and free radicals) are fairly well understood, the effects on physical properties - important to compound binding, adsorption and transport are difficult to predict.

Below are outlined some of the properties of fluorine itself and a brief outlining of some its effects when present in organic molecules.

1.2.1 Atomic physical properties

The unique behaviour of fluorinated systems is attributed to the atomic properties of fluorine itself. Its high electronegativity (4.0 on the Pauling scale) and small van de Waal's radius (1.47 Å) lead to an increase in oxidative, hydrolytic and thermal stability (the C-F bond averages 116 kcal/mol).

1.2.2 Lipophilicity

Incorporation of fluorine into a given molecule is expected to greatly increase its lipophilicity, though this is not always the case. When aromatic fluorination has taken place, there is always an observed increase in lipophilicity,[28,29] and whilst per/polyfluorination increase lipophilicity, monofluorination and trifluoromethylation of

saturated alkyl groups can actually decrease lipophilicity. This is a direct consequence of the strongly polarized nature of C-F and C-CF_3 bonds.

1.2.3 Acidity and basicity

With its highly electronegative nature (fluorine is always inductively electron withdrawing, but can be electron donating by resonance), fluorine can be expected to play a significant role in altering the acidity and basicity of any system it is introduced into. Whilst β-fluorination always increases C-H acidity, α-fluorination is less acidifying than α-halogenations due to donation of a lone pair of electrons from fluorine itself. A further effect of the electron withdrawing nature of fluorine or fluoroalkyl groups is the increase in hydrogen bond acidity observed in molecules with the prerequisite functionalities.

1.2.4 Hydrogen bonding

The fact that C-F bonds are lipophilic, and their effects on acidity, basicity and proximal heteroatom H-bonding are now well known, the importance of C-F bonds in hydrogen bonding has been intensely debated over the last decade. Whilst polar fluorinated hydrocarbons can act as hydrogen bond acceptors in the gas phase,[30] generally, hydrogen bonding to C-F is not observed in solution with polar solvents.[31] The reasoning behind this fact is that while the polar C-F bond can interact with ionic or permanent dipolar groups through electrostatic interactions, time-dependent interactions (dipole-induced dipole etc.) are not as favourable for the non-polarizable C-F bond as they are for solvent heteroatoms.

The H-bonding observed in the gas phase shows that C-F dipolar interactions are possible in the absence of competing heteroatoms. This leads to the possibility that in the solid state or highly organized macrocyclic systems C-F bonds can participate in strong dipolar interactions.[32,33]

1.2.5 Fluorine steric effects[34]

Originally, Pauling determined the van de Waal's radius for fluorine to be 1.35 Å, close to that of an H atom (1.20 Å). This has resulted in many reports where it is claimed that fluorine is nearly the same size as hydrogen. This statement was proved incorrect when the van de Waals's radii for these two atoms were recalculated more recently (Table 1). This has meant that there are now fewer reports citing the "isosteric" nature of fluorine and hydrogen, though some confusion about the steric size and steric effects of fluorine and fluorinated groups still exists.

	Pauling	Bondi[35]	Williams and Houpt[36]
H	1.20 Å	1.20 Å	1.15 Å
F	1.35 Å	1.47 Å	1.44 Å
O	1.40 Å	1.52 Å	1.44 Å

Table 1

What these new data did reveal, was that fluorine was a more than satisfactory isostere for oxygen. When this similarity in atomic radii is expanded to include a comparison of the size of common oxygen functional groups several interesting conclusions can be drawn (Table 2).

Bond	Length (Å)	van de Waal's radius (Å)	Total size (Å)
C-F	1.35	1.47	2.82
C=O	1.23	1.50	2.73
C-O-H	1.43	1.52	2.95

Table 2

What can be seen is that C-F is an excellent match for C=O and slightly smaller than C-OH. To attempt to find a better steric match for the C-OH group a comparison with relative size of the *gem*-difluoromethylene group can be made (Figure 5).

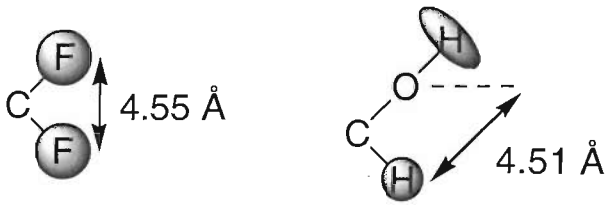


Figure 5

Although the dihedral angles are different, the spatial arrangement of the groups is very similar. From these comparisons we can conclude that, when considering only steric factors, the CF_2 group should serve as a superior substitute for C-OH compared to H-C-F a similarity which has proved especially important for fluorinated carbohydrate.

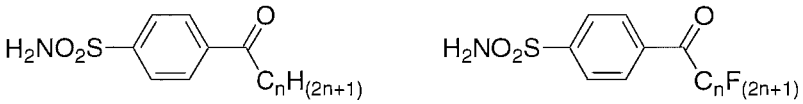
It is also worth noting that fluorination always increases the size of alkyl groups, with a trifluoromethyl group being at least as large as a hydrocarbon isopropyl group, much bigger than its hydrocarbon counterpart.

1.3 POLAR HYDROPHOBICITY

The vast biological significance of carbohydrates is well known and in Section 1.1 we listed several important roles these molecules play in the body and other biological systems. Many of these functions depend on protein-carbohydrate recognition. With the significance of protein-carbohydrate recognition, it is surprising that the binding affinities for these interactions are typically very weak. This observation can be attributed to the hydrophilic nature of carbohydrate molecules. With their large number of hydrophilic hydroxyl groups, carbohydrate molecules must undergo desolvation prior to receptor binding. This desolvation constitutes an energetic penalty to the binding, with compensation being provided by the energetically favourable formation of hydrogen bonds upon binding. This solvation/desolvation process is common to all protein binding events but in carbohydrates, due to their hydrophilic nature, it is the main energetic term and therefore is thought to be the cause of the low *binding affinity* of the interactions.[37]

This low binding affinity associated with protein-carbohydrate interactions has attracted considerable interest and one suggested approach to overcoming the problem was to incorporate hydrophobic groups into the substrate.

In contrast to hydrophilic groups, the desolvation of a hydrophobic compound is actually an entropically favourable process. This is due to the fact that water molecules solvated to an hydrophobic group will actually exist in an ordered state.[38-42] Hence, upon binding to a receptor site, the liberation of water molecules to the bulk solvent has large, positive entropy. One approach to exploit this phenomenon was developed by the group of Whitesides.[43]



1.15 **1.16**

Figure 6

In this work, the hydrophobic portion of the molecule was remote to the binding site, but the binding of the inhibitors **1.15** and **1.16** to carbonic anhydrase was directly proportional to the total surface area of the hydrophobic group. Whitesides observed greater binding affinities for fluorinated substrates compared to hydrocarbon substrates of corresponding carbon chain length. This he explained by stating that the intrinsic hydrophobicity (free energy of partioning per unit surface area) of fluorocarbons and hydrocarbons are similar but that fluorocarbons are possessed of a larger surface area than hydrocarbon units of equivalent chain length.

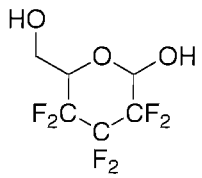
The exploitation of the hydrophobic effect to improve protein receptor affinities is now a well developed concept.[38,40,42,44,45] An evolution of this effect, coined "polar hydrophobicity",[46,47] where polar hydrophobic groups are introduced has been put forward as a possible mechanism for further improving binding affinities.

The hydrophobic nature of fluorocarbon moieties has never been in doubt.[48] What has been debated, is whether a single, polar, C-F bond can take part in strong polar interactions. The ability of fluorine to participate in hydrogen bonding in highly organized and macrocyclic systems has been generally accepted and the receptor site of a protein molecule could be considered just such an environment. Hence, the ability of the C-F bond to participate in hydrogen bonding in organised systems provides another means to improve receptor affinities. If the energetics of the binding, with respect to the solvation/desolvation of the carbohydrate molecule, can be improved, and the energetically favourable polar interactions within the receptor site can be retained, then the favourability of protein-carbohydrate binding could be significantly improved.

In carbohydrate chemistry, replacement of carbohydrate hydroxyl groups with fluorine atoms has been advanced as a way to probe receptor site structure.[49-51] The majority of this work has been carried out with selectively fluorinated deoxyhexoses, though multiply fluorinated hexose analogues have been used. These results include the preferential binding of 2-deoxy-2,2-difluoro-D-glucose to yeast hexokinase[52], and the enhanced inhibition of glycogen phosphorylase by 2-deoxy-2-fluoro-α-D-glucosyl fluoride.[50] In these examples, the mono-fluorinated derivatives had greater affinities compared to the unmodified carbohydrate and the difluorinated substrates even greater affinities than that.

The improved free energies of binding (caused by the hydrophobic nature of fluorocarbon moieties, and the ordered nature of that hydration) and the retention of enthalpically favourable dipolar interactions within the receptor site (caused by the polar nature of the C-F bond) lead to a general strategy for improving molecular recognition.

This principal of enhancing molecular recognition through manipulation of polar hydrophobicity was demonstrated particularly well by the group of DiMagno who synthesized a racemic heavily fluorinated hexose **1.17** as a probe for the concept.[46,47]



1.17

Figure 7

The rate of trans-membrane-transport across the red blood cell membrane for D-glucose and **1.17** were compared and it was found that **1.17** crossed the membrane at an approximately tenfold higher rate. DiMagno also established that this increase in transport rate was due to enhanced transport protein affinity and not the increased lipopholicity of **1.17** compared to glucose.

With the exploitation of polar hydrophobicity promising to be a valuable tool in improving molecular recognition the need for methodology to synthesize other, non-racemic fluorinated carbohydrates was obvious. The development of such methodology was to be the aim of this project.

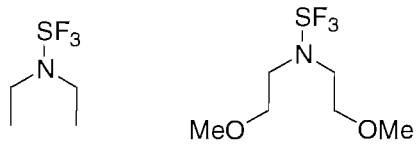
1.4 SYNTHESIS OF FLUORINATED CARBOHYDRATES

1.4.1 Methods of fluoro-organic synthesis

Due to the rarity of naturally occurring fluorine containing compounds, target organofluorine molecules are only accessible *via* organic synthesis. Unfortunately, due to the unique characteristic of fluorine, conventional synthetic methods are not always applicable.

There are two main approaches to fluoro-organic synthesis: the direct fluorination method and the building block approach[53]. Fluorination involves C-F bond formation through the transformation of C-H or a functional group by treatment with a fluorinating

agent such as F_2, HF, DAST, Deoxofluor (Figure 8) or one of many other derivatives. While this method can be useful when incorporating one or two atoms of fluorine into a molecule, incorporation of a higher degree of fluorination by this methodology is inefficient with reactions being unreliable and low yielding. Additionally, the handling of these reagents is far from trivial with special apparatus and techniques required due to their extreme reactivity and toxicity.



DAST (**1.18**) Deoxofluor (**1.19**)

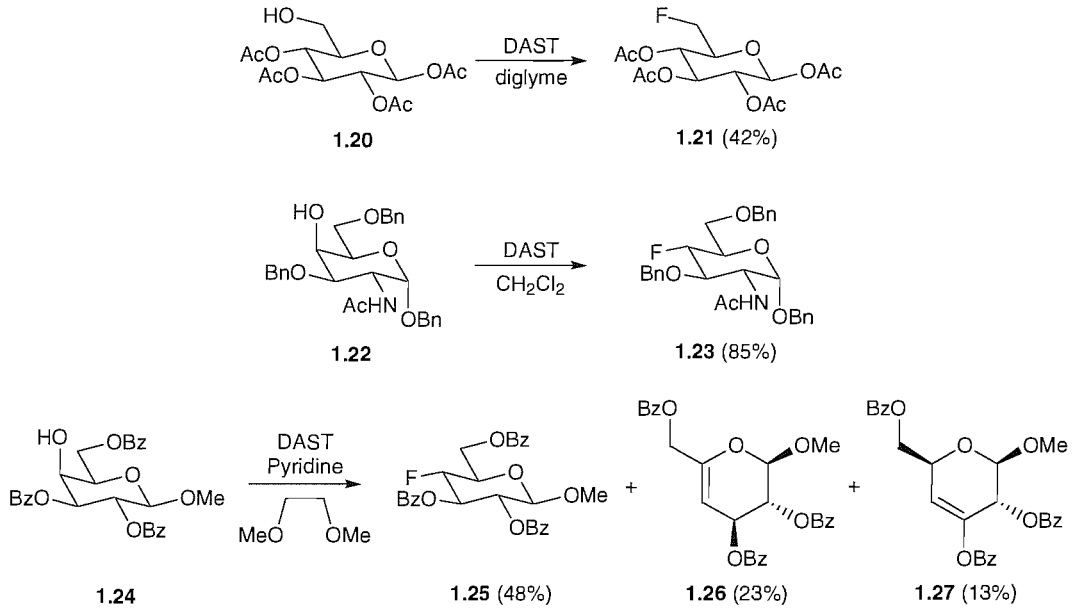
Figure 8

The building block approach involves appropriate transformations starting from small, commercially available, fluorinated molecules. These molecules allow the use of traditional synthetic methodologies, though results are not always as expected, providing a significant challenge to the chemist. This method also facilitates the synthesis of heavily fluorinated molecules, though building blocks with a high degree of fluorination are often expensive.

The synthesis of fluorinated carbohydrates has, in the past, used both methods with great success. There are an enormous variety of fluorinated carbohydrate structures, and for the sake of brevity we shall limit the scope of our discussion to carbohydrates where one or more hydroxyl group has been replaced with a fluorine atom or fluorine atoms. For more information on carbohydrate structures bearing *C*-difluoromethylene, *C*-trifluoromethyl and *C*-perfluoroalkyl substituents and see the review of Portella.[54]

1.4.2 Synthesis of mono-fluorinated carbohydrates

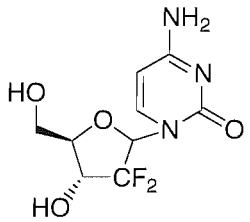
Due to the considerable research that has gone into protecting group strategies in carbohydrate synthesis,[55] and the relative ease of fluorination reactions when substituting only a single fluorine atom , mono-fluorinated monosaccharides are almost exclusively synthesised by fluorination methods (Scheme 1).[56]



Scheme 1

The syntheses of **1.21**[57] and **1.23**[58] proceed smoothly, although in the case of **1.21** in poor yield. The synthesis of **1.25** illustrates the problems inherent in the fluorination method. A poor yield of the desired compound resulting from elimination reactions leading to **1.26** and **1.27**.[59]

1.4.3 Synthesis of gem-difluoromethylene containing carbohydrates

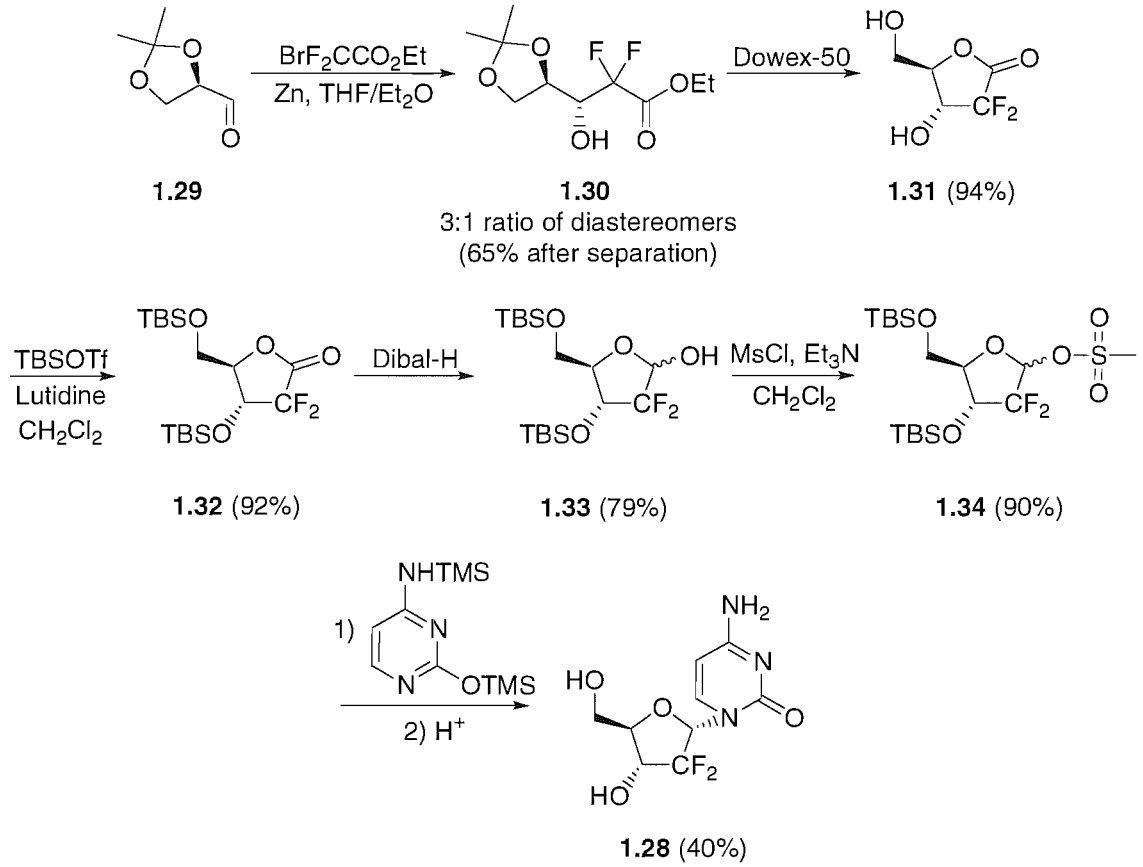


Gemcitabine (**1.28**)

Figure 9

The synthesis of gem-difluoromethylene containing compounds is a particularly well-studied area with many methods available to synthesize these compounds.[60] The synthesis of *gem*-difluoromethylene containing carbohydrates is a less well explored area but has produced one of the most exciting fluorinated molecules to emerge in recent years; Gemcitabine (**1.28**) (Figure 9).

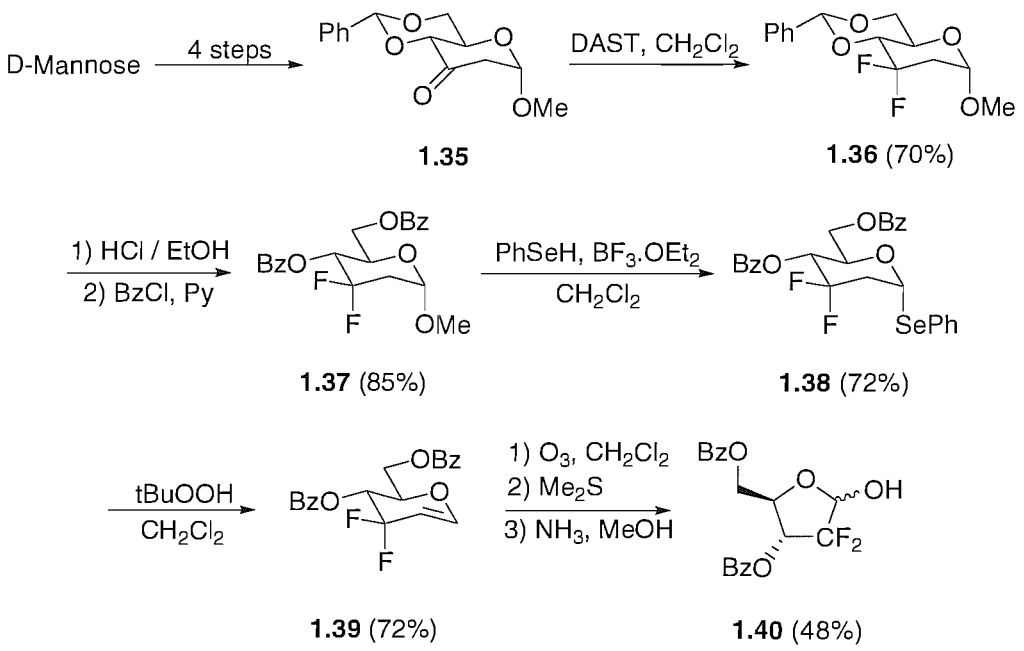
Gemcitabine was first synthesized by the group of Hertel[61] and has since shown great efficacy in the treatment of solid tumours.[62] To install his gem-difluoromethylene functionality, Hertel used a Reformatsky type reaction between 2,3-*O*-isopropylideneglyceraldehyde (**1.29**) and the widely used fluorinated building block ethyl bromodifluoroacetate (Scheme 2).



Scheme 2

The use of Felkin-Anh stereoselectivity in conjunction with the incorporation of a fluorinated building block illustrates the potential advantages of a building block approach to this class of compounds, though in this case the stereoselectivity obtained is only moderate. The subsequent functionalisation of **1.30** to **1.28** was accomplished using traditional methods, with the fluorine atoms not significantly complicating the synthesis until incorporation of the nucleobase. This required much more forcing conditions than usual due to the lack of anchiomeric assistance and the destabilising effect of the fluorine atoms with respect to nucleophilic substitution..

To compare the procedure of Hertel's with a fluorination approach we can turn to the work of Castillón, who has reported a formal synthesis of Gemcitabine from both D-glucose and D-mannose (Scheme 3).[63]

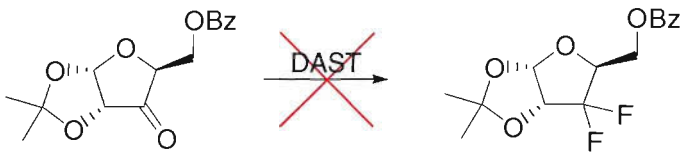


Scheme 3

Conversion of D-mannose to the ulose **1.35** is accomplished *via* a literature procedure,[64] after which difluorination with DAST furnishes the difluorosugar **1.36**. Another reaction of note is the oxidative conversion of **1.38** to the glycal **1.39**; this was to be of particular interest in our own research (Section 5.2.1). With Castillón's procedure using a starting material from the chiral pool it avoids the stereoselectivity issues seen in Hertel's synthesis. However, the use of DAST is undesirable due to the difficulty in handling the reagent and because the reactions that use this material frequently produce poor yields and a wide range of by-products. In fact the Castillón was forced to use D-mannose as a starting material was that the treatment of methyl riboside-2-ulose with DAST only gave degradation products.[63] Since this work Castillón has further expanded the scope of the methodology to synthesize pyranosyl nucleoside analogues of Gemcitabine.[65]

Whilst 2-deoxy-2,2-difluorosugars have been the centre of much research, the closely related 3-deoxy-3,3-difluorosugars have only recently been stereoselectively synthesised

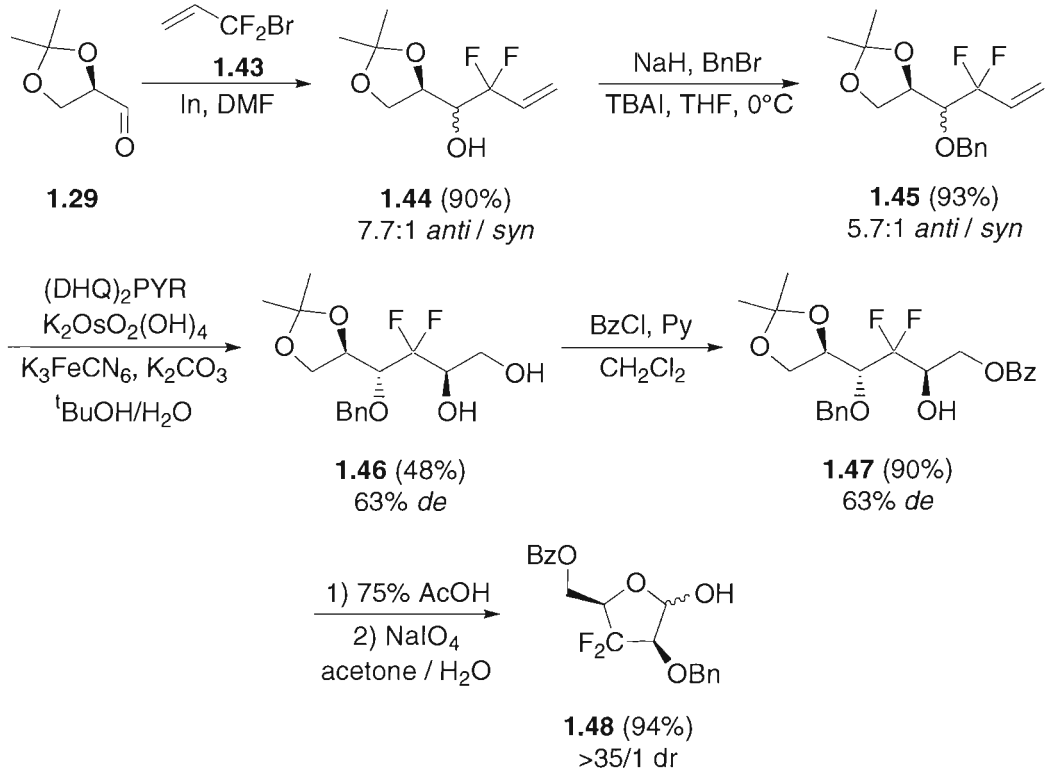
(the synthesis of 2,3-deoxy-3,3-difluoro nucleosides has been reported but yields are low).[66,67]



1.41 **1.42**

Scheme 4

The lack of published research in this area is supposed to be due to the difficulty in fluorinating hindered five-membered cyclic ketones such as **1.41**. In fact in the only example of difluorination of an α.α′-*trans*-disubstituted five-membered cyclic ketone, the carbonyl group is relatively unhindered and yet still the yield is low (25%).



1.29

1.44 (90%)
7.7:1 *anti* / *syn*

1.45 (93%)
5.7:1 *anti* / *syn*

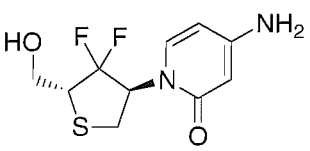
1.46 (48%)
63% *de*

1.47 (90%)
63% *de*

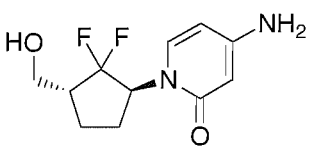
1.48 (94%)
>35/1 dr

Scheme 5

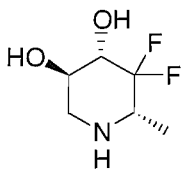
During the course of our research the synthesis of 3-deoxy-3,3-difluoro-D-arabinofuranose **1.48** was reported by Qing *et al* and there are several features of interest (Scheme 5).[68] First we see a problem similar to that discussed with the building block approach to Gemcitabine, namely the stereoselectivity upon introduction of another popular fluorinated building block, 1-bromo-1,1-difluoropropene (**1.43**). In this case this problem is exacerbated by epimerization during the basic benzylation of **1.44**. Again, this epimerization is of particular interest for reasons to be discussed in section 3.1.1. Another step which drew our attention to this particular synthesis is the use of an asymmetric dihydroxylation on a terminal, α-fluorinated alkene (Chapter 2 for further discussion). The group of Qing have been particularly active in this field in recent years and have accomplished the synthesis of several interesting molecules (Figure 10) including, 2,3-dideoxy-6,6-difluoro-3-thionucleosides (**1.49**),[69] 2,3-dideoxy-6,6-difluorocarbocyclic nucleosides (**1.50**)[70]and *gem*-difluoromethylated azasugars (**1.51**).[71]



1.49



1.50

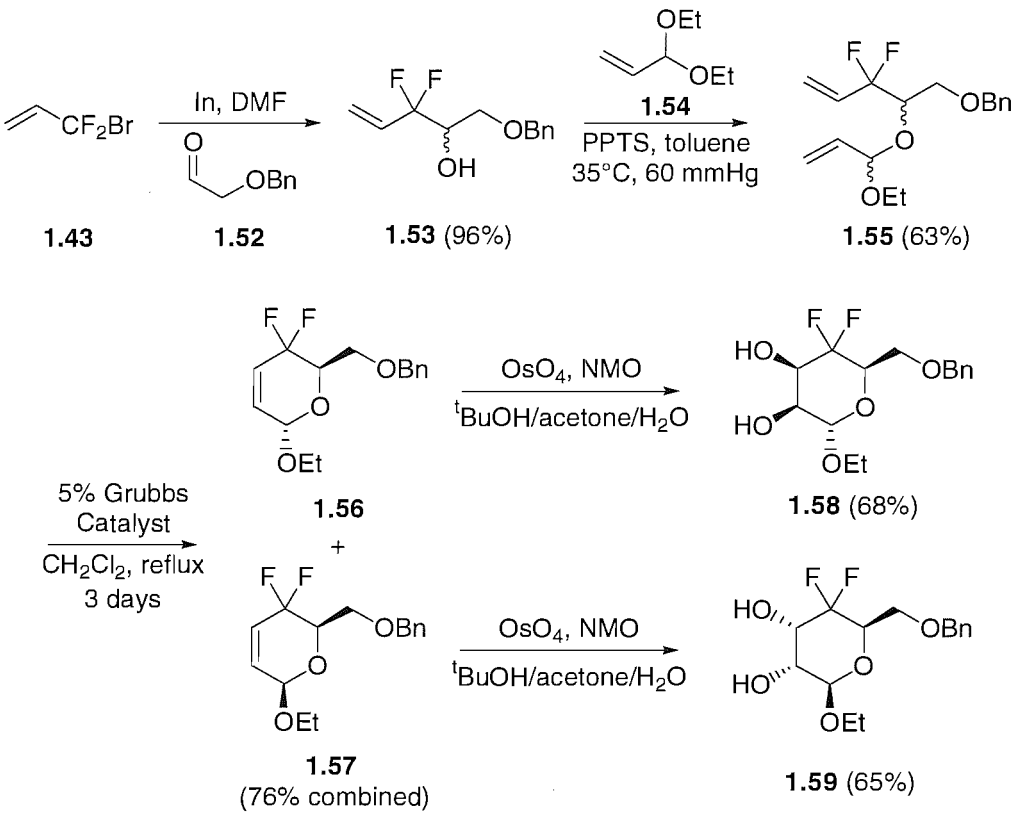


1.51

Figure 10

The interesting feature of both **1.49** and **1.50** is that the 6,6-difluoromethylene group has been suggested as an isopolar isostere for the ring oxygen present in non-carbocyclic carbohydrates,[72-74] a property which may be investigated within our own group in the future.

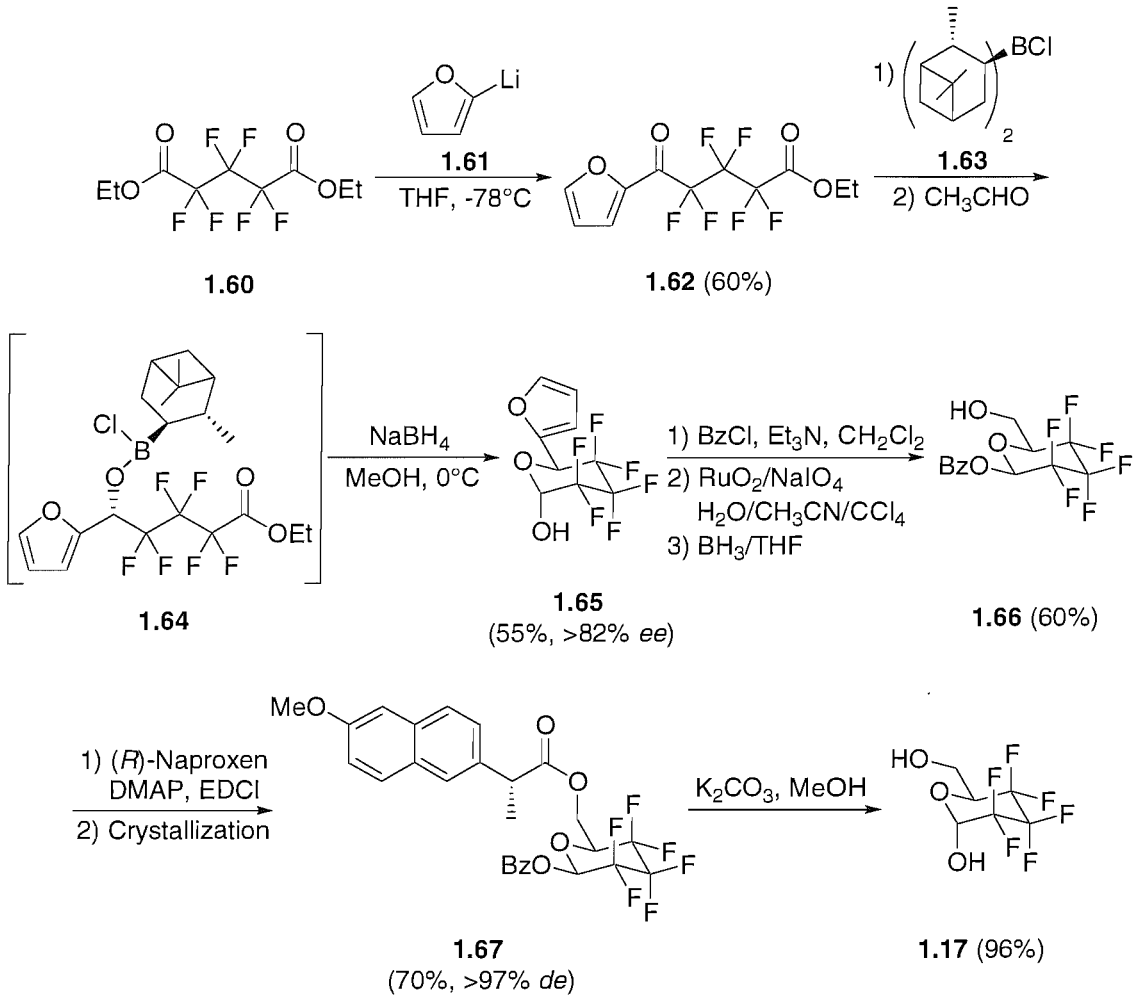
As a final example, Percy has recently disclosed a synthesis of 4,4,difluoroglycoside *via* a ring-closing metathesis reaction (Scheme 6).[75]



Scheme 6

The use of RCM with a α-fluorinated alkene is worthy of note, as metathesis reactions with this class of substrate remain rare. This synthesis makes good use of the building block approach, with the introduction of the fluorinated moiety being high yielding, though unfortunately, racemic. Again, the dihydroxylation of a α-fluorinated alkene was of particular interest to us, especially as it is completely diastereoselective.

1.4.4 Synthesis of carbohydrates bearing an internal perfluoroalkanediyl fragment (IPF)



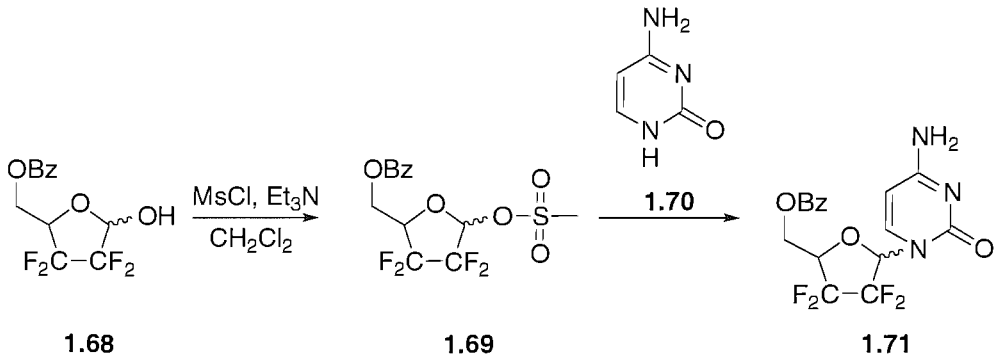
Scheme 7

Synthesis of compounds bearing *internal* perfluoroalkanediyl fragments(IPF's) is still comparatively rare,[46,47,76-78] with the synthesis of IPF bearing carbohydrates and nucleosides being an almost unexplored area. In fact, the only examples found by the author were those reported by the group of DiMagno.[46,47,76] Initially DiMagno disclosed only a racemic synthesis of the hexafluoropyranose **1.17**, but has more recently published, an improved, enantioselective synthesis (Scheme 7).

The enantioselective synthesis of **1.17** begins with the attack of furanyl lithium on diethyl hexafluoroglutarate to yield ketone**1.62**. Enantioselective reduction followed by

borohydride reduction yields the hemi-acetal **1.65**. Whilst the enantioselectivity of this reaction is acceptable, the product is further enantioenriched by means of a resolution with Naproxen later in the synthesis.

DiMagno has also disclosed the only example of an IPF containing nucleoside. This is synthesised by a method analogous to that shown in Scheme 7 but with the required tetrafluorinated diethyl tartrate. This gave the tetrafluoropentose **1.68** which could then be converted to the nucleoside **1.71** in two steps as shown in Scheme 8.



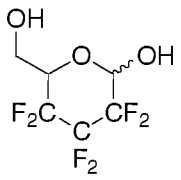
1.68 **1.69** **1.71**

Scheme 8

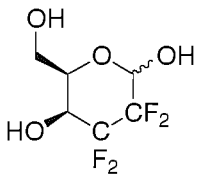
These syntheses, whilst they target molecules of great interest to us, are non-selective, with enantioselectivity coming through resolution procedures, they are also considerably longer than is desirable for such small molecules. These factors, and the interesting impact of IPF incorporation on receptor affinity discussed above, illustrate the need for a short, enantioselective methodology with wide scope to allow the synthesis of such modified carbohydrates.

1.5 SYNTHETIC TARGETS AND RETROSYNTHESIS

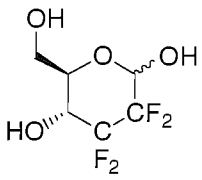
Whilst the exploitation of polar hydrophobicity as a means to improve carbohydrate-protein binding affinities is of great interest, the scope of the investigations is limited by the scarcity of polyfluorinated carbohydrates available.



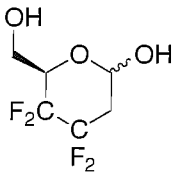
1.17



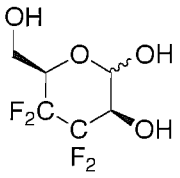
1.72



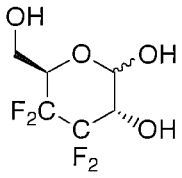
1.73



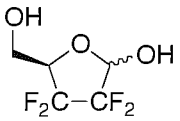
1.74



1.75



1.76

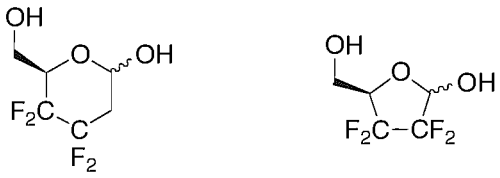


1.77

Figure 11

DiMagno's synthesis of **1.17** provided valuable insight as to the efficiency of improving receptor affinity through fluorination. However, by replacing 3 hydroxyl groups the potential for selectivity in binding is greatly reduced. As hydrogen bonds are highly directional, the orientation of O-2, O-3 and O-4 are critical to the selectivity of protein-carbohydrate binding.[79,80] It is hoped that if at least one hydroxyl group is retained then selectivity of binding will be possible, whilst still improving receptor binding affinities. In structures **1.72**, **1.73**, **1.75** and **1.76** a tetrafluoroethylidene fragment has been substituted for two of the hydroxyl groups whilst either O-2 or O-4 has been retained. These positions are key as they allow for the distinction of glucose, galactose and mannose, major components of biological saccharides. **1.74** and **1.77** are simpler structures and would serve as ideal targets when attempting to develop a methodology which could be applied to the synthesis of the more complex structures.

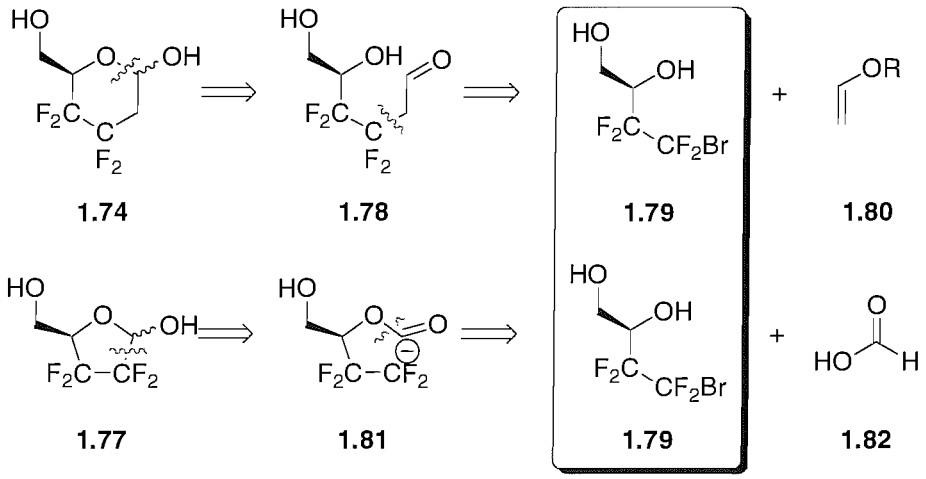
1.5.1 Retrosynthesis of ***1.74*** *and* ***1.77***



1.74 **1.77**

Figure 12

With a tetrafluoroethylidene unit the significant motif in the target molecules a method for installation of the fluorine had to be developed. Section 1.4.1 discussed the two methods available. A fluorination approach would use a reagent such as DAST or Deoxofluor to fluorinate and α-diketone. When this approach has been tried previously on simple α-diketones, yields have been low with difluorinated compounds being the major products.[81] With fluorination methods being unsuitable a building block approach was clearly preferable.



1.74 **1.78** **1.79** **1.80**

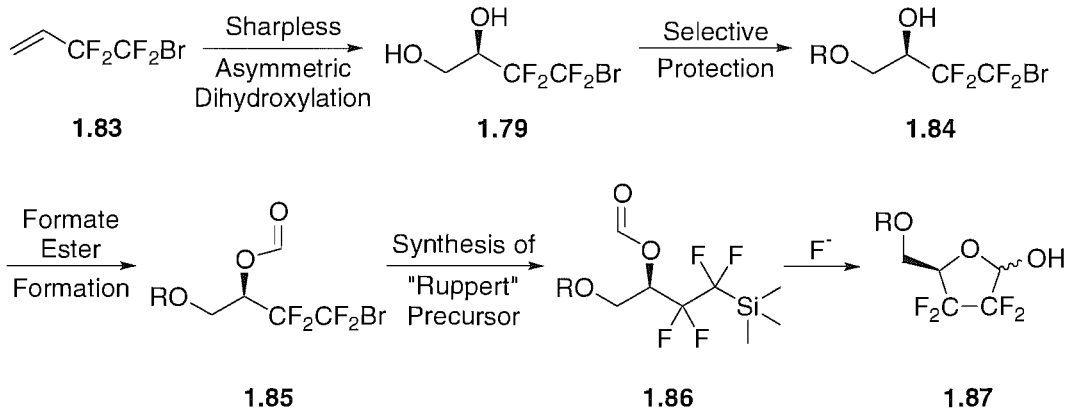
1.77 **1.81** **1.79** **1.82**

Scheme 9

Looking at **1.74** and **1.77** there are two clear disconnections. Disconnection of the O-CH bond in both molecules is a reasonable strategy as these bonds are simple to form using traditional synthetic methods.[82] CF_2-C bond disconnection is also a clear choice as these

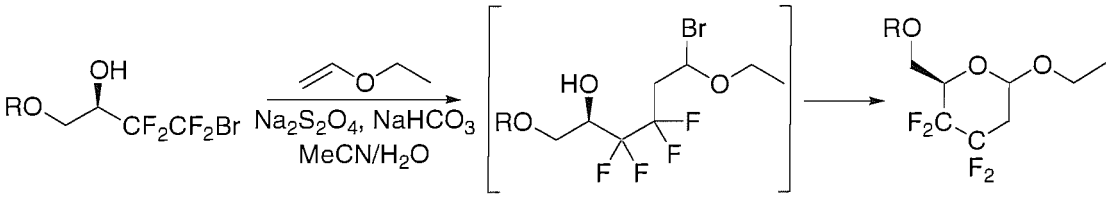
bonds can be formed by several different methods known in fluoro-organic chemistry. Disconnection of these two bonds leads to a 1,2-diol **1.79**. This chiral diol should be accessible from a Sharpless asymmetric dihydroxylation[83] (AD) of the commercially available alkene **1.83**.[84]

*1.5.2 Planned Synthesis of **1.74** and **1.77***



Scheme 10

AD of **1.83** should lead to the 1,2-diol **1.79**. A key section of the project will be to ensure a good enantioselectivity for this transformation. For the diol **1.79** to be synthetically useful to us as an intermediate we must differentiate the two hydroxyl functions. This will be accomplished *via* a selective primary protection to yield **1.84**, the common intermediate for the synthesis of **1.74** and **1.77**. A DCC mediated coupling of **1.84** with formic acid will form the O-CH bond disconnected in the retrosynthetic analysis. Cyclisation of **1.85** to the desired tetrafluorinated pentafuranose **1.87** will be accomplished *via* either a Ruppert reaction[85,86] or Li-Br exchange/cyclisation sequence.

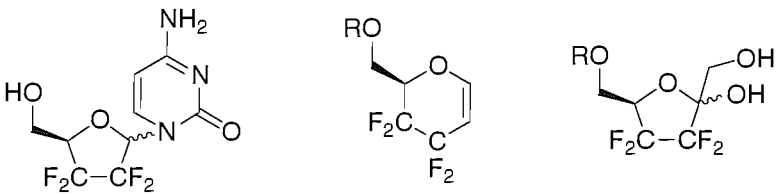


1.84 **1.88** **1.89**

Scheme 11

For the synthesis of the tetrafluorinated hexapyranose **1.89** treatment of the common intermediate **1.84** with ethyl vinyl ether under known fluororalkyl radical generating conditions should lead to the α-bromoether **1.88**. It was hoped that this will spontaneously cyclise to form the target molecule **1.89**.

When a satisfactory methodology for the synthesis of **1.87** and **1.89** has been developed, attention shall be turned to their functionalisation and broadening the scope of the methodology (Figure 13), with particular attention paid to the synthesis of a tetrafluorinated nucleoside (**1.90**).[87]



1.90 **1.91** **1.92**

Figure 13

2.0 THE SHARPLESS AD OF 4-BROMO-3,3,4,4-TETRAFLUOROBUT-1-ENE

2.1 INTRODUCTION

In Section 1.5.2 the planned synthesis of **1.77** was outlined. The first step in this synthesis was the enantioselective dihydroxylation of the fluorinated building block 4-bromo-3,3,4,4-tetrafluorobut1-ene (**1.83**).[84] In this section we shall outline our attempts to accomplish this transformation and subsequent optimisation of yield, enantioselectivity and confirmation of configuration..

2.1.1 The Sharpless Asymmetric Dihydroxylation (SAD)

The importance of asymmetric synthesis has grown significantly in the last two decades as its utility in the synthesis of enantiomerically pure compounds has increased. This is mainly due to the restrictions placed on the marketing of racemic pharmaceuticals, by drug regulatory bodies such as the FDA in the United States of America.

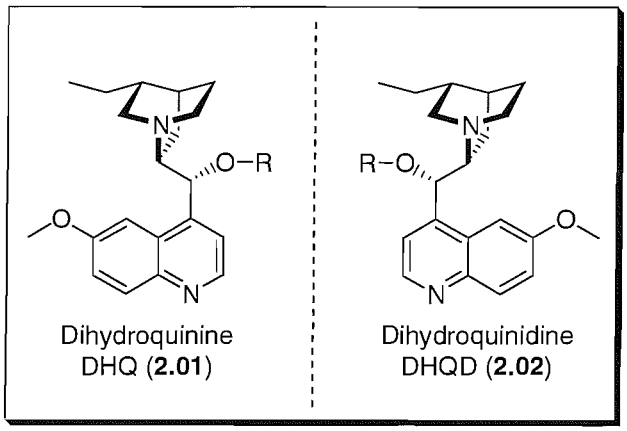
Organic chemists have to given considerable attention to existing oxidative reactions of olefins and attempted to make them enantioselective processes. The development of the Sharpless-Katsuki asymmetric epoxidation of allylic alcohols in 1980 was a major breakthrough,[88,89] not only in the oxidation of olefins but in asymmetric synthesis in general. Major advances followed, including the Sharpless asymmetric dihydroxylation,[83,90-94] the Jacobsen-Katsuki epoxidation of unfunctionalised olefins,[95-97] and the Sharpless asymmetric aminohydroxylation.[98,99]

Since the advent of the asymmetric dihydroxylation (AD) as a practically useful process,[93] it has become one of the most useful tools available to organic chemists wishing to undertake asymmetric synthesis. The reaction has wide scope, providing

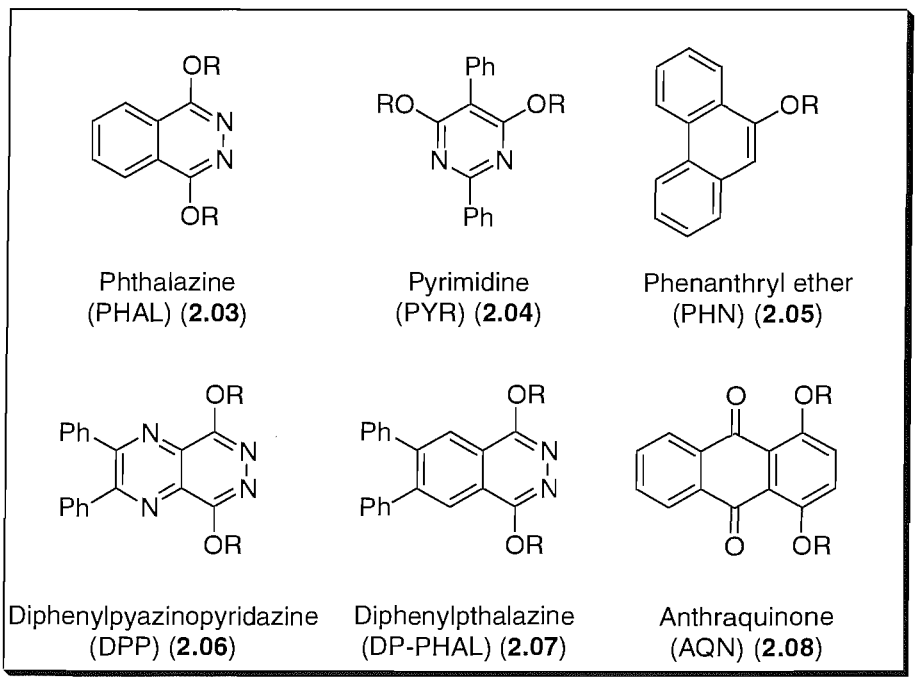
products in excellent enantiomeric excess (*ee*) whilst being catalytic in both OsO_4 and chiral ligand.

2.1.2 Ligand choice: Structure and scope

Perhaps the area in which optimisation of the SAD is most important is in the choice of chiral ligand. The ligand chosen can have a huge effect on the *ee* of the transformation, with different classes of olefin each requiring a different ligand to ensure optimal enantioselectivity.



Cinchona Alkaloid Cores



Heterocyclic Spacers

Figure 14

The first generation ligands for the AD were substituted cinchona alkaloids (e.g. **2.01** and **2.02**). It was found that variation of the cinchona core had little effect on the *ee* whilst modification of the O-9 substituent could have a dramatic effect. With this discovery, the second generation of ligands was developed; these were dimeric structures with C_2-symmetry, composed of two independent cinchona alkaloid units and a heterocyclic spacer (**2.03** to **2.08**).

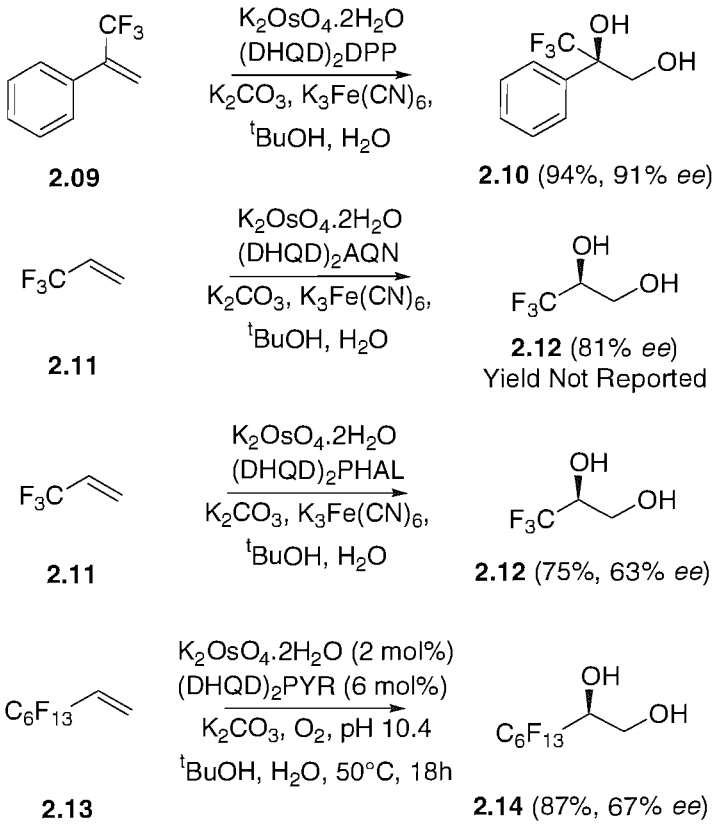
The original second generation ligands, $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ have been shown to give excellent *ee*'s with internal olefins and aromatically substituted terminal olefins such as styrene.[83,93] However, they usually give unsatisfactory results with other terminal olefins (particularly aliphatic terminal alkenes).[83,93,100] The pyrimidine (PYR) class of ligands have been found superior for sterically congested olefins and shown to be an improvement over the PHAL ligand class in the case of terminal olefins.[100] The diphenyl pyrazinopyradizine spacer (DPP) and the diphenyl pthalazine spacer (DP-PHAL) give excellent *ee's* when employed with aromatically substituted terminal olefins but are rarely used due to their commercial unavailability.[101] The first generation ligand DHQ-PHN is suggested as a ligand for terminal olefins as "*In rare situations, the phenanthryl ether ligand can provide a solution.*".[83] The anthraquinone based ligands (AQN) show superior *ee*'s for almost all olefins bearing aliphatic substituents, particularly terminal substrates.[102]

2.1.3 Osmium catalyst loading with respect to olefin reactivity

Usually the AD is performed using only 0.2 mol% of Os reagent (added either as OsO_4 or as the non-volatile $K_2OsO_4.2H_2O$) and 1 mol% of the ligand.[83] In some cases, such as stilbene, this low ligand loading can be dropped even further without adversely affecting the *ee* of the product.[103] Alternatively, it is possible to increase the amount of Os to 1 mol% while maintaining the ligand concentration. This is useful for accelerating the reaction rate of relatively unreactive olefins.[83] This could solve the anticipated reactivity problem with using the AD reaction to form **1.79**. OsO_4 is an electrophilic reagent, and

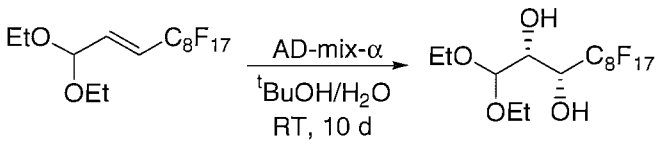
hence, the rate of osmylation of electron deficient olefins can be very slow. The electron withdrawing effect of the 4 fluorine atoms in **1.83** will lead to the alkene being very electron poor, and hence particularly unreactive under standard AD conditions. This increased loading of OsO_4 has been shown to be effective when applied to α,β-unsaturated carbonyl compounds, another class of compounds with electron poor olefins.[104] Another possibility is the addition of 1 equivalent of $MeSO_2NH_2$. This additive is usually added to the AD reaction as it greatly increases the rate of osmium glycolate hydrolysis, increasing the rate of the reaction by as much as 50 times.[93] However, this additive is not normally recommended for terminal olefins, and in some cases is reported to slow the reaction.[93]

2.1.3 AD of fluorinated olefins[105]



Scheme 12

At the outset of our research, literature precedent for the AD reaction on α-polyfluorinated alkenes was scarce and in most cases the fluorine substitution is limited to a trifluoromethyl group (Scheme 12). Sharpless used the AD reaction in his synthesis of a Mosher's acid precursor **2.10** starting from α-trifluoromethyl styrene.[106] His reaction time is extended over normal AD reactions though **2.10** is yielded in an excellent *ee* of 91% using $(DHQD)_2DPP$. In a later paper he reports the AD of 3,3,3-trifluoropropene **2.11**, a substrate more similar to ours, where diol **2.12** is obtained in 63% *ee* using $(DHQD)_2PHAL$, before recrystallisation to enantiopurity.[107] This *ee* was later improved to 81% when $(DHQD)_2AQN$ was used.[102] Beller has reported the dihydroxylation of **2.13** using O_2 as co-oxidant and $(DHQD)_2PYR$ as ligand, acheving a 67% *ee*.[108] When the anthraquinone based ligand is used a decreased 45% *ee* is observed. The need for a much increased loading of Os and increased temperature are good indicators of the unreactive nature of polyfluorinated alkenes.

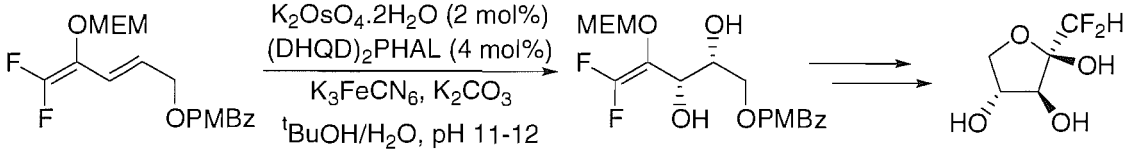


2.15 **2.16** (63%, 90% *ee*)

Scheme 13

Li et al synthesised a range of internal diols from perfluoroalkylacrolein diethyl acetals such as **2.15**.[109] He found that even when the quantity of AD-mix used was doubled, the reaction still took 10 days to give even moderate conversions. He did however, report the excellent *ee's* typical for *trans*-disubstituted alkenes.

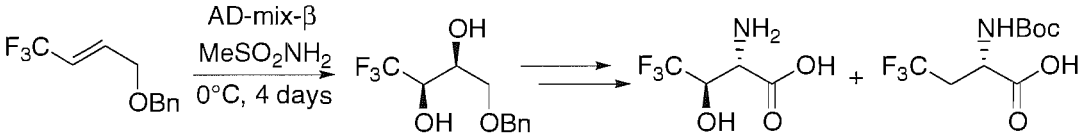
During the course of our research, several interesting approaches to fluorinated compounds *via* AD reactions were reported. Percy *et al* have reported the selective AD of a difluorinated diene **2.17** (Scheme 14) in which he found, again, that the rate of dihydroxylation was extremely slow (70-85% in 1 week).[110] Percy found that by using a procedure whereby the pH of the reaction is maintained between 11-12[111] the reaction could be driven to completion in only 1h.



2.17 **2.18** (54%) **2.19**

Scheme 14

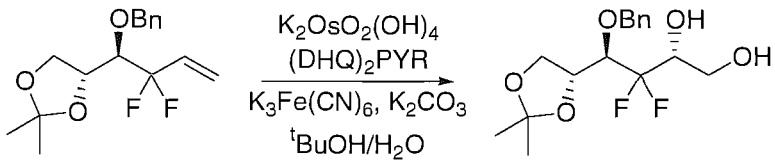
The group of Qing has made good use of the AD reaction in the synthesis of several fluorinated molecules.[112,113] The dihydroxylation of **2.20** (Scheme 15) was used in the synthesis of several fluorinated amino acids. Once again, the slow reaction is noted, though after 4 days he reports an excellent 95% yield and 93% *ee*.



2.20 **2.21** (95%, 93% *ee*) **2.22** **2.23**

Scheme 15

Qing has also used the AD of **1.45** to synthesize 3-deoxy-3,3-difluoro-D-arabinofuranose.[68] Here, using the procedure outlined by Sharpless et al in his AD of **2.11**,[107] Qing reports an average yield and diastereomeric ratio. His use of the $(DHQ)_2PYR$ ligand shows the suitability of this ligand for terminal fluorinated alkenes such as our building block **1.83**.

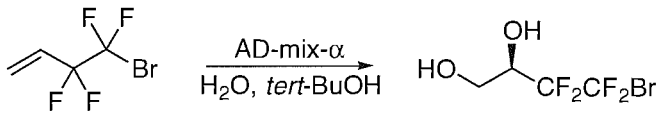


1.45 **1.46** (61%, 4.4:1 dr)

Scheme 16

2.2 SHARPLESS AD OF **1.83**

2.2.1 Yield Optimisation



1.83 **1.79**

Scheme 17

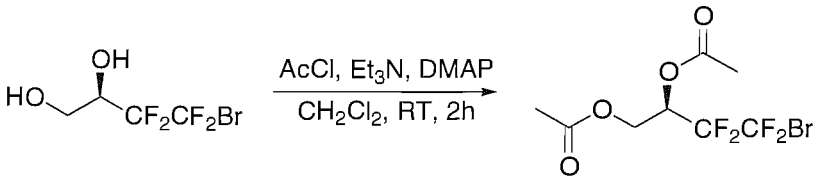
The first step in the synthesis of our common intermediate **1.84** is the AD of 4-bromo-3,3,4,4-tetrafluorobut-1-ene **1.83**. The first attempts at this reaction followed a literature precedent where a AD-mix recipe which corresponds to double the recommended amount of commercially available AD-mix is used to overcome the unreactive nature of fluorinated alkenes.[109] Reactions left for 24 hours at 4 °C yielded only trace amounts of **1.79**. An extension in reaction time to 6 days at the same temperature gave **1.79** in reasonable yields (47-76%) although problems with removal of *tert*-BuOH from the crude product (it was initially feared that the product was volatile) rendered much of the information gleaned from these early results questionable. A procedure in which the majority of *tert*-BuOH was removed from the crude product by fractional distillation before column chromatography resulted in the isolation of **1.79** in improved purity and enabled proper optimisation of the reaction. Initially we turned our attention to improving the yield of this transformation.

Commercial AD-mix cocktails, when used at the recommended levels of 1.4 g $mmol^{-1}$, gives 0.4 mol% of OsO_4 and 1 mol% ligand.[83] Hence, when using almost double the recommended amount (3.0 g $mmol^{-1}$), this corresponds to an Os loading of 0.8 mol% and 2 mol% ligand. However, **1.83** is such an unreactive substrate that even this, higher, loading of Os was insufficient to force the reaction to completion. Even after 18 days under the above conditions **1.79** was isolated in only 74% yield. An in house AD-mix formulation that when used at the 3.0 g $mmol^{-1}$ level gave an Os loading of 2 mol% was

trialled, and gave the desired product in consistently high yields (91-98%) after 7 days, although the product was usually contaminated with *tert*-BuOH and other trace impurities. Whilst this procedure resulted in a much improved rate and yield, it also uses double the normal quantity of $K_2Fe(CN)_6$ and K_2CO_3. This was undesirable due to the difficulty in dissolving all this material in the reaction mixture and due to increased cost.

As noted above, the amount of AD-mix used in the AD reaction is usually 1.4 g $mmol^{-1}$.[83] To lower the quantity of $K_3Fe(CN)_6$ and K_2CO_3 used it was decided to return to this loading whilst retaining the higher level of osmium. To achieve this, another AD formulation was developed, one in which the standard 3 equivalents of $K_3Fe(CN)_6$ and K_2CO_3 were present, but where the loading of chiral ligand and osmium were at an elevated level. This reaction yielded an excellent 93% of **1.79** after 9 days.

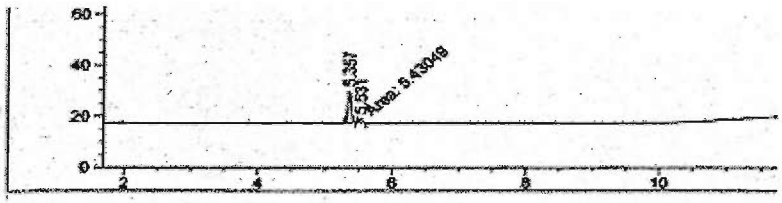
2.2.2 Determination of the enantioselectivity



1.79 **2.24** (83%)

Scheme 18

At this juncture, we made our first attempted to determine the enantioselectivity of the dihydroxylation of **1.79**. The standard method for *ee* determination of 1,2-diols is either the chiral HPLC analysis of bis-benzoate derivatives or NMR/GC analysis of the bis-Mosher's esters. In our case the bis-benzoate derivatives were found to be unsuitable for analysis by available chiral HPLC methods. Mosher's acid and it's corresponding acid chloride are prohibitively expensive, so we desired a more economical alternative. Fortuitously, comparison of the bis-acetate of both racemic and enantioenriched **2.24** by chiral GC (Chiradex G9511-16) was found to give satisfactory results and became the preferred method (Scheme 18 and Figure 15).



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	5.357	BB	0.0503	41.14046	12.39569	88.33933
2	5.531	MM	0.0557	5.43049	1.62436	11.66067
Totals :				46.57094	14.02004	

= 78% ee

Figure 15

2.2.3 Optimisation of the enantioselectivity – Ligand Screening

After the analysis outlined above, the AD reaction utilising 3.0 g $mmol^{-1}$ of the commercial AD-mix (equivalent to 0.8 mol% Os and 2.0 mol% ligand) was shown to give an *ee* of 50% (entry 1). The AD reaction utilising 1.4 g $mmol^{-1}$ of the in house AD-mix (equivalent to 2 mol% Os and 2 mol% ligand) gave **1.79** in 54% *ee* (entry 2). As both of these reactions used the $(DHQ)_2PHAL$ ligand which does not generally yield terminal diols in high *ee* it was decided to screen the other commercially available ligands.

Entry	Ligand	Loading (mol %)	OsO_4 (mol %)	Temp (°C)	Time (d)	Yield (%)	*ee* (%)
1	$(DHQ)_2PHAL$	2	0.8	4	18	74	50
2	$(DHQ)_2PHAL$	2	2	4	7	98	54
3	$(DHQ)_2PYR$	2	2	4	9	93	78
4	$(DHQ)_2AQN$	2	2	4	7	76	56
5	$(DHQ)_2PYR$	10	2	4	9	96	81

Table 3

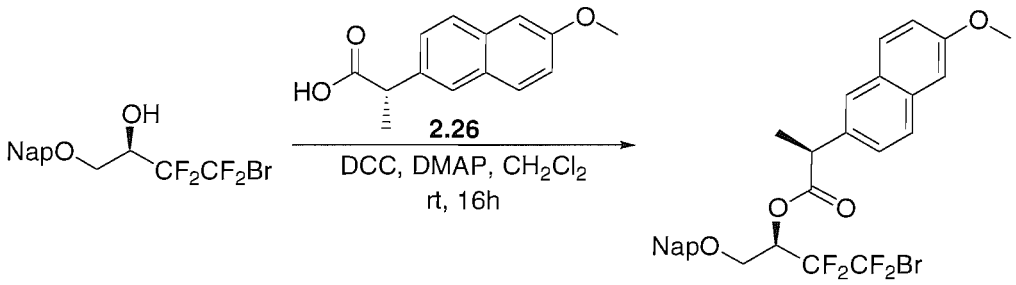
Sharpless, during the continuing development of the AD reaction has described several different ligands and the properties of these were discussed earlier (Section 2.1.2). $(DHQ)_2AQN$, the ligand expected to give the best result (based on the 81% *ee* achieved when used in an AD with 1,1,1-trifluoropropene)[102] gives only a 56% *ee*, a meagre improvement over the pthalazine based ligand. Another problem with the anthraquinone ligand was that though commercially available, it comes in need of considerable purification, with normally two column chromatographs required to achieve purity. $(DHQ)_2PYR$ was the only other commercially available ligand and resulted in a much improved *ee* of 78%. This result is a considerable improvement and results in a reaction which gives one of the best enantioselectivities so far reported for an AD of a fluoroalkyl substituted terminal olefin (see section 2.1.3).

2.2.4 Optimisation of the enantioselectivity – Ligand:Osmium Ratio

As can be seen from Table 3 all of the enantioselectivities established so far (apart from the 50% *ee* obtained with commercial AD-mix) arise from AD-mix formulations designed to give a 1:1 ligand:osmium ratio. The recommended ratio from early AD literature is 5:1,[83,93] this ratio can be modified with little difference to the *ee* but is reported to give small increases in ee when compared to lower ratios of ligand : osmium. However, in order to obtain this ratio, whilst maintaining our high Os loading we have to use a very high loading of chiral ligand. The problem that arises is that this large amount

of chiral ligand is not completely soluble in the reaction when conducted at 4°C and at its normal concentration. A reaction was attempted with a 2 mol% Os loading and the 10 mol% $(DHQ)_2PYR$ required to maintain the 5:1 ratio dictated by the literature. This reaction yielded **1.79** with an *ee* of 81%. Given this marginal increase in *ee*, and that dilution of the reaction to facilitate the dissolution of excess ligand would further decrease reaction rate, this unpromising line of experimentation was abandoned.

*2.2.5 Confirmation of the Absolute Stereochemistry of **1.79***



2.25 **2.27** (97%)

Scheme 19

To confirm the absolute stereochemistry of **1.79** we synthesised the chiral ester **2.27** from the primary naphthyl ether **2.25** (see section 3.2.2 for the discussion of the synthesis of these compounds) for analysis by X-ray crystallography.

X-ray crystallography of **2.27** showed that the chiral centre possesses the expected *R* configuration (Figure 16). This matches the configuration predicted by Sharpless' mnemonic system.[83]

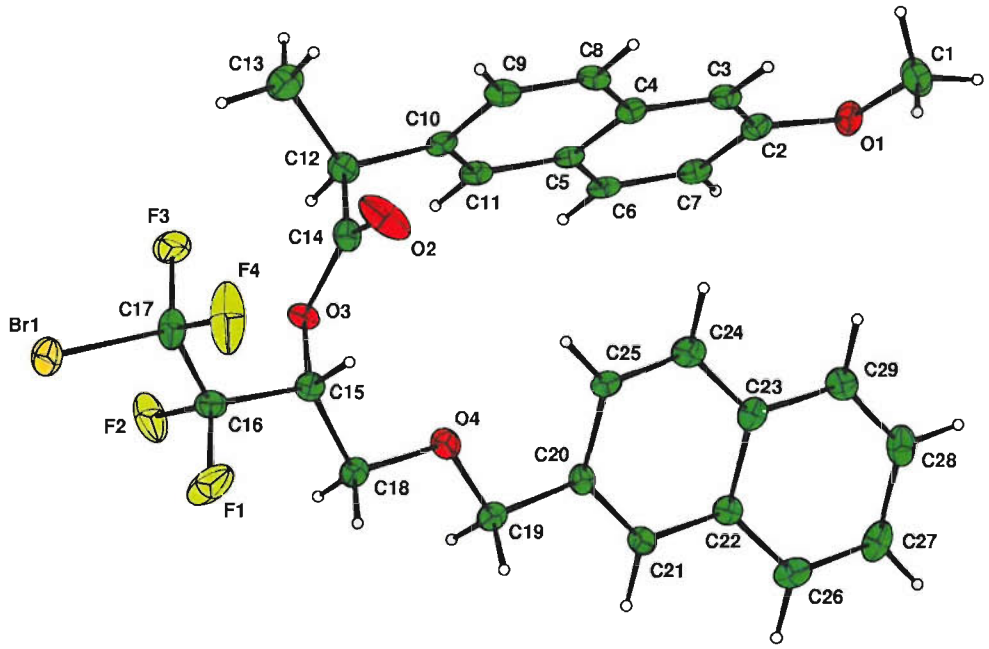


Figure 16

2.2.6 Controlling the pH during the AD of ***1.83***

It has been reported that there is a marked decrease in the pH of the reaction mixture during AD reactions, and that maintaining the pH at approximately 12 can dramatically increase the rate of reaction.[111] If the rate of the AD of **1.83** could be increased significantly, then the loading of Os could be lowered, allowing us to use higher ligand:osmium ratios, thereby providing another route to further improving the *ee*. An attempted reaction at a constant pH of 11.3 with 2 mol% Os reached 54% completion in only 10 hours, a result which may allow us to significantly shorten reaction times and possibly lower the amount of osmium used, decreasing both cost of reagents and disposal of heavy metal waste. However, the requirement that the pH of the reaction be constantly monitored and adjusted over more than 10 hours renders this unattractive and inefficient. Potential automation of this monitoring/titration procedure would be highly attractive should the equipment be available. Another possible solution that has been reported is the use of $NaClO_2$ as a co-oxidant. $NaClO_2$ yields hydroxyl ions on reduction, buffering the pH of the AD and hence greatly increasing the rate of dihydroxylation[114] without

significant effect on the *ee*. While this reaction has not been attempted it is a possible avenue for further optimisation of the AD of fluoro-olefins.

With a process in hand to provide us with **1.79** in high yield, and with the pyrimidine ligand providing a satisfactory *ee* at only a 2 mol% loading, attention turned to increasing the scale of the reaction to a point at which large quantities of **1.79** could be made in the most efficient fashion.

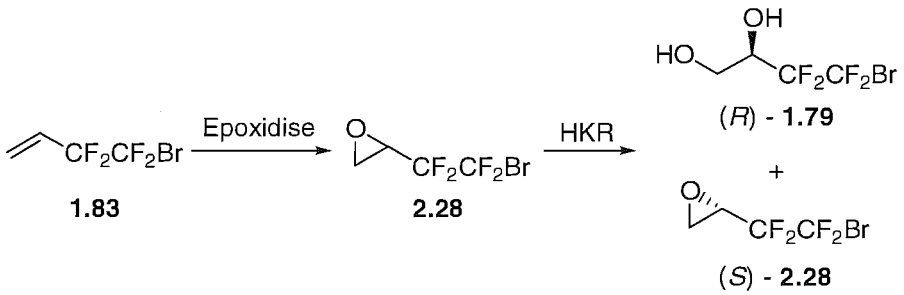
*2.2.7 Scale up of the AD of **1.83***

Given the cost of the $(DHQ)_2PYR$, a method to recycle the chiral ligand was desirable. Sharpless outlines a procedure by which the combined organic phases of the aqueous workup are extracted with H_2SO_4 (3%, aq.) saturated with K_2SO_4 (ca. 40 mL per 1 g of ligand), after which the resulting solution of ligand hydrogen sulphate salt is used directly in the next AD.[83] We found however that extraction of the organic phases with HCl (2M, aq.), neutralisation of the aqueous extracts with NaOH (2M, aq.), extraction with EtOAc, concentration and recrystallization from EtOAc was optimal. Our procedure provided easily stored and reused solid ligand without the need for readjustment of conditions in subsequent AD reactions as does Sharpless' method.

Increasing the scale of our AD reactions also highlighted issues of purification. On large scale our previous procedure of fractional distillation of the *tert*-BuOH and subsequent purification by chromatography became unwieldy. Large scale chromatography uses large quantities of solvent and silica and requires long periods of time for evaporation of eluent from the product. Therefore, a procedure by which the combined organic phases from the aqueous extraction were dried, filtered and then concentrated *carefully* under rotary evaporation was used; subsequent fractional vacuum distillation (55°C, 0.1 mm Hg) of the crude product yielded **1.79** in an excellent 93% yield (on 10 g scale) and purity without the need for chromatography.

2.3 SYNTHESIS OF **1.79** THROUGH EPOXIDATION/RESOLUTION

Whilst the AD reaction is the preferred method for asymmetric synthesis of vicinal 1,2-diols, it is by no means the only possibility. One of the most attractive alternatives, especially for terminal olefins, is the epoxidation of the olefin followed by subsequent kinetic resolution.



Scheme 20

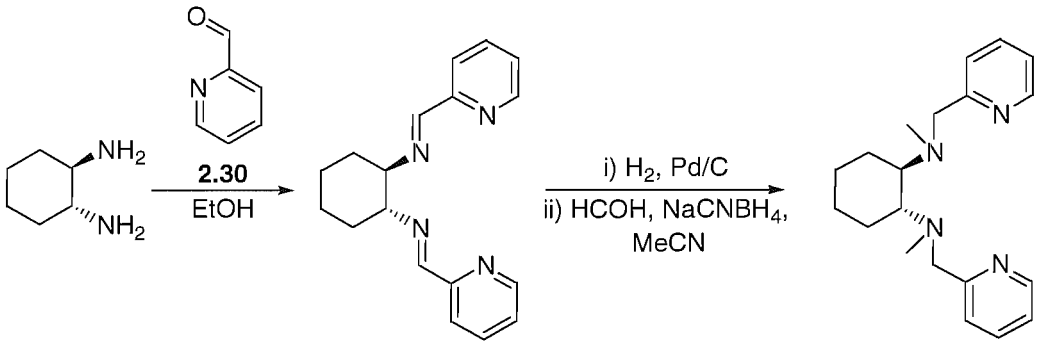
The recently disclosed Jacobsen hydrolytic kinetic resolution (HKR) is an extremely powerful tool for resolution of racemic terminal epoxides, yielding the enantiopure epoxide and the corresponding enantiomeric diol.[115] This procedure is particularly suited to our substrate as the resultant epoxide can easily be recovered by distillation of the crude reaction mixture, before simple chromatography should yield **1.79** as a single enantiomer.

The epoxidation of fluorinated olefins is a significant synthetic challenge, and as with the AD reaction few literature procedures are available. Initial attempts with a well recognized system,[116] using NaOCl as oxidant with a MeCN co-solvent, were unsuccessful in displaying any reaction, even after several days with monitoring by ^{19}F NMR. When the reaction was warmed to 45°C, in a sealed system, the starting material evaporated through glass joints before any product was observed by NMR.

Other reaction conditions, previously successful for fluorinated substrates, including trimethylamine *N*-oxide with mCPBA[117] and mCPBA in refluxing CH_2Cl_2[118] were

attempted with the former showing no reaction.. The reaction with mCPBA in refluxing CH_2Cl_2 showed a trace product by ^{19}F NMR after 3 weeks, with a NMR pattern similar to that expected for **2.28**.

The potential success with mCPBA in refluxing CH_2Cl_2 caused us to consider a recently reported system for the epoxidation of electron deficient olefins with a manganese complex that rapidly epoxidises a wide range of olefins using 1.2 eq. of peracetic acid. The ligand required to form the desired manganese complex, (*R,R*)-mcp **2.32**, is not commercially available and must be synthesized before the epoxidation can be undertaken. Despite the presence of a chiral catalyst this epoxidation is not expected to induce significant *ee*.[119]

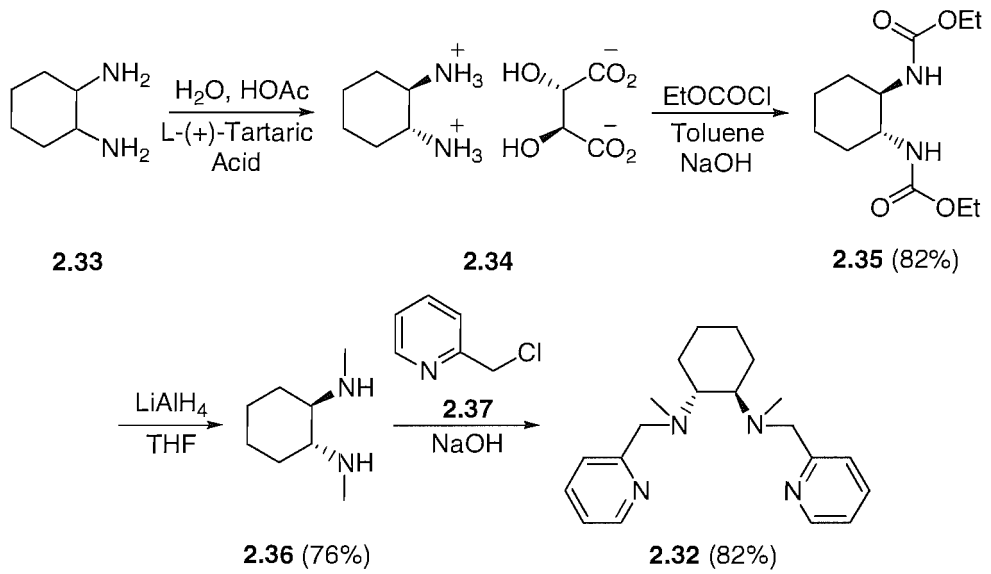


2.29 **2.31** (*R,R*)-mcp (**2.32**)

Scheme 21

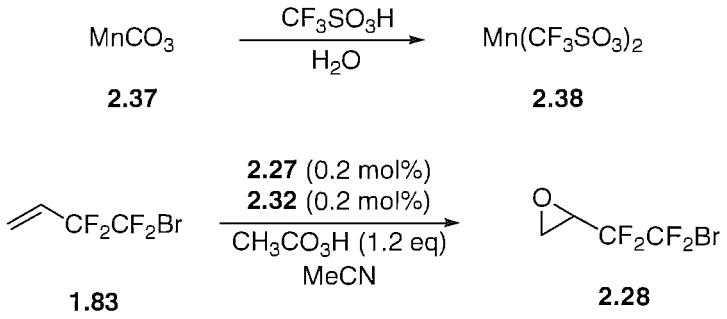
The standard procedure to form (*R,R*)-mcp is the conversion of 1,2-diaminocyclohexane into the bis-imine **2.31** followed by reduction and then a reductive amination. Whilst this transformation is reportedly reliable and high yielding, the cost of enantiopure **2.29** made this method unattractive.

With the known route to **2.32** proving undesirable, a novel route based on a recent reported synthesis of *N,N'*-dimethyl-*N,N'*-bis(2-pyridylmethyl)-ethane-1,2-diamine (mep) was undertaken.[120]



Scheme 22

The synthesis of **2.36** had been previously developed in our laboratory.[121] The initial step is the resolution of 1,2-diaminocyclohexane, and is conducted on a 1.94 mol scale in a repeat of a procedure used in the synthesis of Jacobsen's epoxidation catalyst.[122] The subsequent carbamate formation is an adaptation of a procedure in which **2.34** has been isolated as its free base prior to reaction with ethyl chloroformate.[123] In our case, using **2.34** directly, it is necessary to remove sodium tartrate produced from the *in situ* liberation of the free base prior to crystallisation. An aqueous workup achieves this with ease and **2.35** is isolated in an excellent 82% yield after recrystallisation from ethanol. A $LiAlH_4$ reduction of **2.35** in THF yields the diamine **2.36** as a waxy solid which was relatively unstable to air above -20°C. Treatment of **2.36** with 2-picolyl chloride (isolated from it's commercially available hydrochloride salt[124]) in refluxing $CHCl_3$/aqueous NaOH (1M) for 48h, followed by basic work-up and chromatography yielded the desired **2.32** in a 82% yield.



Scheme 23

With **2.32** in hand, and $Mn(CF_3SO_3)_2$ prepared according to a literature procedure[125] the epoxidation could be attempted (Scheme 13). Unfortunately, even after 4 days at room temperature, ^{19}F NMR showed only a small amount of product formed. A repeat experiment with catalyst loading increased from 0.2% to 2% was left for 1 week and still significant reaction was not observed by ^{19}F NMR.

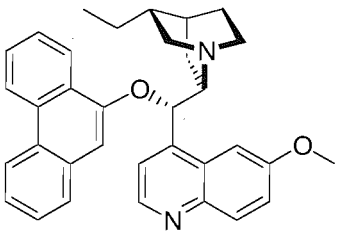
It was at this point that further work on this approach was terminated. The epoxidation/HKR is a highly attractive route but with the difficulties in epoxidising **1.83** and the AD reaction operating satisfactorily any further work was not worthwhile.

2.4 SYNTHESIS OF POLYFLUORINATED CHIRAL LIGANDS FOR USE IN THE AD REACTION

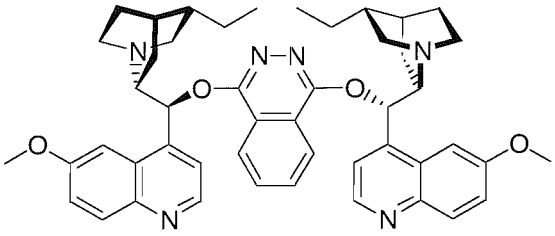
2.4.1 Proposed syntheses of the polyfluorinated ligands

As seen in Section 2.2 we utilized the AD to synthesize a fluorinated building block for use in carbohydrate synthesis.[126] During our research we became interested in the possibility of using fluorous-fluorous interactions as a force to improve the *ee* of this class of transformations by restraining the substrate to a single orientation within the chiral pocket formed by the ligand.

Sharpless initially developed the AD using various aromatic fragments bearing a single chiral substituent (Figure 17, DHQD-PHN, **2.05**).[127] These molecules were further developed into the current generation of ligands, where the aromatic core is flanked by two chiral units, resulting in C_2-symmetric molecules with a clearly defined "chiral pocket" (Figure 17, $(DHQD)_2PHAL$, **2.03**).[128]



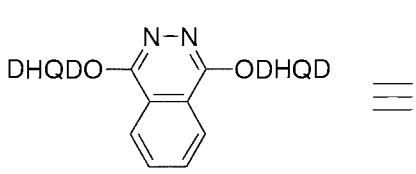
2.05



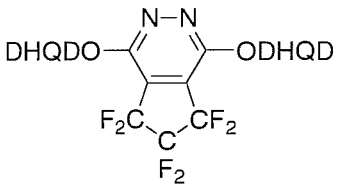
2.03

Figure 17

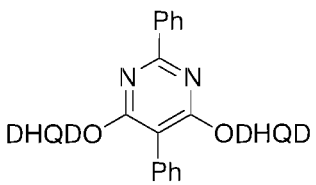
For an initial study into the feasibility of using fluorous-fluorous interactions in the AD, two ligands were to be synthesised. These structures were to be analogous to the two most widely used ligands: **2.03** and $(DHQD)_2PYR$ **2.04** (Figure 18).[100]



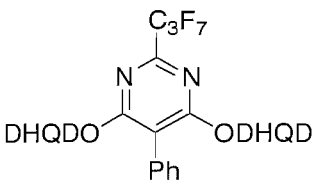
2.03



2.39



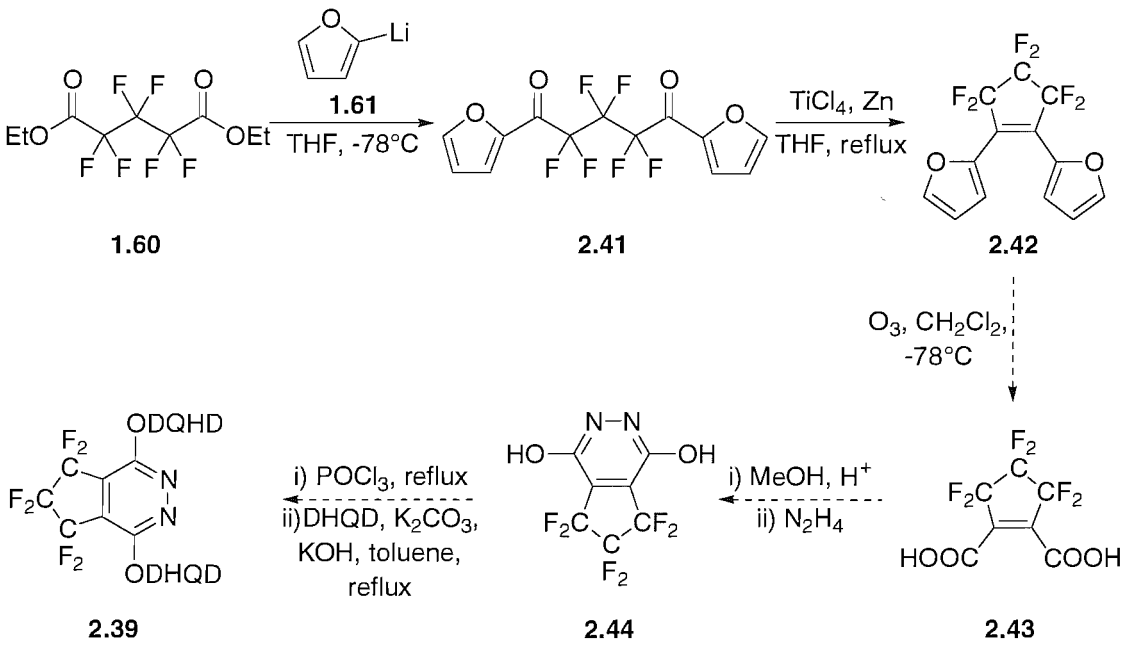
2.04



2.40

Figure 18

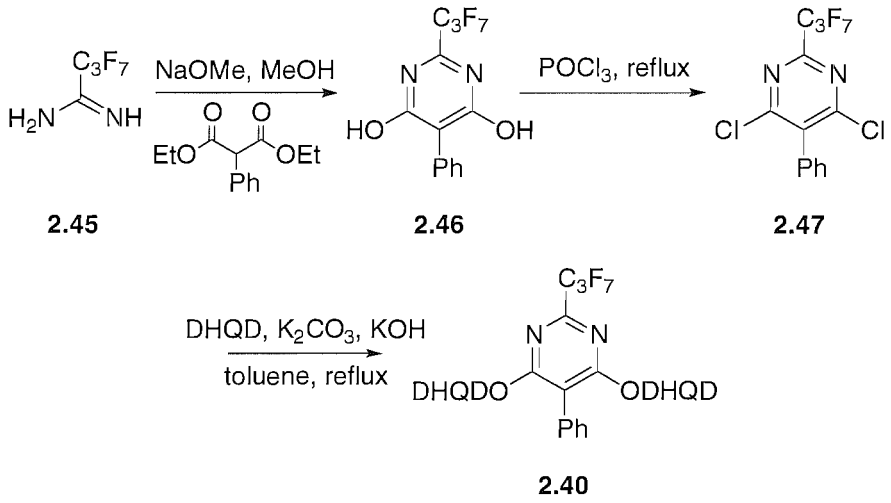
The synthesis of **2.39** was to be undertaken from a commercially available fluorous building block and is outlined in Scheme 24.



Scheme 24

Treatment of diethyl hexafluoroglutarate with furanyl lithium should yield **2.41**. A McMurry reaction,[129] in which conditions can be altered to favour intramolecular cyclisation rather than intermolecular metathesis should yield **2.42**. The oxidation of the furan moieties in **2.42** to the corresponding carboxylic acids is likely to be a difficult procedure. Typically, alkenes will oxidize much faster than aromatic groups,[130] however, it is hoped that the electron withdrawing effects of the fluorine atoms will sufficiently deactivate the alkene in **2.42** so that the aromatic furans will oxidize first. The subsequent steps to arrive at **2.39** should be relatively straightforward as they closely parallel existing literature.

To synthesize the pyrimidine **2.40** we intended to use a synthesis analogous to that outlined by Sharpless, using a fluorinated precursor (Scheme 25).[100]

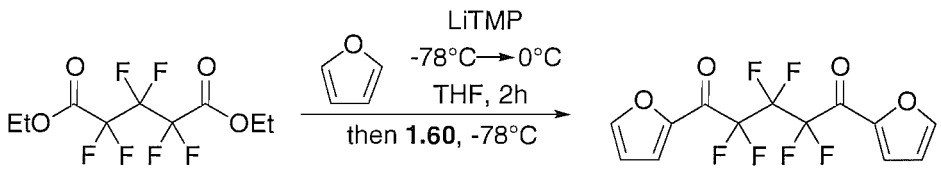


2.45 **2.46** **2.47**

2.40

Scheme 25

2.4.2 Synthesis of fluorinated pthalazine equivalent ***2.39***

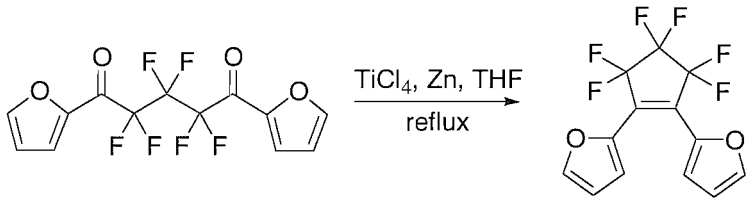


1.60 **2.41** (81%)

Scheme 26

To determine the optimum conditions for the above transformation (Scheme 26), the reaction was attempted in both THF and Et_2O. Furan was treated with *n*-BuLi at -78°C and the solution was then warmed to 0°C. The control of temperature during this period was found to be critical. If the temperature rose above 0°C, then the yield of the reaction was significantly reduced due to decomposition of the furanyl lithium. After 2h at 0°C the reaction was recooled to -78°C and a solution of diethyl hexafluoroglutarate in the chosen solvent was added dropwise over 5 minutes. The reaction was immediately quenched with HCl (aq.) and then worked up in the normal fashion. When conducted in THF 44% of the crude **2.41** was recovered, with Et_2O as solvent, 36% of crude **2.41** was recovered. On repetition of these experiments, it was found that these yields could be

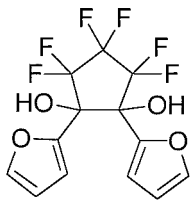
significantly improved upon on a large scale, eventually leading to a reaction on 2.5g of **1.60** giving 81% yield after column chromatography.



2.41 **2.42** (83%)

Scheme 27

McMurry reaction[129] of **2.41** is analogous to a procedure developed by Feringa,[131-133] during his research into dithienylcyclopentene optical molecular switches. Initially, $TiCl_4$ is reduced by dropwise addition to a suspension of zinc in THF, followed by stirring at reflux for 1h. After cooling, a solution of the diarylglutarate in THF is added to the solution and the reaction warmed to reflux and stirred for 16h.



2.48

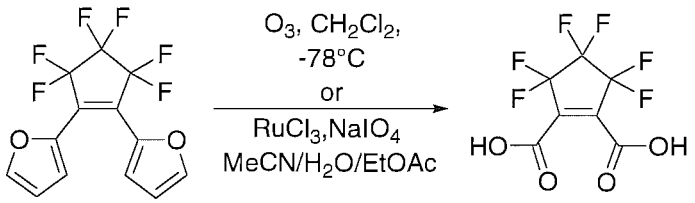
Figure 19

Feringa outlines a procedure in which 1.5eq of $TiCl_4$ and 2eq of zinc are used with a reaction concentration (with respect to **2.41**) of 0.36M.[131] When this procedure was applied to **2.41** none of the desired product was obtained. However, 75% of the intermediate diol **2.48** was recovered (Figure 19).

A procedure outlined by Huang,[134] using 1.5eq of $TiCl_4$ and 3eq of zinc with a 0.1M reaction concentration, was followed and yielded **2.42** in 25% yield. A reaction with 3eq of $TiCl_4$ and 9eq of zinc at the same concentration gave **2.42** in 59% yield. Huang has

since updated his procedure to use a much larger excess of zinc (20eq) a similarly increased amount of $TiCl_4$ (6eq) and a further decreased concentration (0.025M).[135] When this procedure was followed **2.42** was obtained in 83% yield.

These results indicate that whilst the pinacol reaction that occurs as the first step of the McMurry reaction occurs readily with our substrate (as it does with most substrates),[129] the subsequent Ti(0) induced deoxygenation requires more forcing conditions than would normally be expected. The increase in dilution may have an effect in inhibiting competing intermolecular reactions but plays a more important role in keeping the large quantities of zinc properly suspended, and in controlling the exotherm that develops on addition of $TiCl_4$ to THF.



2.42 **2.43**

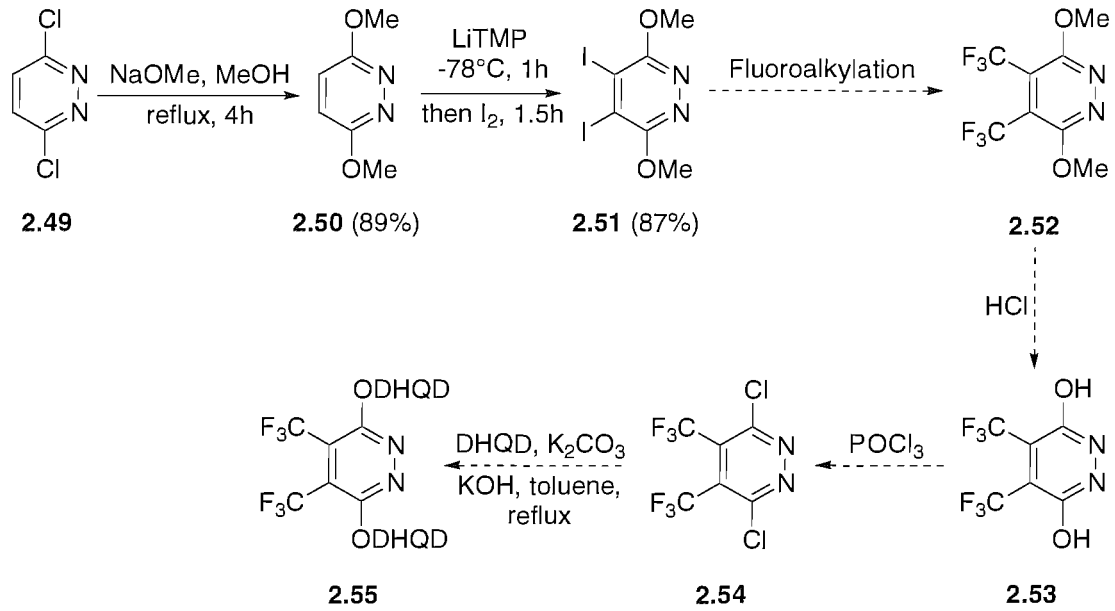
Scheme 28

Oxidation of furan moieties to carboxylic acids is a well known process, which can be accomplished by a number of methods. Initial attempts to synthesize **2.43** utilized established RuO_4 oxidation methodology.[130] Using 2 mol% $RuCl_3$ as the active species with 2 equiv. of $NaIO_4$ co-oxidant the reaction was left for 46h. After this the crude reaction was eluted through an aminopropyl ion exchange column to recover any acidic products. Analysis (LC-MS) of the obtained compounds showed none of the desired product. The reaction was repeated with 20 mol% $RuCl_3$ for 90h after which time none of the desired compounds was recovered.

With the apparent failure of the RuO_4 catalysed oxidation we decided to investigate the possibility of ozonolysis. A solution of **2.42** in CH_2Cl_2 was cooled to -78°C before ozone was bubbled through the solvent for 30 minutes. Initially the reaction goes a bright

yellow colour before fading back to a colourless solution before going the pale blue colour associated with O_3 saturation. LCMS of the reaction mixture however, showed a complex mixture of compounds, with none of the desired product detected. A series of experiments, where O_3 was bubbled through a solution of **2.42** for 2.5min, 5min, 15min and 2h, were conducted. In none of these reactions was the desired product observed by LCMS.

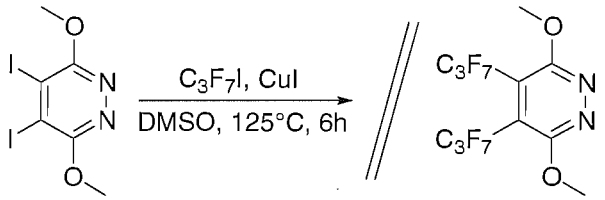
With the oxidation of **2.42** proving to be a taxing reaction, an alternative pthalazine type ligand was envisaged. (Scheme 29)



Scheme 29

Whilst **2.50** is commercially available, it is expensive and obtainable only in small quantities. Hence, synthesis of **2.50** from **2.49** was planned. This reaction exists in the literature but normally requires high temperatures and long reaction times. It was found that a short treatment of **2.49** with sodium methoxide in methanol at reflux gave, after aqueous workup, **2.50** in excellent yield and high purity. Following this, synthesis of **2.51** was easily accomplished using a procedure reported by Knochel *et al.*[136] Fluoroalkylation of aryl halides is a well researched area of fluorine chemistry and as

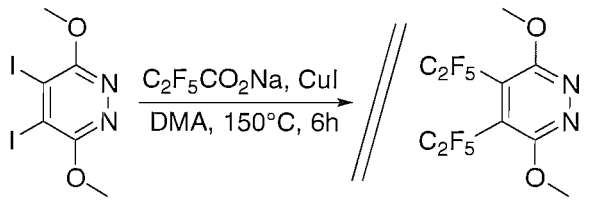
such there is a plethora of potential procedures.[137] Our initial attempt used C_3F_7I and CuI in warm DMSO to affect a heptafluoropropylation (Scheme 30).



2.51 **2.56**

Scheme 30

The procedure entails the addition of C_3F_7I to a solution of CuI and **2.51** in DMSO at 125°C. When this reaction was first attempted, a large exotherm was observed on the addition of C_3F_7I. This exotherm caused the DMSO to reach reflux temperature. After stirring for 6h, none of the desired product was observed by LCMS. It has been shown that an increase in temperature above 125°C in this reaction causes thermal decomposition of the active fluoroalkylcopper species.[138] Hence, a repeat experiment was conducted where the C_3F_7I was added at a rate such that the internal temperature of the reaction remained constant. However, LCMS of the crude product of this reaction showed there to be no **2.56** present in the mixture.

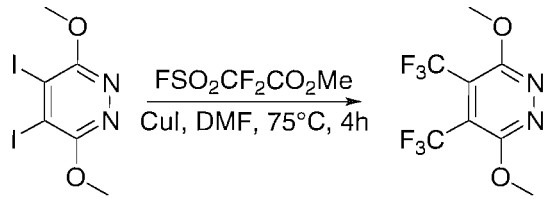


2.51 **2.57**

Scheme 31

Use of sodium perfluoroalkane carboxylates as a source of perfluoroalkyl groups is well known and served as the next technique we investigated in the fluoroalkylation of **2.51**.[139] Pentafluoroethylation is reported to be the most successful reaction of this type.[139] Hence, we treated a solution of **2.51** and CuI (both azeotropically dried with toluene) in

DMA with sodium pentafluoropropionate at 150°C (Scheme 31).[140] The reaction was stirred for 6 hours prior to workup and chromatography after which none of the desired product was isolated.

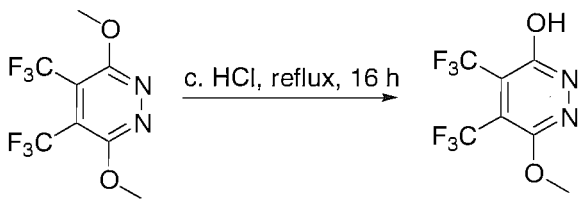


2.51 **2.52** (81%)

Scheme 32

Treatment of aryl halides with methyl fluorosulfonyldifluoroacetate has been shown to yield trifluoromethylated products in good yield.[141] Treatment of **2.51** and CuI in DMF with $FSO_2CF_2CO_2Me$ at 75°C for 4h gave, after workup and chromatography, **2.52** in 65% yield (Scheme 32). When repeating this reaction on a larger scale, an improved yield of 81% was obtained.

With **2.52** in hand, a method to deprotect the hydroxyl groups prior to chlorination was required. Attempts to deprotect the two methyl ethers of **2.52** involved, initially, treatment with HCl (37% aq) at reflux. After reactions with duration of 1 h, 3.5 h and 16h no **2.53** was observed by NMR of the crude material. We observed product which shows the presence of a OCH_3 moiety and two ^{19}F environments by NMR rather than the single ^{19}F environment expected. This leads us to believe that it is the mono-deprotected species.

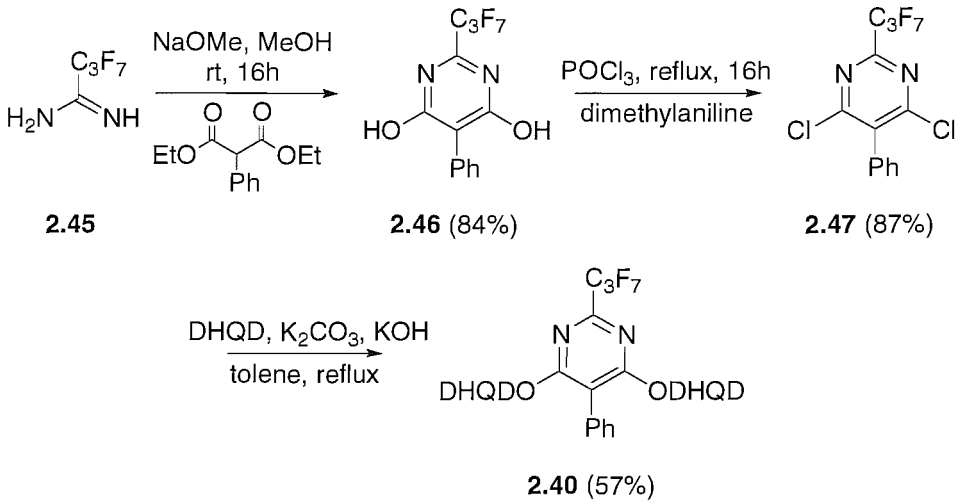


2.52 **2.58**

Scheme 33

BBr_3 is an extremely common reagent in the deprotection of phenol methyl ethers and was therefore of interest.[142] Unfortunately, this reaction also only yielded **2.52**. With the oxygen atom of the methyl ethers likely to be a poor nucleophile due to the electron withdrawing effect of the trifluoromethyl groups; attempts to deprotect **2.47** under basic conditions were attempted. A procedure where **2.47** was refluxed for 16h in morpholine gave a complex mixture of compounds with no signals in the ^{19}F NMR. Two procedures under basic conditions, one with NaOH (2M, aq) another with NaOMe (10 eq in MeOH) both returned complex mixtures of products.

*2.4.3 Synthesis of fluoroalkyl substituted pyrimidine ligand **2.40***



2.45 **2.46** (84%) **2.47** (87%)

2.40 (57%)

Scheme 34

With the synthesis of a pthalazine type ligand proving to be more challenging than expected, our attention turned to the synthesis of a ligand featuring a pyrimidine core (Scheme 34).

The route followed is analogous to that suggested by Sharpless with heptafluorobutyrylamidine (**2.45**) taking the place of benzamidine.[100] The condensation between **2.45** and ethyl phenylmalonate in the presence of NaOMe proceeded smoothly

in 84% yield. The resulting dihydroxypyrimidine can be converted in to the corresponding dichloride in good yield by treatment with phosphorous oxychloride and *N,N*-dimethylaniline. This reaction could be undertaken at reflux temperatures overnight or, alternatively, at 150°C in a microwave reactor. If undertaken in a microwave the reaction time could be shortened to 5 minutes (0.3mmol scale), although on a larger scale (2mmol) up to 8½ minutes were necessary. The presence of *N,N*-dimethylaniline was also found to be essential. In its absence the reaction did not occur even after 30 minutes at 150°C under microwave irradiation.

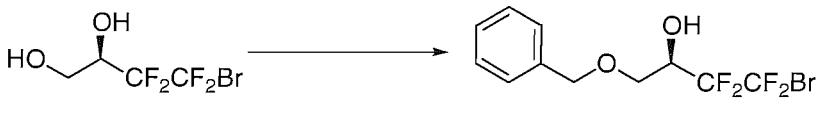
Displacement of the chlorides with the dihydroquinidine moieties was likely to be the most challenging step both in terms of yield and in difficulty of purification. The reaction proceeded well under the conditions outlined by Sharpless,[100] purification by column chromatography led to **2.40** in a 57% yield.

In summary, we have developed the synthesis of a chiral fluorinated building block *via* a Sharpless asymmetric dihydroxylation. After considerable optimisation, both the yield and enantioselectivity of this transformation are amongst the highest reported for this class of substrates. The absolute stereochemistry of the building block has been confirmed by X-ray crystallography and a suitable procedure for large scale synthesis has been outlined. We have also reported work towards the synthesis of a series of fluorinated chiral ligands for the AD, with a view to increasing the utility of this transformation when applied to fluorinated substrates. However, to date no evaluation of this ligand in the AD has been undertaken.

3.0 SYNTHESIS OF TETRAFLUORINATED CARBOHYDRATES VIA ANIONIC CYCLISATION

3.1 SELECTIVE PROTECTION OF **1.79**

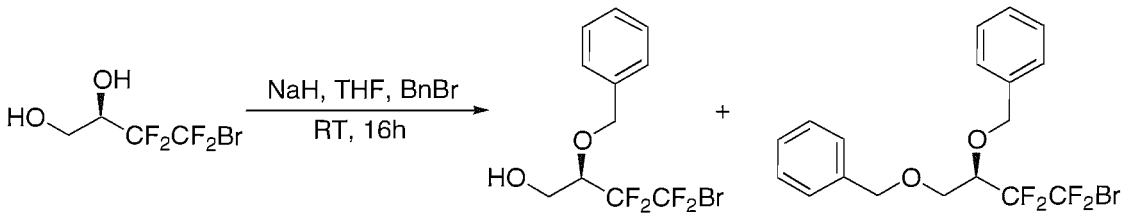
With a satisfactory AD reaction in hand attention turned to the selective protection of the 1,2–diol. This transformation was expected to be complicated by the presence of the fluorinated substituent, as this could significantly affect both the nucleophilicity and pKa of the hydroxyl functionalities.



1.79 **3.01**

Scheme 35

Treatment of **1.79** with 1.1 eq of NaH in THF, followed by addition of 1.1 eq of BnBr led to a selective protection of the secondary hydroxyl group in 49% yield with a further 27% of **3.03**.



1.79 **3.02** (49%) **3.03** (27%)

Scheme 36

Careful searching of the patent literature revealed a reaction by Katagiri *et al*[143,144] where a similar selectivity was observed in the basic protection of trifluoropropane-1,2-diol. The regioselectivity of the reaction is easily explained by the increased acidity of the secondary hydroxyl proton, caused by the electron withdrawing effect of the fluoroalkyl

substituent. Whilst the result of this reaction was not what was desired the high degree of regioselectivity was of interested us and merited further investigation.

*3.1.1 Selective Secondary Protection of **1.79***

Entry	Base	Alkyl Halide	Solvent	Temp (°C)	Yield **3.02** (%)	Yield **3.03** (%)
1	KO^{t}Bu	BnBr	THF	RT	41	30
2	KO^{t}Bu	BnBr	THF (0.07M)	RT	44	19
3	K_2CO_3	BnBr	THF	RT	15	0
4	DBU	BnBr	THF	RT	0	0
5	BEMP	BnBr	THF	RT	52	16
6	NaOH	BnBr	H_2O	RT	3	44
7	NaOH	BnI	H_2O	RT	4	37
8	KO^{t}Bu	BnBr	THF	Reflux	47	4
9	KO^{t}Bu	BnI	THF	RT	52	8

Table 4

With the initial attempts at a basic benzylation giving regioselective protection of the secondary hydroxyl group an investigation was undertaken to see if this reaction could be optimised. To this end a small series of reactions to determine the optimum base was undertaken. A reaction with KO^{t}Bu (1 eq) gave a 41% yield of **3.02** with 30% of **3.03** (Entry 1), with K_2CO_3 (1 eq, Entry 3) 15% of **3.02** was isolated, use of DBU (1 eq, Entry 4) gave no reaction and use of BEMP (1 eq, Entry 5) as the base gave 52% of **3.02** with 16% of **3.03** also recovered (all reactions used BnBr (1 eq) and were undertaken as a 0.2M solution in THF at RT).

A phase transfer procedure outlined by Percy[75] using $Bu_4N(HSO_4)$ and NaOH (7 eq) gave only 3% of **3.02** with 44% of **3.03** (Entry 6). When BnI was used under these same conditions we isolated 37 % of the diprotected species and still only 4% of **3.02** (Entry 7).

When BnI was used in conjunction with KO^{t}Bu 52% of **3.02** was isolated as was 8% of **3.03** (Entry 9).

A reaction utilising a higher dilution was attempted. Treating a 0.07M solution of **1.79** in THF with KO^{t}Bu (1eq) and BnBr gave us a 44% yield of **3.02**, a slight increase, with 19% of diprotected **3.03**, a significant decrease (Entry 2).

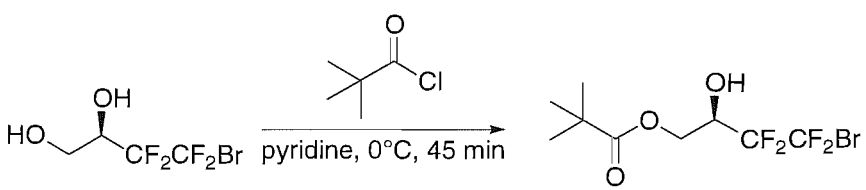
A procedure from the literature[145] whereby 1,1,1,-trifluorobutane-2,3-diol is refluxed with KO^{t}Bu for 15 min, BnBr added and the reaction refluxed for a further 2.5h was applied to our substrate yielding 47% of **3.02** with 4% of **3.03** (Entry 8).

Whilst the optimisation of this reaction has resulted in no significant increase in yield it has produced a useful transformation; which utilises the often frustrating electronegativity of fluorine, to provide a complementary process to other selective primary protection methods. It is expected to be of even more use when applied to internal diols bearing fluoroalkyl substituents as without the more reactive terminal hydroxyl the selectivity for mono-protection proximal to the CF_2 should increase.

Unfortunately, studies conducted since the completion of this work have shown that all the conditions for secondary benzylation detailed above result in epimerisation of the product; giving racemic **3.02**.[146]

*3.1.2 Selective Primary Protection of **1.79***

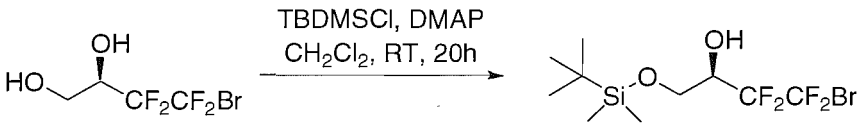
With selective benzylation proving difficult alternative protection strategies were sought.



1.79 **3.04** (81%)

Scheme 37

The use of esters as selective protecting groups in fluorinated 1,2-diols is well known.[147,148] Treatment of **1.79** with pivaloyl chloride in pyridine at 0°C yielded **3.04** as a white solid in 81% yield.

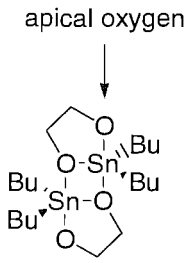


1.79 **3.05** (71%)

Scheme 38

Whilst the protection of the primary hydroxyl as a pivaloate ester was proving satisfactory, the concerns over potential chemoselectivity issues later in the synthesis led us to investigate the protection of **3.05** as its mono-silyl ether. A procedure reported by Kornilov *et al*[149] using DMAP as a nucleophilic catalyst in CH_2Cl_2 yielded 71% of the desired product, while another procedure outlined by Kitazume *et al*[150] uses imidazole in DMF and when applied to **1.79** gave 42% of the primary protected **3.05** and 7% of the secondary protected product.

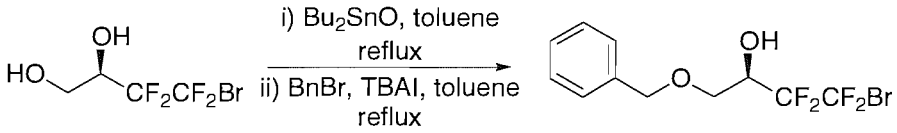
The use of stannylene acetals as a means to effect regioselective transformations is well known[151] and we wished to see if it could be applied to our fluorinated substrates.



3.07

Figure 20

We were interested to see if, even though both hydroxyl groups of **1.79** are likely to be deactivated as nucleophiles, formation of the stannylene acetal of **1.79** would increase their nucleophilicity enough to induce attack on an alkyl bromide. We were also interested to see if the electron withdrawing effect of the fluoroalkyl substituent would affect the reported regioselective activation of a specific hydroxyl function,[152] and hence the regioselectivity of the reaction. Whilst the origin of the regioselective activation of a specific hydroxyl functionality is not known, there is structural and X-ray evidence that suggests dimeric stannylene structures (Figure 20).[142] In these structures, it is the apical oxygen atoms that are selectively alkylated, which in non-fluorinated substrates can be predicted to be the primary hydroxyl group of a given 1,2 diol. It has been reported that typically, the more electronegative atom occupies the apical position[153] which in our case would result in the opposite regioselectivity.



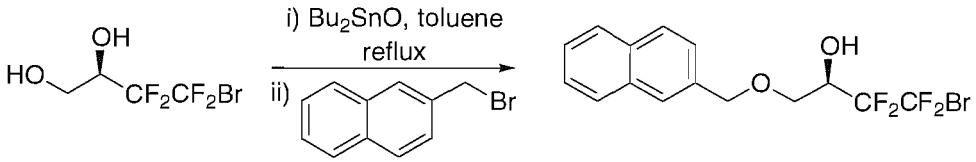
1.79 **3.06** (96%)

Scheme 39

An initial reaction in which **1.79** was refluxed with Bu_2SnO in toluene under Dean and Stark conditions for 20 hours, followed by addition of benzyl bromide and TBAI, then a further 20 hours reflux, then concentration followed by chromatography yielded the desired primary protected **3.06** in 94% yield (Scheme 39). Whilst this reaction proceeded in good yield and, more pleasingly, with total regioselectivity there were still some issues that required attention. The initial reflux to form the stannylene acetal, at 20 hours, was too long and so was shortened to 6 hours with no noticeable drop in yield, allowing the reaction to be completed in a single 24 hour period. Purification of the crude product by chromatography was complicated by the large quantity of organotin byproducts that passed through the column and contaminated the product. The majority of these organotin compounds could be removed by means of an aqueous workup where the

cooled reaction mixture was washed with KF (10% w/v, aq.) solution. Subsequent chromatography gave **3.06** as a white solid in 96% yield, found to be pure by NMR.

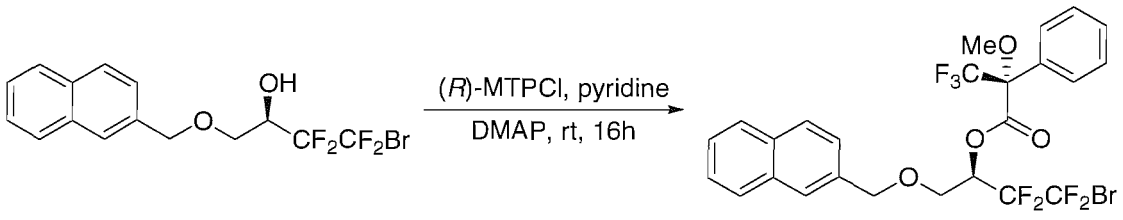
Whilst **3.06** was obtained as a white solid, it could not be crystallised. It was hoped that the subsequent functionalisation of this molecule would provide us with a crystalline intermediate, but this proved not to be the case. The desire for a crystalline intermediate was driven by the knowledge that a recrystallisation could provide a route to further enantiomerically enriching our compounds.



1.79 **3.08** (88%)

Scheme 40

It was hoped that synthesis of the primary naphthylmethyl ether would furnish a crystalline intermediate due to the increased level of π-stacking associated with the naphthyl moiety. In the event, using the same stannylene acetal methodology that yielded the benzyl ether, just substituting 2-naphthylmethyl bromide for benzyl bromide, after chromatography, yielded **3.08** in a 88% yield as pale yellow crystals.



3.08 **3.09** (99% crude)

Scheme 41

Recrystallisation, followed by Mosher's ester formation and NMR analysis (^{19}F), was attempted from several solvents including toluene, hexane and propan-2-ol but no improvement in *ee* was ever observed.

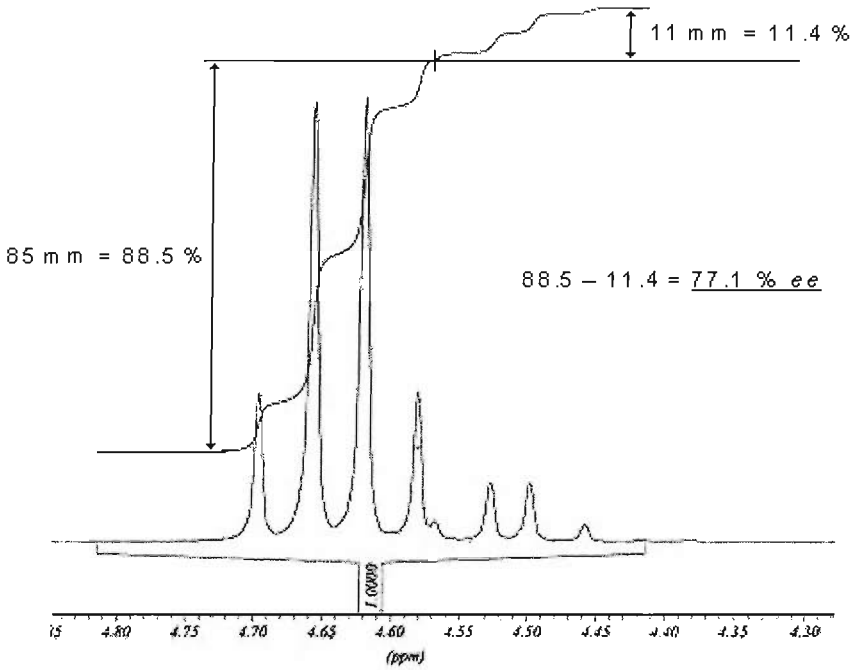
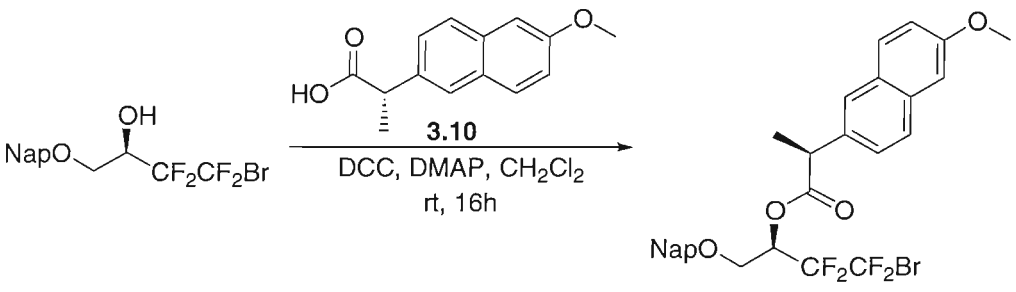


Figure 21

However, ^{1}H NMR analysis of a Mosher's ester synthesised from crude **3.09** did confirm that the stannylene acetal methodology does not alter the *ee* of the substrate in the course of the protection (Figure 21).



3.08 **3.11** (97%)

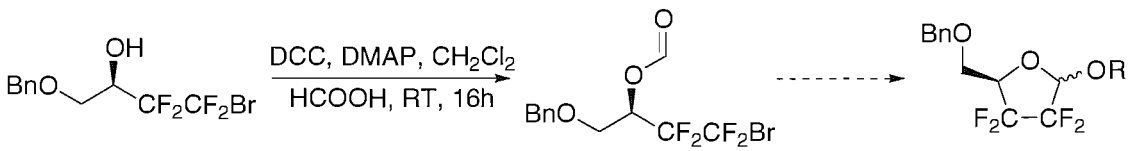
Scheme 42

A DCC mediated coupling of (*S*)-Naproxen and **3.08** yielded the ester **3.11** in 97% yield as a 6.9:1 mixture of diastereomers (75% *de* by NMR of the crude reaction mixture). HPLC followed by crystallisation gave 63% of **3.11** as a single diastereomer which was analysed by X-ray crystallography (see section 2.2.5 for structure). This allowed us to confirm that the absolute configuration of the chiral centre in **1.79** matched that predicted by Sharpless' results for enantioselection in the AD.

3.2 SYNTHESIS OF TETRAFLUOROETHYLIDENE PENTOSES

3.2.1 Synthesis of formate ester ***3.12***

Having developed a robust and efficient synthesis of our common synthetic intermediate **3.06** we turned to the synthesis of the tetrafluoro-substituted monosaccharides.



3.06 **3.12** (95%) **3.13** (R = TMS) **3.14** (R = H)

Scheme 43

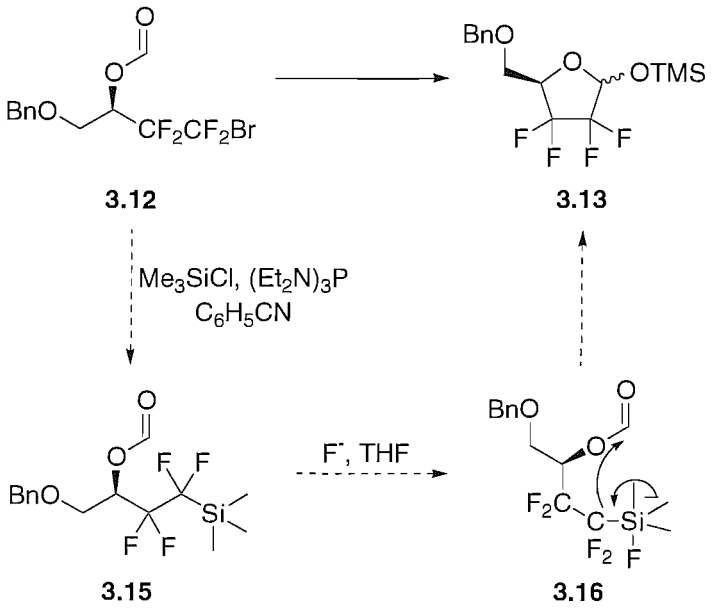
The first challenge was the conversion of the free hydroxyl group in **3.06** to a formate ester, thereby forming the C-O bond as outlined in the retrosynthetic analysis (section 1.5.1). Reaction of **3.06** in refluxing formic acid was ineffective,[154] as was reaction with ethyl formate and a $Ce(SO_4)_2$ catalyst.[155] A possible solution was to effect the transformation *via* a Mitsunobu reaction.[156] The resulting inversion of configuration would require the use of the dihydroquinidine (DHQD) based ligands in the preceding AD. The DHQD ligands are reported to give better enantioselectivities than the dihydroquinine (DHQ),[83] making the Mitsunobu an attractive option. However, the reaction was unsuccessful. After 2 days at room temperature and 16 hours at reflux the reaction had still not gone to completion. The difficulty in effecting the Mitsunobu

reaction can be explained by the disfavoured nature of any S_N2 attack next to a CF_2 moiety. The difluoromethylene group has a particularly high electron density, which leads to the repulsion of the incoming nucleophile, thus inhibiting S_N2 attack.

A DCC mediated coupling between **3.06** and formic acid was attempted and proved successful yielding 95% of **3.12** in 16 hours.[157] The dicyclohexylurea (DCU) formed during this reaction can often be difficult to remove. In this case a simple filtration, followed by column chromatography was sufficient to yield **3.12** in excellent purity. On larger scale however, it was found that the DCU was not completely removed by chromatography and caused problems with subsequent transformations. The solution was to adjust the workup procedure for the reaction. Previously the reaction had been filtered to remove the DCU prior to concentration *in vacuo*. By removing the CH_2Cl_2 *in vacuo*, suspending the resultant slurry in pentane, stirring for 10 min, then filtering the reaction we removed a much greater proportion of the DCU than previously, allowing straightforward chromatography to yield large quantities of pure **3.12**.

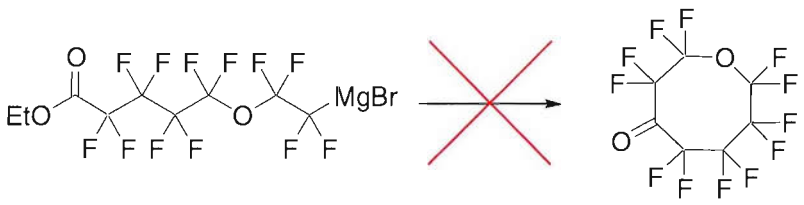
*3.2.2 Cyclisation of **3.12** to form a tetrafluoroethylidene substituted pentose (**3.14**)*

With the synthesis of the formate ester **3.12** complete, attention turned to the cyclisation forming the tetrafluorofuranose ring. As discussed earlier the instability of tetrafluroalkyl lithium species, even at low temperatures, led us to initially investigate a cyclisation procedure based on the Ruppert reaction.[85,86,137] Conversion of **3.12** into the organosilicon compound **3.15**, followed by treatment with TBAF should lead to the anomerically trimethylsilyl protected **3.13**.



Scheme 44

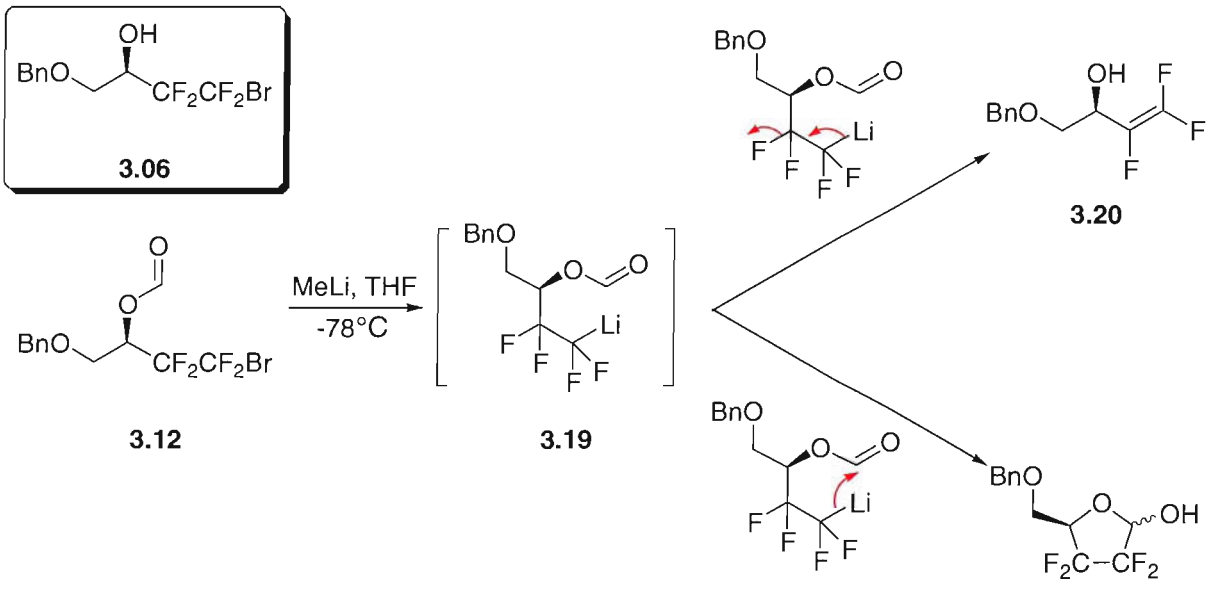
In the event, early attempts to synthesise **3.15** were unsuccessful and whilst these failed attempts were investigated the treatment of **3.12** with alkyl lithiums was trialled.
It was hoped that bromine/lithium exchange of **3.12** would result in spontaneous 5-*exo*-trig cyclisation to yield **3.14**. Unfortunately, the instability of perfluoroalkyl lithiums is well known and lithiated **3.12** was expected to readily undergo β-elimination of fluoride .[158-160] However, the *in situ* trapping of such species by aldehydes, ketones and esters is known[161,162] though in these reactions a large excess of R_fLi is normally used, a situation not possible in our case. Furthermore, the synthesis of *functionalised* perfluoroalkyl metal species is rare; to the best of our knowledge the only case is the synthesis of a perfluoroalkylether Grignard, containing an ester group (**3.17**).[163] In this example it was reported that none of the product formed by cyclisation (**3.18**) was observed (Scheme 45), instead intermolecular attack of the Grignard onto another molecule of **3.17** was preferred.



3.17 **3.18**

Scheme 45

Given that our desired cyclisation is forming a 5-membered rather than a 8-membered ring, it was hoped that the rate of cyclisation would outstrip that of elimination and intermolecular attack. Reaction of **3.12** with several alkyl lithiums was attempted. Reaction with 1eq of *n*-BuLi in THF at -78°C for 1 hour resulted in the isolation of the desired sugar derivative **3.14** as an inseparable mixture of anomers in 43% yield. Also isolated was **3.20** (11%), produced by the expected β-elimination of fluoride followed by nucleophilic attack of BuLi on the ester moiety and the product resulting solely from nucleophilic attack on the formate ester, **3.06** (17%) (Scheme 46).



3.06 **3.12** **3.19** **3.20** **3.14**

Scheme 46

Reaction of **3.12** with 2 equiv. of *tert*-BuLi under identical conditions resulted in the same three products: **3.14** (11%), **3.20** (29%) and **3.06** (49%). Another reaction with

only 1 equiv. of *tert*-BuLi gave a much reduced 15% of **3.06**, a comparable 22% of the elimination product **3.20** and an improved 43% of the desired **3.14**.

Two reactions with 1 equiv. of MeLi; one for 1 hour and another for 2 hours (all at -78°C in THF) gave 60% and 70% of pure **3.14** respectively. **3.20** was still visible by TLC in both of these experiments but was not recovered after column chromatography.

With a Li-Br exchange system proving promising, we chose to investigate a Mg-Br exchange reaction. Fluoroalkyl magnesium species are known to be more stable[159,160] than their lithium counterparts and so it was hoped that the risk of β-elimination could be reduced and the yield of **3.14** improved. Treatment of **3.12** with PhMgBr[164-167] in THF at -78°C for 3 h, after workup and chromatography, gave recovered **3.12** (11%) and **3.06** (63%). An exchange reaction with iPrMgCl as the magnesium source gave only a 8% yield of recovered **3.12**, with 2% of **3.06**, 18% of **3.20** and 59% of the desired **3.14**.[168]

Attempts were also made to effect the cyclisation to **3.14** via a fluoroalkyl zinc species. A reaction of **3.12** with zinc in pyridine for 16h yielded 13% of the desired **3.14** and 16% of **3.06**.[169-172] A procedure with Zn and Cp_2TiCl_2 as a Lewis acid yielded no product.[173] Finally, a procedure where a Zn-Br exchange between **3.12** and Et_2Zn in pyridine was attempted, but no reaction was detected by TLC after 16 h.[174]

These results were extremely promising as not only were the yields acceptable even without optimisation, but the metal – bromine exchange cyclisation shortened the synthesis in comparison to the organosilicon based procedures.

3.2.3 Optimisation of the Li-Br exchange/cyclisation reaction

Initial attempts to attempt to improve the yield of the reaction involved a simple screening of appropriate solvents. With our initial few experiments the solvent used was THF but the literature suggested that Et_2O would be more suitable.

Entry	Temperature (°C)	Solvent	Time (h)	Concentration (mol dm^{-3})	Yield **3.14** (%)
1	-78°C	Et_2O	3	0.1	58
2	-78°C	THF	3	0.1	78
3	-78°C	Pentane	3	0.1	27
4	-78°C	Toluene	3	0.1	55

Table 5

As can be seen from Table 5, despite the literature precedent that Et_2O is the preferred solvent for fluoroalkyl lithium reactions, we found that THF provided significantly better yields. Pentane was a solvent of interest to probe whether an apolar solvent would improve the stability of the fluoroalkyl lithium species. Unfortunately, it was found that **3.12** was only sparingly soluble in pentane at the low temperatures required for the reaction. This led to **3.12** crashing out of solution on cooling. Despite this, the reaction was attempted but after the 3 hours normally required for complete reaction starting material remained. After work up and chromatography we recovered 19% of the starting material, 31% of **3.06** and 27% of the desired **3.14**.

Entry	Temperature (°C)	Solvent	Time (h)	Concentration (mol dm^{-3})	Yield **3.14** (%)
1	-78	THF	3	0.1	78
2	-100	THF	3	0.1	81
3	-116	THF	4½	0.1	58

Table 6

Due to the known instability of fluoroalkyl lithium species no reactions above -78°C were attempted. A reaction conducted at -100°C (MeOH / liquid N_2 bath) gave a small increase in yield, the drawback being the difficulty of maintaining a constant temperature, even in a heavily insulated Dewar bath. The reaction at -116°C (EtOH / liquid N_2) showed a marked decrease in yield, despite that after 4½ hours the starting material had been consumed (as identified by TLC). The Trapp solvent mixture (4:1:1, THF:Et_2O:Pentane)[175] is designed for use at extremely low temperatures; when we attempted a reaction in this mixture at -116°C we isolated 55% of **3.14** after 4 hours.

Addition of HMPA to the reaction mixture was expected to complex the lithium ion present in the intermediate species **3.19,** destabilising the carbanion further. When a cyclisation was conducted in the presence of HMPA (3 equiv) we obtained only 34% of **3.14**. It was suggested that the presence of LiBr as a contaminant in MeLi was a factor in the as yet unexplained prominence of MeLi as a Li source. It was possible LiBr acted as a Lewis acid, complexing the carbonyl group of the formate ester, hence activating it to nucleophilic attack and further improving the rate of cyclisation as oppose to β-elimination. To test this, a reaction was undertaken with MeLi.LiBr (2.2 M in Et_2O; unfortunately, this reaction yielded only 60% of **3.14**. Reactions have also been reported where MeLi.LiBr is used in conjunction with $BF_3.OEt_2$. We applied these conditions to our cyclisation, however, the reaction yielded only 32% of the desired **3.14**. The same conditions with MeLi exchanged for the MeLi.LiBr gave an even lower yield of 21%.

When dealing with alkyl lithium reagents an obvious concern is the exclusion of even trace amounts of water from the reaction. It has been shown that addition of 4Å molecular sieves to reactions can remove any remaining trace of water and hence significantly improve yields.[176] It was to this end that a reaction was undertaken where sieves were added and the reaction stirred for 1 hour prior to cooling and addition of MeLi. This reaction was conducted in parallel with a control experiment were no molecular sieves were added.

Entry	Temperature (°C)	Time (h)	Concentration (mol dm^{-3})	Molecular Sieves	Yield **3.14** (%)
1	-78	3	0.1	Yes	61
2	-78	3	0.1	No	65

Table 7

As can be seen from Table 7 the addition of sieves to the reaction actually lowered the yield of this transformation in comparison to the control reaction that accompanied it.

One of the difficulties on optimising this reaction was it's relatively capricious nature, and another was the difficulties associated with purification. The outcome of the reaction

is very sensitive to the dryness of reagents and solvents, and while utmost care was taken repeatability was difficult to obtain in this respect . The condition of the MeLi used in the reaction was also key to its success, older bottles giving inferior yields and careful handling needed to ensure consistent addition. This problem is evidenced by comparison of Table 6, entry 1 and Table 7, entry 2; two reactions with exactly the same conditions giving two different yields 78 and 65% respectively). The problems associated with purification of the products from this reaction were also not insignificant. Column chromatography usually yielded **3.14** contaminated with trace amounts of **3.06** and **3.20**. Purification by HPLC was necessary to remove these by-products and even after this the product was not always 100% pure.

When left to stand, **3.14** crystallised giving colourless needles which were ideal for X-ray crystallography.

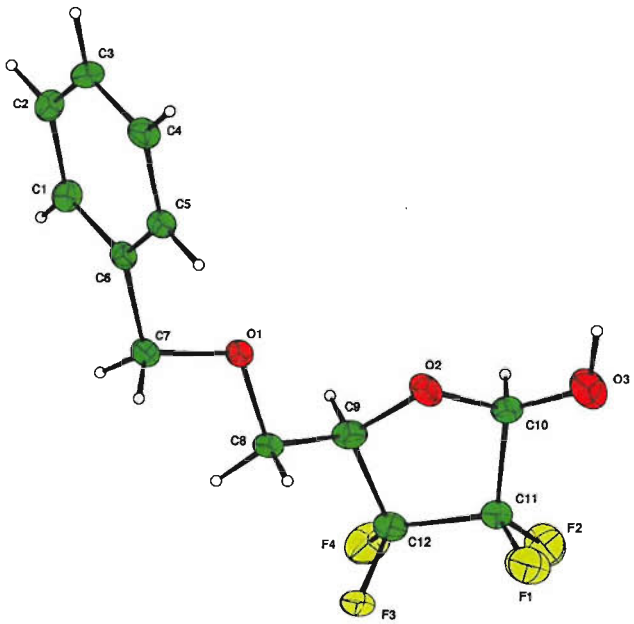


Figure 22

It was interesting to note that **3.14** crystallised as the β-anomer, further analysis detailed the formation of a hydrogen bonded chain of **3.14** molecules; a particularly interesting arrangement.

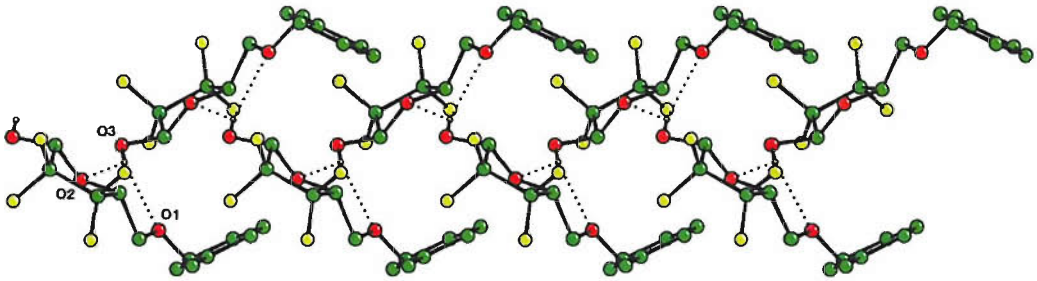
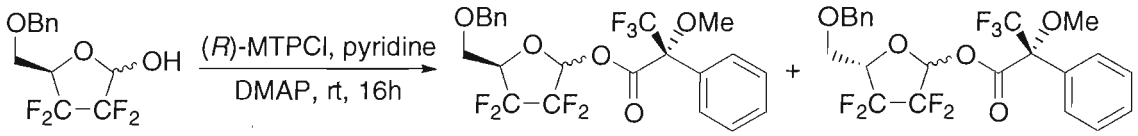


Figure 23

With a cyclisation procedure providing **3.14** in good yields, it was necessary to determine whether the transformation altered the enantiomeric excess of the material.



3.14 (78% *ee*) **3.21** **3.22**

Scheme 47

To aid in this determination the Mosher's ester of both racemic and enantioenriched **3.14** (Scheme 47) was undertaken and the CF_3 signals in the ^{19}F NMR compared. In the racemic sample (Figure 24) there was no consistent *ee* observed; whilst in the enatioenriched sample (Figure 25) a repeatable 78% *ee* is observed for both sets of diastereomers.

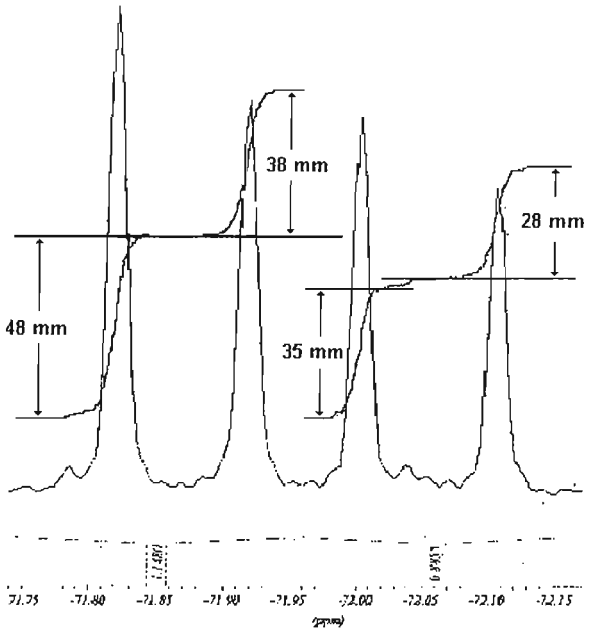
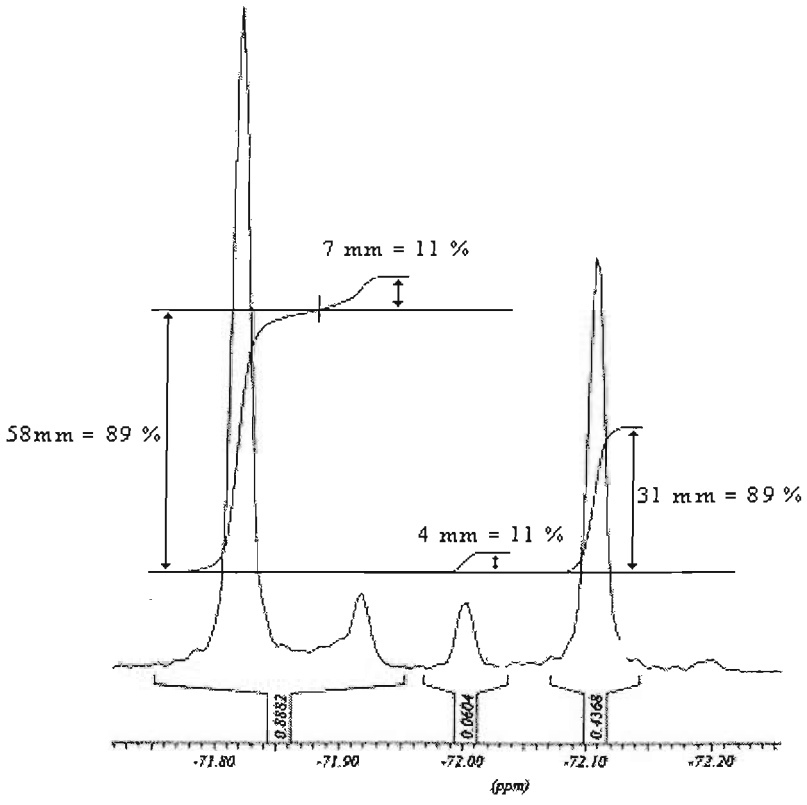


Figure 24

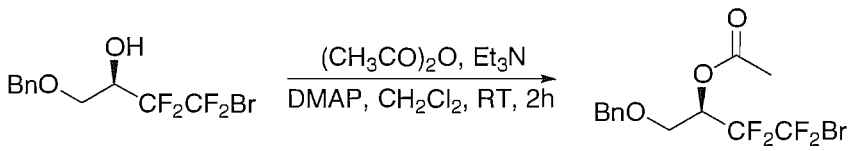


89 – 11 = 78 % *e.e*

Figure 25

3.2.4 Anionic cyclisation of acetate and substituted acetates

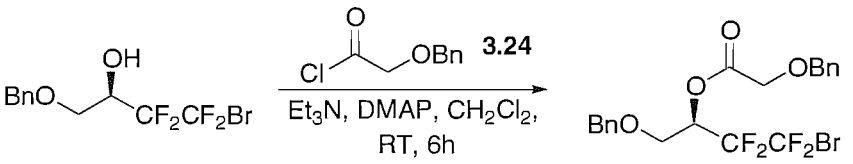
With a novel and efficient cyclisation reaction in hand we looked towards broadening the scope of the reaction with a view to increasing its usefulness as a process. The major aim was to extend the cyclisation to include acetate and substituted acetates. We therefore undertook the synthesis of the acetate and the α-benxyloxy-acetate of **3.06**.



3.06 **3.23** (95%)

Scheme 48

Synthesis of the acetate **3.23** required simple treatment of **3.06** with acetic anhydride in CH_2Cl_2 for 2h at RT and gave, after chromatography, 95% of the desired compound (Scheme 48).



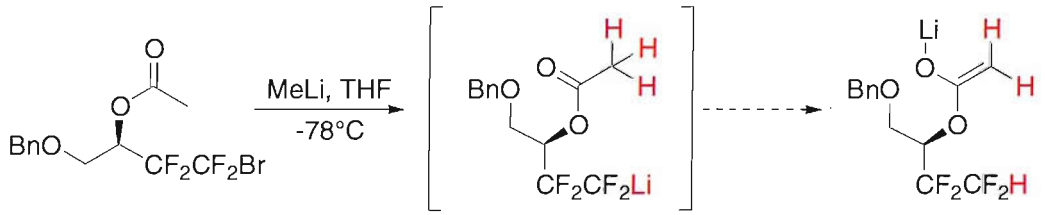
3.06 **3.25** (93%)

Scheme 49

Initial attempts to synthesise **3.25** involved the treatment of **3.06** with α-benzyloxyacetyl chloride (**3.24**, 1.2 eq) and Et_3N (1.2 eq) at RT. Unfortunately after 40h and addition of a further 1.2 eq of **3.25** and Et_3N only a 30% yield of the desired product was isolated, with 44% of recovered starting material. This sluggish rate of reaction illustrates the decreased nucleophilicity of the α-CF_2 hydroxyl group. A subsequent reaction with

addition of DMAP as a nucleophilic catalyst[177] yielded a 93% yield of **3.25** after 16h at RT.

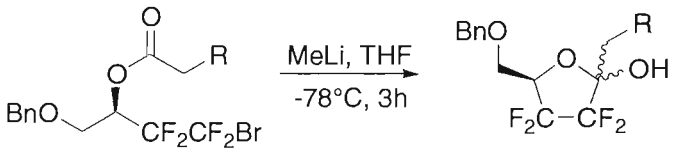
The main concern in the use of **3.23** and **3.25** in the cyclisation reaction was the potential for an intramolecular acid / base reaction (Scheme 50).



3.23 **3.26** **3.27**

Scheme 50

If this acid / base reaction did take place then obviously the cyclisation could not, and the desired reaction would fail, making a wide range of molecules inaccessible to us *via* this route.



3.23 (R=H)
3.25 (R=OBn)

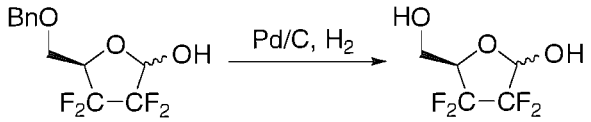
3.28 (R=H) (63%)
3.29 (R=OBn) (79%)

Scheme 51

In the event, treatment of **3.23** with MeLi in THF at -78°C gave 63% of the desired **3.28**, as an inseparable mixture of anomers, and only a trace amount of a mixture of byproducts (Scheme 51). Subjection of **3.25** to the same conditions as above yielded an excellent 79% of the desired **3.29** as a mixture of anomer. Once again, after HPLC a mixture of by-products was only isolated in small amounts.

*3.2.5 Hydrogenolysis of **3.14** to give an unprotected tetrafluoropentose*

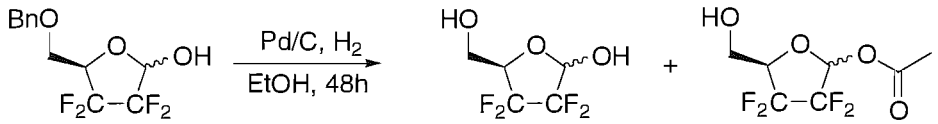
With the cyclisation proving to be a successful reaction with broad scope for synthesis of furanoses, our attention turned to the subsequent removal of the benzyl protecting groups to furnish the unprotected pentoses (Scheme 52).



3.14 **1.77**

Scheme 52

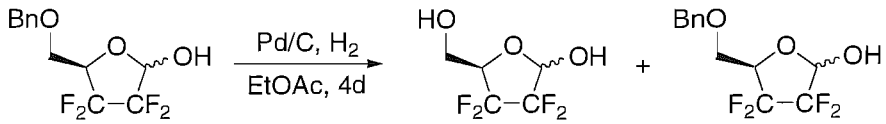
This transformation was expected to be trivial, yet resulted in some unexpected results. An initial experiment using palladium on charcoal (10% Pd) suspended in EtOH under a hydrogen atmosphere as the hydrogenolysis conditions led, confusingly to a, what appeared to be, a mixture of the desired product **1.77** and the anomeric acetate **3.30** (Scheme 53).



3.14 **1.77** (31%) **3.30** (41%)

Scheme 53

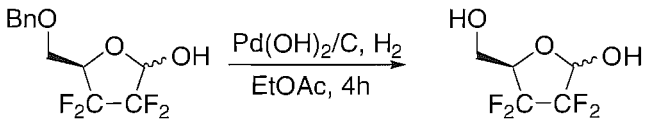
This unusual result has still not been properly explained, but is easily avoided by the use of EtOAc as the solvent for the transformation.



3.14 **1.77** (85%) **3.14** (14%)

Scheme 54

This transformation was still incomplete after 4 days, but yielded only returned starting material and **1.77**. To facilitate a faster reaction the more active Pearlman's catalyst ($Pd(OH)_2/C$) can be used (Scheme 55).



3.14 **1.77** (98%)

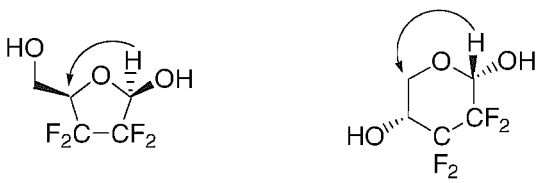
Scheme 55

The more active palladium hydroxide on carbon (Pearlman's catalyst, 10% Pd) gave us an excellent yield of **1.77** in only 16 hours. Unfortunately, it was at this point, after careful analysis of 2D NMR spectra that we found that the obtained structure was not actually **1.77** but an isomer **3.31** (Figure 26). Whether the acetylated **3.30** isolated earlier had isomerised from the furanose to the pyranose was not established.

1.77 **3.31**

Figure 26

This isomerism is not totally unexpected, but due to signal broadening in the NMR making analysis of coupling constants impossible, accurate characterisation of which isomer is present is difficult.



1.77 **3.31**

Figure 27

The only method we have found to confirm the structure is via a 2D HMBC experiment, by which the long range C-H coupling of the anomeric CH across the ring oxygen is revealed (Figure 27). In the case of **1.77** we would see the proton of C-1 coupling to C-4, but as is shown below (Figure 28) we see the coupling of the anomeric CH to a CH_2 group, which can only be C-5.

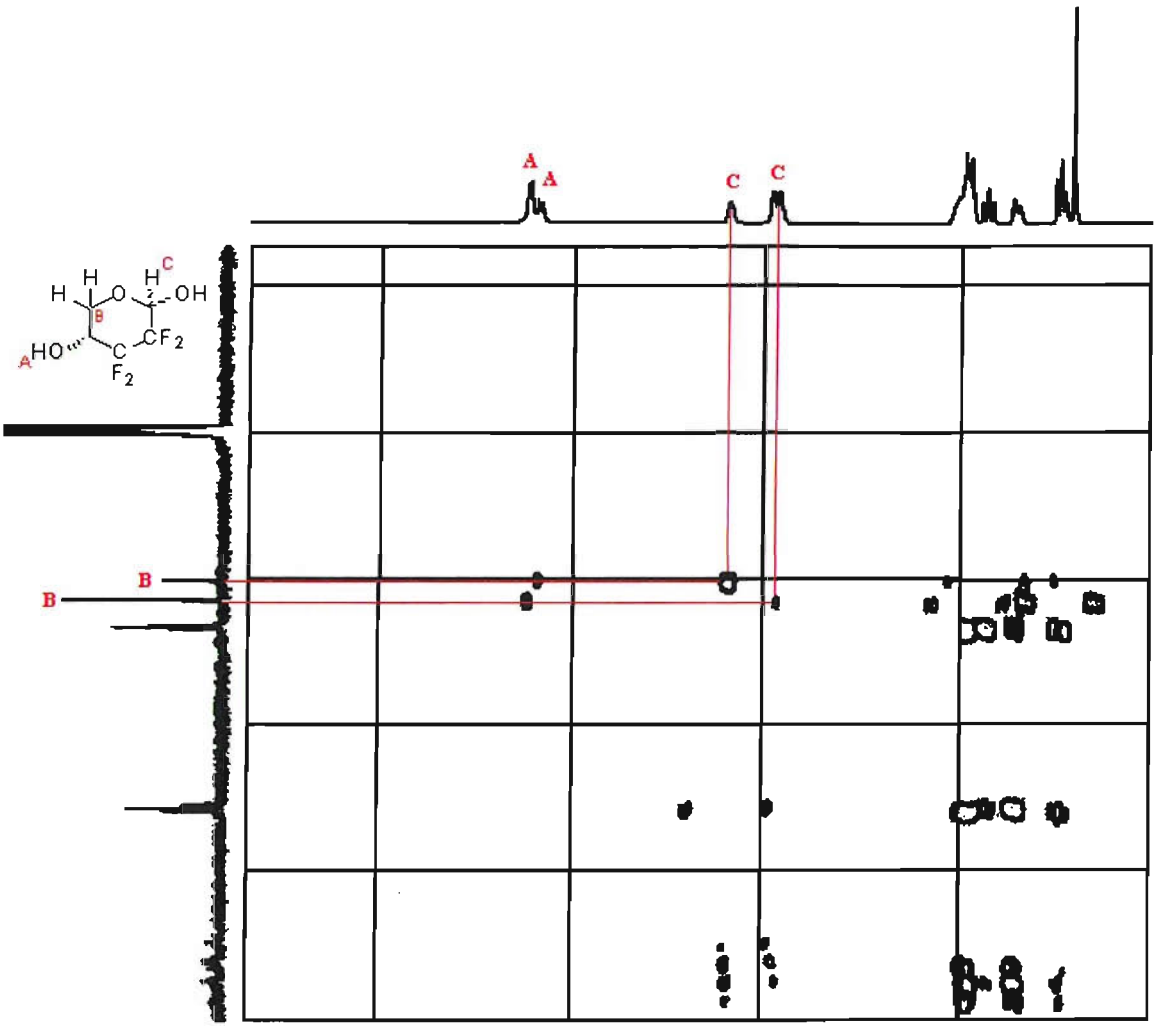
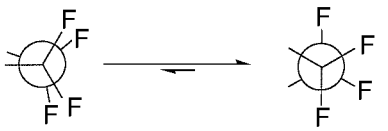


Figure 28

As was mentioned above, the isomerisation of unprotected pentafuranoses to their pyranose forms is well known.[2,5] When looking at a Newman projection along the C2-C3 bond it becomes clear why we see complete regioselectivity for the pyranose form (Figure 29).



3.32
Furanose

3.33
Pyranose

Figure 29

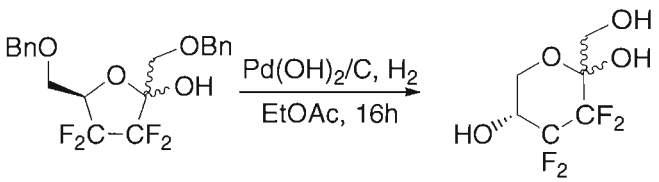
In the projection on the left, representing the furanose structure **3.32**, we can see that the electron rich fluorines are in a near eclipsed conformation. This is obviously disfavoured as the high electron density atoms that are eclipsed will attempt to repel each other. In the projection to the right, representing the pyranose structure **3.33**, we can see that the electron dense fluorine atoms are as distant from one another is as possible. Another factor which needs to be considered when discussing this isomerisation is the "fluorine *gauche* effect".[178,179]

3.34
gauche

3.35
anti

Figure 30

It has been shown than the *gauche* conformer **3.34** of 1,2-difluoroethane is lower in energy than the *anti* conformer (Figure 30).[178] This is believed to be due to optimal C-C σ-bond overlap,[180] as well as improved vicinal hyperconjugation possibilities between the electron rich C-H (HOMO) bond and C-F σ*-orbital (LUMO).[181] This effect is enough to ensure that in any sample of 1,2-difluoroethane at RT 85% of the molecules adopt a *gauche* configuration. This large stability of *gauche* orientations, when combined with the eclipsed conformation in **3.32** will ensure the favoured nature of the pyranose structure **3.31** when compared to the furanose **1.77**.



3.29 **3.36** (96%)

Scheme 56

With the deprotection of **3.14** showing regioisomerisation we were interested to see if the same transformation would occur on deprotection of the tetrafluoroketose **3.29** (Scheme 55). It is known that ketosugars isomerise less easily that their aldose counterparts, but with the disfavoured configuration of the eclipsed fluorine atoms the pyranose form could have been favoured.

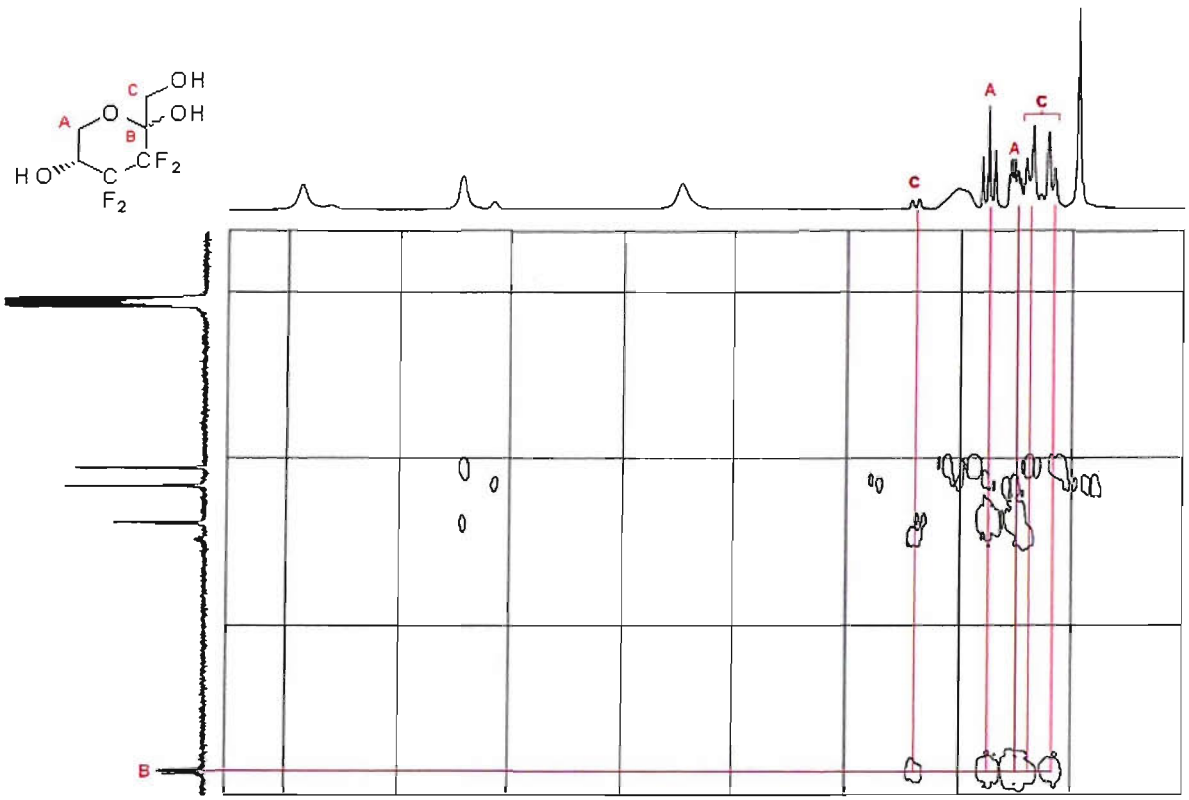
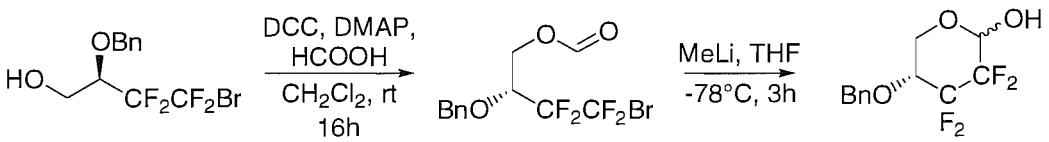


Figure 31

Confirmation of the structure of **3.36** by the same method as for **3.31** was not possible due to the lack of a proton on the anomeric centre. Instead the C-H coupling between the CH_2 protons (labelled A in Figure 31) and the quaternary anomeric carbon were observed. This analysis of the HMBC spectrum allowed us to confirm that **3.36** exists primarily in the pyranose form.

3.2.6 Synthesis of protected tetrafluoro-pentapyranose

With the structure of **3.31** established we wished to see if we could synthesise this pyranose structures independently *via* the previously developed anionic cyclisation.

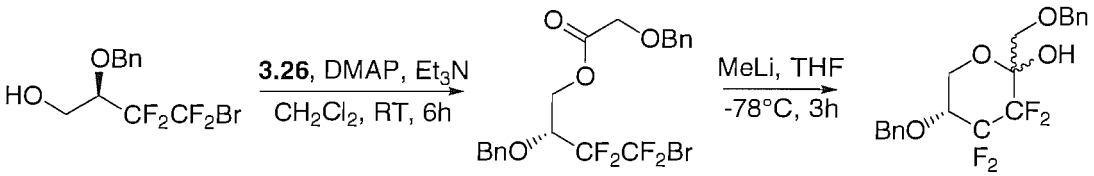


3.02 **3.37** (98%) **3.38** (69%)

Scheme 57

Fortuitously, this presented an opportunity to utilise our selective secondary protection of fluoroalkyl substituted 1,2-diols outlined in Section 2.2.1. When **3.02** was subjected to the conditions described earlier for formate ester formation, the reaction proceeded smoothly, giving **3.37** in excellent yield. Subjecting **3.37** to the conditions utilised for the anionic cyclisation yielded 69% of **3.38** as a white solid, which proved to be a mixture of anomers separable by HPLC, though it was observed that anomeric isomerisation did take place over time (Scheme 57).

With the synthesis of **3.38** so successful we wished to see if a similar route would be successful for a cyclisation with the primary α-benzyloxyacetate.



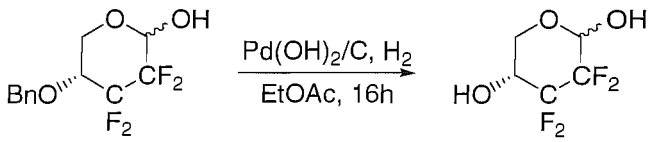
3.02 **3.39** (98%) **3.40** (65%)

Scheme 58

Treating **3.02** with the same conditions as outlined above for formation of α-benzyloxyacetates gave **3.39** in 98% yield after chromatography. The anionic cyclisation, when conducted using **3.39** as the substrate, gave a satisfying 65% yield of the desired bis-benzyl protected fructopyranose **3.40**.

These syntheses not only yielded the desired pyranose structures **3.38** and **3.40** with no difficulties, they have also considerably increased the utility of our Li-Br exchange / cyclisation process. It has so far been shown to be to synthesise various pentoses: furanose structures, ketofuranoses (from acetates and substituted acetates) and both aldo and ketopyranoses. At time of writing a synthesis where it has been used to synthesise tetraflurorethylidene substituted gluco and galactopyranoses is underway and shows great promise.[182]

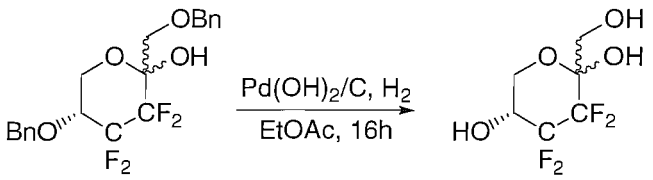
Having synthesized **3.38** and **3.40** we undertook a deprotection of these structures under similar conditions.



3.38 **3.31** (94%)

Scheme 59

As was expected we observed a high yield of a structure matching that seen in the deprotection of **3.14**, thus further confirming the stability of the pyranose structure **3.31** (Scheme 59).



3.40 **3.36** (94%)

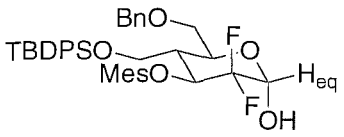
Scheme 60

Deprotection of **3.40** also proceeded smoothly giving a 94% yield of the expected **3.36** (Scheme 60).

*3.2.7 NMR Studies of the Mutarotation of **3.38***

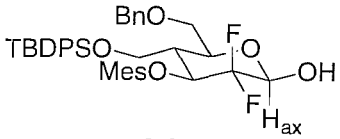
During the synthesis of **3.38** it was noted that while the anomers were separable and stable in their pure forms, in solution they slowly isomerised to a mixture of α and β anomers. In order to determine the nature of this equilibration we undertook a short NMR study to observe the behaviour of **3.38** in a variety of solvents.

The first task was to assign the anomeric configuration of each isomer. Given that crystallisation could not be achieved, and that coupling constants of the relevant signals could not be observed, the chemical shift of the anomeric proton signals became our only recourse.



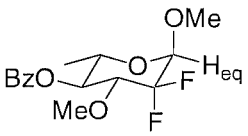
3.41

δH_{eq} = 5.27 ppm



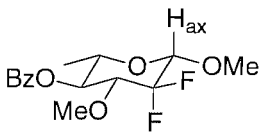
3.42

δH_{ax} = 4.72 ppm



3.43

δH_{eq} = 5.14 ppm



3.44

δH_{ax} = 4.80 ppm

Figure 32

As can be seen in Figure 32 an equatorial proton at the anomeric centre tends to a higher chemical shift that that of the corresponding axial proton.[183,184] From this we could tentatively assign the anomeric configuration of **3.38a** (5.09 ppm = α) and **3.38b** (4.94 ppm = β)

A study of both anomers in $CDCl_3$ showed that no isomerisation took place with either anomer for at least 45 hours. After that isomerisation was very slow though an accurate rate was difficult to establish due to overlap of the characteristic signals. However, an accurate rate of isomerisation could be observed when d^6-DMSO was used as solvent with the anomeric protons being easily distinguished.

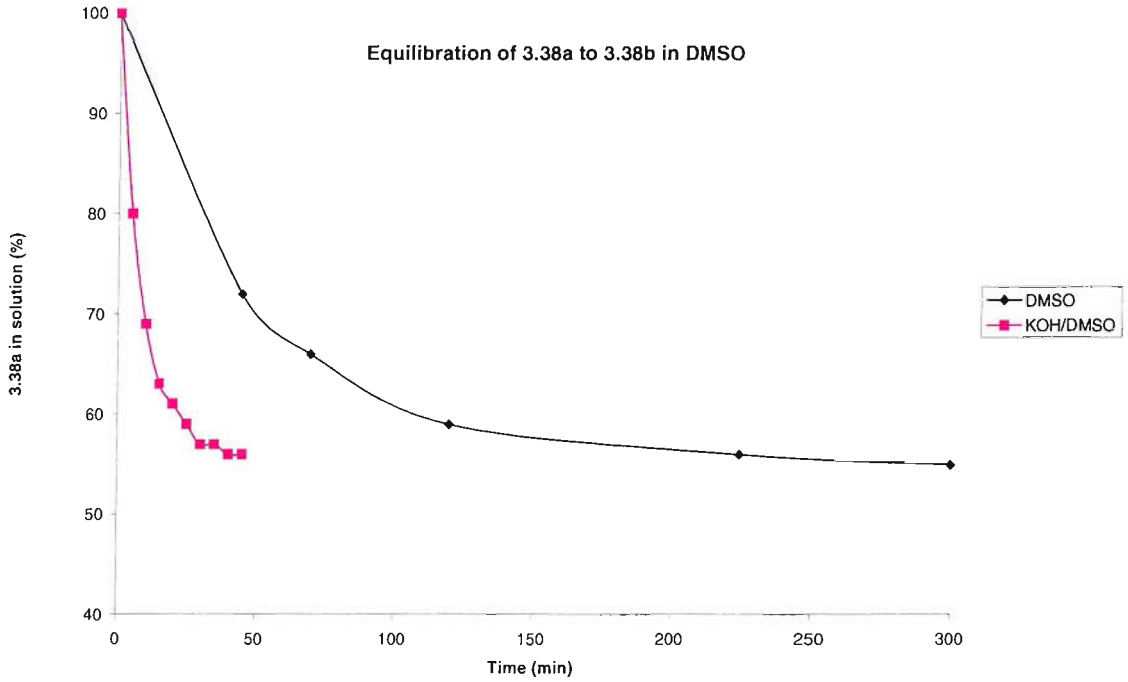
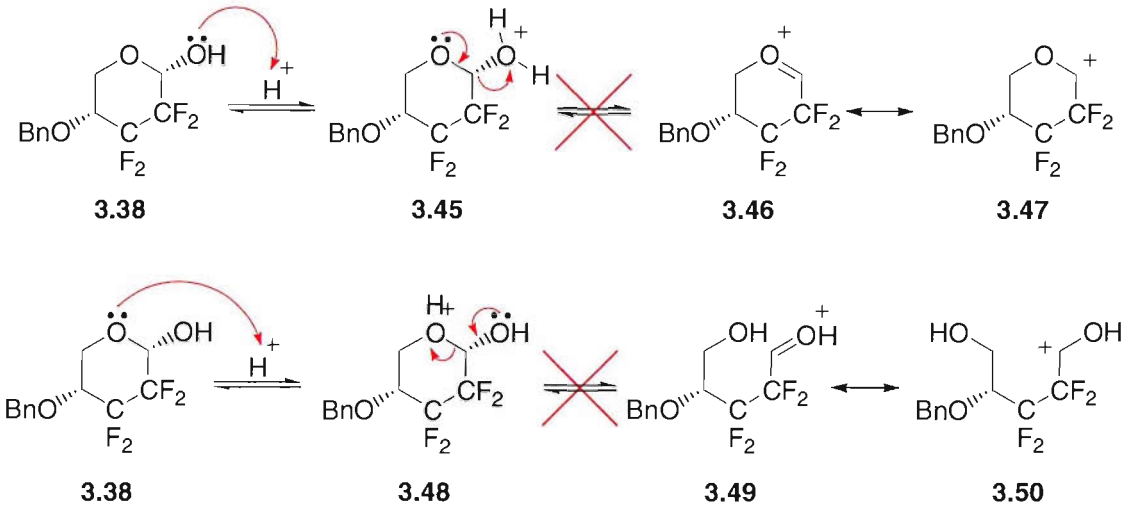


Chart 1

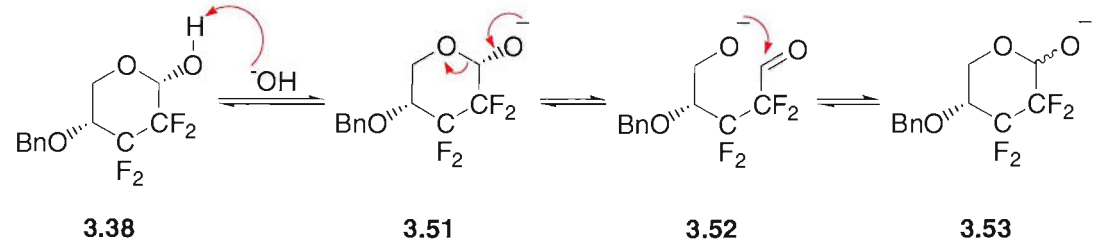
As can be seen from Chart 1, when dissolved in d^6-DMSO isomerisation occurred relatively rapidly with an equilibrium position being reached after 225 minutes. Typically, in acid solution hemi-acetals undergo rapid isomerisation, or hydrolysis; therefore it was decided to study the stability of **3.38a** in a 0.03M solution of HCl in d^6-DMSO. When studied by NMR it was found that **3.38a** had a dramatically increased stability in acid solution, with only a 12% conversion after 4639 minutes (3 days, 5 hours and 19 mins). This unexpected stability can be explained by the electron withdrawing effect of the fluorines destabilising the intermediate oxonium species (**3.46** and **3.49**) necessary for isomerisation in acidic media (Scheme 61).



Scheme 61

This slow reaction under acidic conditions is of considerable interest, not only because it is the reverse of expected carbohydrate reactivity but because it has significant consequences for future glycosylation chemistry.

With the acidic solution considerably slowing isomerisation we wanted to observe the isomerisation under basic conditions. Chart 1 shows that when dissolved in a 0.03M solution of KOH in d^6-DMSO anomeric isomerisation is extremely rapid with an equilibrium point being reached in 30 minutes.



Scheme 62

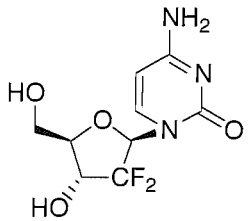
This rapid isomerism in basic conditions is due to the electron withdrawing effect of the fluorine atoms increasing the acidity off the hydrogen atom of the anomeric hydroxyl group. Deprotonation of the anomeric hydroxyl group leads to the oxyanion **3.51**. This intermediate can result in mutarotation via the mechanism outlined in Scheme 62.

In conclusion, we have outlined complementary protocols for the selective protection of fluorinated 1,2-diols. We have also developed methods for the esterification of the remaining unprotected hydroxyl function and a novel anionic cyclisation of wide scope. The cyclisation can be used to synthesis pentoses, hexoses, furanoses, pyranoses, aldoses and ketoses and gives good yields for all of these. We have detailed the subsequent deprotection of these compounds and noted the destabilising effect of tetrafluoroethylidene groups on furanose structures. We have also, briefly, investigated the effect of fluorine substitution on the rate mutarotation.

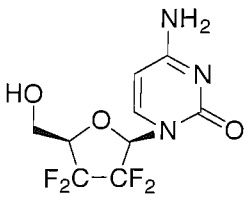
4.0 THE SYNTHESIS OF A TETRAFLUORINATED NUCLEOSIDE

4.1 INTRODUCTION

With a short and efficient synthesis of **3.14** in hand, we decided that attempts should be made to investigate potential functionalisation. With the vast biological importance of nucleosides beyond doubt, and with the difluoromethylene substituted Gemcitabine being approved as a drug for solid tumour treatment,[185] it was decided that our investigation should focus on the attempted synthesis of **1.90** (Figure 33).



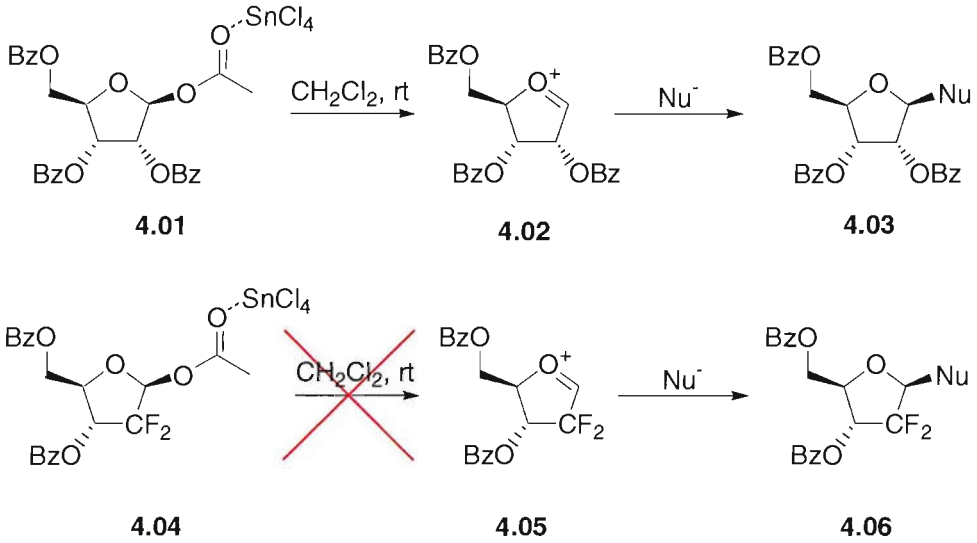
Gemcitabine (**1.28**)



1.90

Figure 33

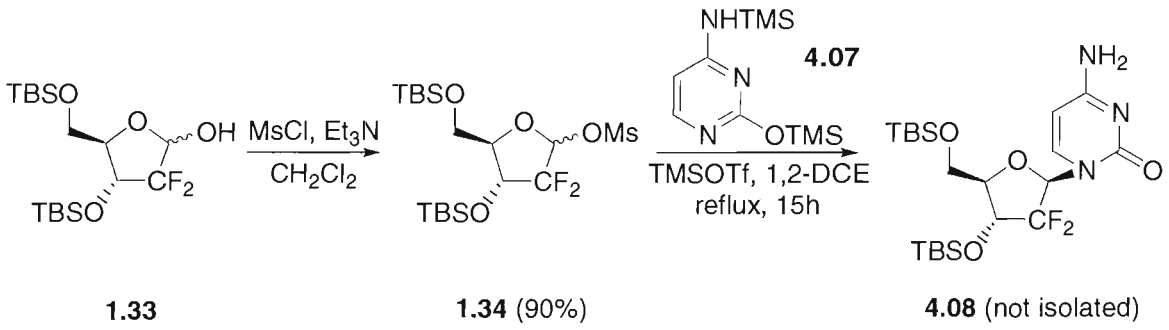
The classic procedure for the synthesis of N-glycosides is that of Vorbrüggen;[186] where conversion of the anomeric hydroxyl group to its acetate is followed by treatment with a silylated nucleobase and $SnCl_4$ (Scheme 63). This procedure gives, in general, good yields of the desired glycosides, and has wide scope with respect to the nucleobase and the structure of the sugar moiety.



Scheme 63

Unfortunately, the standard Vorbrüggen conditions are not suitable for use with sugar moieties with a CF_2 group at the C2 position. This is because the electron-withdrawing CF_2 group destabilises the intermediate oxonium ion, making the reaction unfavourable.

To overcome this difficulty a series of conditions have been reported. The most commonly used is one developed by Hertel *et al*[61] in their synthesis of Gemcitabine (Scheme 64).



Scheme 64

Synthesis of the mesylate **1.34** was reported to be straightforward. Treatment of **1.34** with bis-trimethylsilylated cytosine (**4.07**) and TMSOTf in refluxing 1,2-dichloroethane

yielded the desired **4.08** which was not isolated but was deprotected and then purified by HPLC to give the two anomers in a 25% combined yield (20 % β and 5% α).

Similar conditions have been used by Castillón *et al* in their synthesis of pyranosyl analogues of Gemcitabine,[65] where they achieved a 36% yield of the desired nucleoside. Kotra *et al* have also used these conditions in his syntheses of 2,3-dideoxy-2,2-difluoro-pentafuranosyl nucleosides achieving variable yields.[187,188]

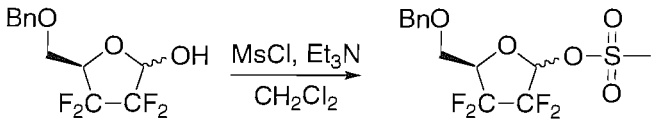
Hertel's procedure has been developed into a multi-gram process by Chou *et al*[189]. Because of the need to make large quantities of Gemcitabine, Chou developed a route less dependent on the use of particularly hazardous or expensive reagents.

Chou has also disclosed a stereoselective process for the synthesis of 2-deoxy-2,2-difluoronucelosides,[190,191] whereby the lactol substrate is reacted with an amine base at low temperature. It is believed that the low temperature shifts the α:β ratio of the lactol in favour of the more stable anomer. This more stable anion can then be trapped by addition of an electrophile, such as mesyl chloride.

In the same report Chou reports a fusion glycosylation process whereby the anomerically enriched mesylates are reacted with molten silylated nucleobases.[190] This procedure is reported to be particularly useful where, such as in our case, the C-2 substituent cannot offer 1,2-anchiomeric assistance. The fusion glycosylation has been shown to give good yields and selectivities when applied to 2-deoxy-2,2-difluorosugars, a substrate . The ability of this transformation to overcome the inherent unreactive nature of difluorosugars could lead to it being ideal for our own work.

4.2 SYNTHESIS OF THE TETRAFLUORINATED NUCLEOSIDE

We first attempted the synthesis of **1.90** using the route outlined by Hertel.[61]



3.14 **4.09** (92%)

Scheme 65

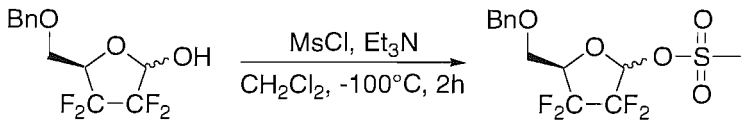
The conversion of **3.14** to its anomeric mesylate proceeded smoothly, giving a 92% of the desired compound on treatment with MsCl and Et_3N in CH_2Cl_2 at room temperature. Unfortunately, initial attempts to convert the mesylate into the desired nucleoside under Hertel's conditions (**4.07**, DCE, TMSOTf, reflux, 15h) failed to produce any of the desired product. When Chou's modified conditions (DCE replaced with xylene)were applied we isolated only 2% of the desired compound.

With the long reaction time and high reaction temperature, this reaction appeared to be a candidate for the use of microwave technology. An attempted reaction using 1,2-dichloroethane (as per Hertel *et al*[61]) gave a satisfying 35% yield after 10 min at 140°C, an additional 40 min at 160°C and then another 30 min at 180°C. This seemingly random sequence of reaction times was used as the temperature of the solvent had to be gradually increased to determine if the sealed vial used as a vessel for the reaction could withstand the pressure generated at these elevated temperatures. It was found that 180°C was the maximum temperature achievable for 1,2-dichloroethane as above this, the pressure within the vial approached the predetermined limit. A reaction at 170°C for 2 h yielded an excellent 53% yield for the transformation. Whilst an attractive process, the reaction at 170°C was unworkable as a reaction time of 2 h meant that the microwave reactor was occupied for a significant portion of the day and this impinged on other research. In order to shorten the reaction time a reaction using *m*-xylene (as per Chou *et al*[189])was

attempted; after 10 min at 200°C and a further 10 min at 225°C, all starting material was consumed by TLC but only 11% of **4.10** was isolated.

With these methods proving unsatisfactory, it was decided to attempt the stereoselective fusion glycosylation outlined by Chou.[190]

The first step was to attempt to improve the anomeric ratio of our mesylate by trapping the most stable anomer with mesyl chloride at low temperature. Treatment of a cold CH_2Cl_2 solution of **3.14** (α:β = 1:1)with Et_3N followed by addition of MsCl furnished the desired mesylate with a much improved 3.5:1 anomeric ratio in an excellent yield.



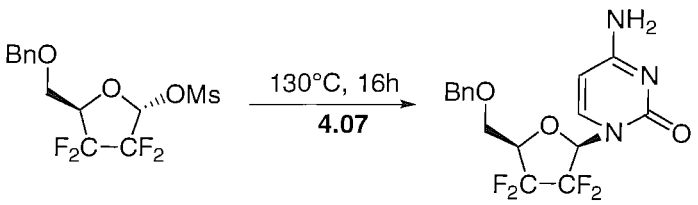
3.14

4.09 (97%)
3.5:1

Scheme 66

In the fusion glycosylation outlined by Chou[190] molten **4.07** becomes the medium for the reaction and after stirring overnight in molten **4.07**, we achieved a 72% of **4.10** as a 2:2 mixture of anomers (Scheme 67). This change in the anomeric ratio shows the possibility that the displacement proceeds via both SN1 and SN2 pathways. If the reaction proceeded purely by SN1 then we would expect a much 1:1 ratio although C5 and it's associated benzyl group may block the "top" face of the oxonium ion giving a ratio where the α anomer would predominate. If the reaction proceeded entirely via SN2 we would expect to see a conservation of the ratio, with complete inversion of the selectivity.

However, it is more likely that the reaction is proceeding by a S_N1 mechanism with a tightly bound ion pair. The tightly bound nature of this pair would mean that the mesylate counter-ion would still partially block one face of the oxonium ion; resulting not in a 1:1 mixture but incomplete inversion, thus giving the appearance of a partial S_N2 mechanism whilst actually being exclusively S_N1.

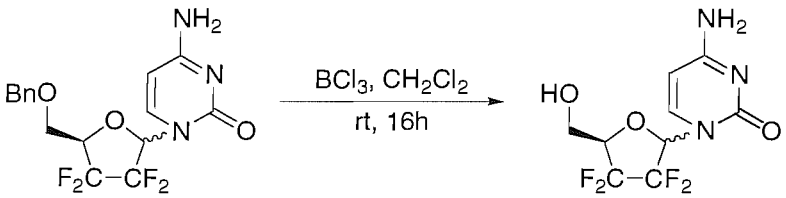


4.09
3.4:1 α:β

4.10 (73%)
2.2:1 β:α

Scheme 67

With a good yield of **4.10** achieved the deprotection of the benzyl ether would furnish the desired nucleoside.



4.10

4.11 (92%)

Scheme 68

The benzyl protecting group is a somewhat unusual protecting group in nucleoside chemistry, as reduction of the base has been observed under the standard hydrogenolysis conditions used for their removal.[192] However, treatment of **4.10** with boron trichloride[192] (Scheme 68) gave an excellent yield of the desired **4.11** after chromatography.

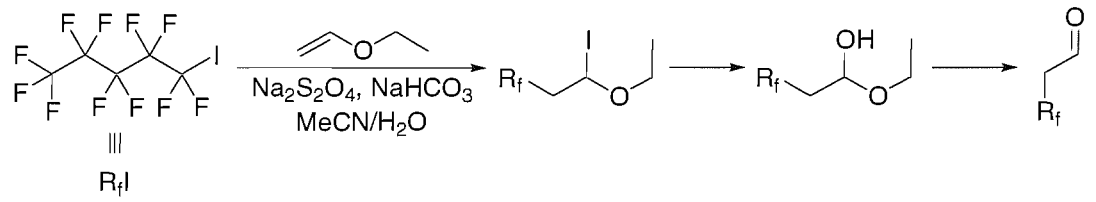
To briefly summarise, we have taken the protected pentafuranose **3.14**, and converted it to the corresponding nucleoside *via* its anomeric mesylate. The anomeric ratio of the compound could be enhanced by trapping the more stable of the anomers with MsCl at low temperature. Conversion of the mesylate to the nucleoside was accomplished by a fusion glycosylation, which gave the desired product in an excellent yield.

5.0 SYNTHESIS OF TETRAFLUOROETHYLIDENE HEXOSES VIA RADICAL METHODOLOGY

5.1 INTRODUCTION

The addition of perfluoroalkyl halides to alkenes and alkynes is one of the most used reactions for introducing perfluoroalkyl groups into organic substrates. Perfluoroalkyl radicals can be generated in a multitude of ways and the advantages and disadvantages of these methods have been well reported.[193-197]

In section 1.5.1 we outlined the retrosynthesis of a tetrafluorohexose **1.74** whereby through two well precedented disconnections we arrived at the primary protected 1,2-diol **3.06** and ethyl vinyl ether as synthons.



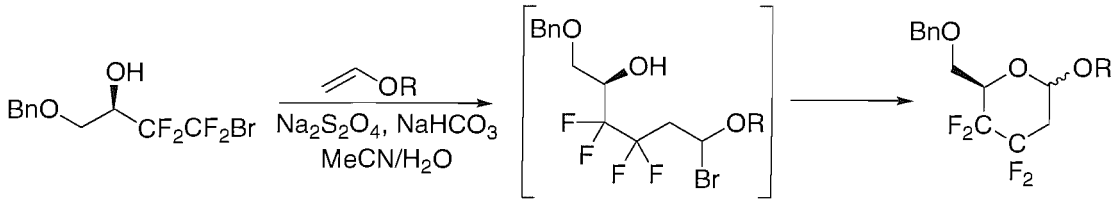
5.01 **5.02** **5.03** **5.04**

Scheme 69

The addition of perfluoroalkyl radicals to vinyl ethers is well known, and has been accomplished using a variety of methodologies.[198-202] Foremost amongst these methods is the use of sodium dithionite as a radical initiator.

Huang, who first developed this methodology noted that after formation of the perfluoroalkyl centred radical, addition to ethyl vinyl ether in aqueous acetonitrile furnished the fluoroalkyl acetaldehydes such as **5.04** (Scheme 69).[200,201,203] The explanation as to how this aldehyde was formed was straightforward; hydrolysis of initial

adduct **5.02** would yield the unstable hemi-acetal **5.03** which would then decompose to the aldehyde **5.04**.

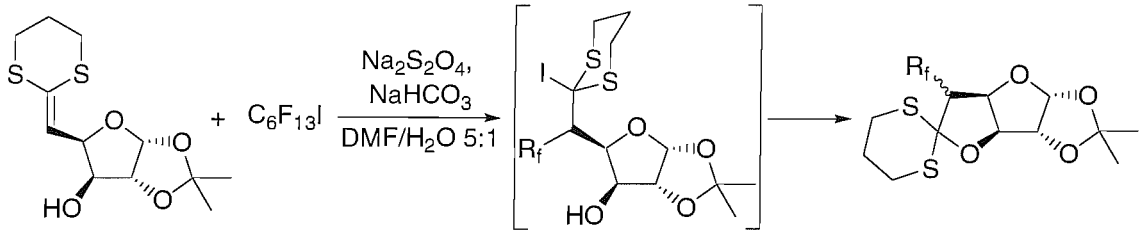


3.06 **5.05** **5.06**

Scheme 70

We hoped that this methodology would facilitate the synthesis of a tetrafluorinated hexose. As shown in Scheme 70, a radical addition / atom transfer / nucleophilic cyclisation sequence was envisaged and, was hoped, would give the desired hexose in a single step from our central intermediate **3.06.**

This reaction sequence has some precedent. Portella has reported the intramolecular trapping of an iodide adduct resulting from the addition of a perfluoroalkyl iodide **5.07** to a ketene dithioacetal **5.06** (Scheme 71).[204]

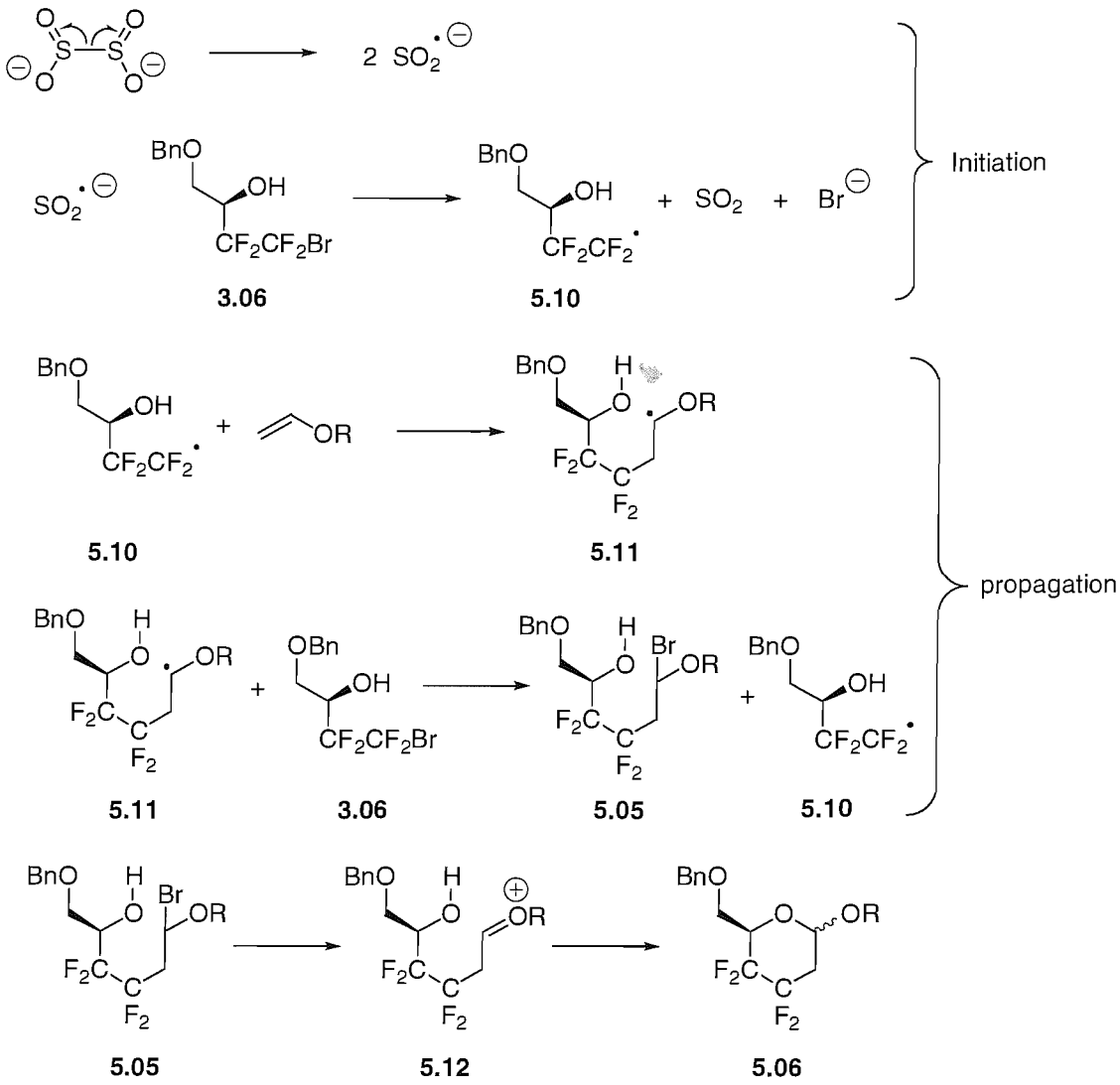


5.06 **5.07** **5.08** **5.09** (60%)

Scheme 71

Portella has further developed this methodology, utilising it in the synthesis of 5-deoxy-5-*C*-trifluoromethyl-aldurono-6,3-lactones,[205] of 2-*C*-trifluorometylated heptopyranoses[206] and in the preparation of 2-perfluoroalkylidenemethyl-1,4-dioxanes.[207]

The detailed reaction mechanism is explained in Scheme 72.

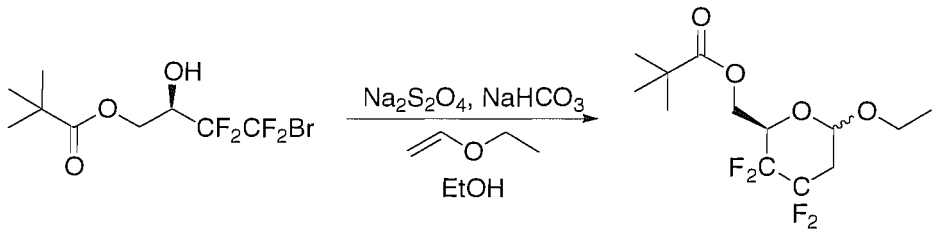


Scheme 72

It begins with the homolysis of the S-S bond in $S_2O_4^{2-}$, which liberates two equivalents of the SO_2 radical anion inducing a single electron transfer to **3.06**. This results in cleavage of a bromide anion, generating a stabilised CF_2 centred radical. Intermolecular addition of this radical to the enol ether gives rise to the secondary radical **5.11**. Propagation occurs by this new, secondary radical undergoing atom transfer, abstracting a bromine from another molecule of the starting material yielding the fluoroalkyl radical **5.10** and

α-bromo ether **5.05**. This would then cyclize either by a SN1 or SN2 type process to give the ethyl glycosides **5.06.**

5.2 DEVELOPMENT OF A RADICAL ADDITION / ATOM TRANSFER / NUCLEOPHILIC CYCLISATION REACTION



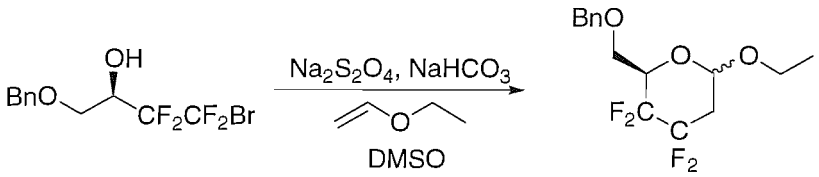
3.04 **5.13** (30%)

Scheme 73

The first procedure involved the addition of $Na_2S_2O_4$ (1 eq)and $NaHCO_3$ (2 eq) to a solution of **3.04** and ethyl vinyl ether (3.3 eq)in refluxing EtOH. The reaction, after 6 days at reflux (with addition of ethyl vinyl ether each day) gave only 30% of the desired **5.13** as a mixture of separable anomers. Another procedure, analogous to the first reaction but with $MeCN/H_2O$ as solvent resulted in a similarly long reaction time, and the problem of the continual evaporation of ethyl vinyl ether. The reaction was still incomplete after 52 h. However, upon continual addition of initiator and vinyl ether (3.3 eq of EVE, 1.28 eq of $Na_2S_2O_4$ and 2.88 eq of $NaHCO_3$ every 30 min), a much shorter reaction time was required with the reaction complete in 5 h giving a 40% yield of **5.13.**

With this procedure proving unsatisfactory, attention was turned to possible alternatives. A reaction conducted in DMSO at 80°C with 1.5 eq of $Na_2S_2O_4$, $NaHCO_3$ and 10 eq of EVE gave a promising 44% of **5.13.** A repeat of the reaction at room temperature gave 60% of **5.13** after 16h.

It was at this point in the research that the selective primary benzylation of the diol was developed and so the rest of the radical chemistry was developed with the primary benzyl ether **3.06.**

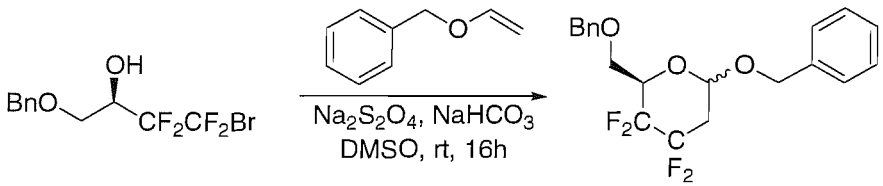


3.06 **5.14** (61%)

Scheme 74

Addition of $Na_2S_2O_4$ and $NaHCO_3$ (1.5 eq each) to a room temperature solution of **3.06** and EVE (10 eq) in dry DMSO resulted, after 16 h at room temperature, in a 61% yield of **5.14**. In comparison to the reactions with $MeCN/H_2O$, which were quite capricious, when DMSO was used as solvent we saw consistently good yields.

Attempts to replace $Na_2S_2O_4$ as the initiator with AIBN and $Pd(PPh_3)_4$ all resulted in the recovery of starting material.



3.06 **5.15** (56%)

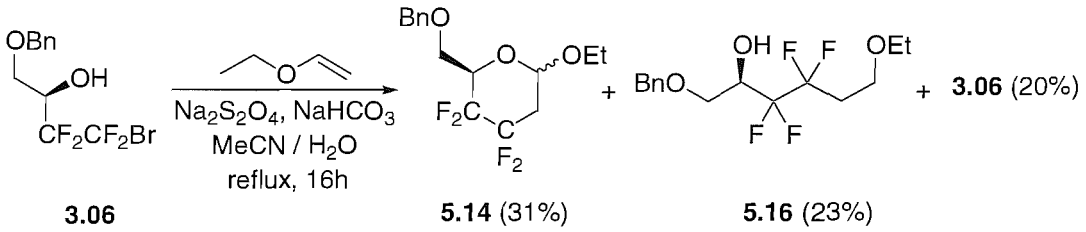
Scheme 75

Reactions with benzyl vinyl ether (1.5 eq) instead of EVE proceeded successfully, though in general, with lower yields than those for EVE (56%). Unfortunately the reaction proved unsuccessful when vinyl acetate was used.

In efforts to improve the yields of these transformations, we varied several factors. Experiments with varying amounts of initiator were trialled, and it was found that a lowering of the amount of $Na_2S_2O_4$ from 1.5 equiv. to 1.2 equiv. resulted in only a 26% yield. An increase in the loading of initiator (3 equiv.) resulted in a 56% yield,

comparable to that obtained previously. In short, a decrease in initiator loading has a considerable adverse effect on the reaction but a larger excess gives no benefit. Efforts to establish the effect of the amount of vinyl ether were conducted using benzyl vinyl ether as the volatility of EVE made it possible that the concentration of the reaction, with respect to EVE, would continually change due to evaporation. In the event, it was found that variation of the amount of vinyl ether used was a minor factor in the transformation; reactions with 1.5 eq, 3.0 eq and 5 eq of benzyl vinyl ether gave 44%, 49% and 47% respectively.

Attention was turned to accounting for the loss of mass balance in the reaction and so, with elution of previously base-line impurities during chromatography we found a series of by-products, whose constituents varied depending on reaction conditions.

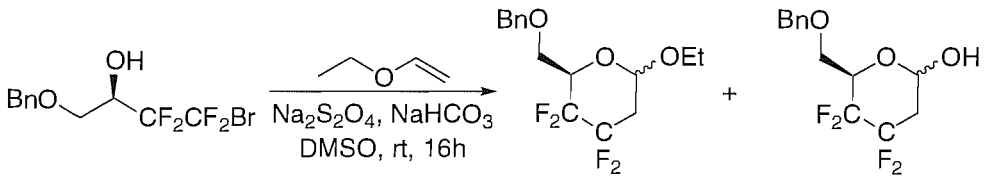


3.06 **5.14** (31%) **5.16** (23%)

Scheme 76

With MeCN/H_2O systems we observed a 31% yield of the desired **5.14** from an incomplete reaction (Scheme 76); we also recovered a 23% yield of the reduced adduct **5.16** formed by what is presumed to be H atom abstraction from the bulk solvent by the intermediate radical species **5.11**.

When wet DMSO was used as solvent we saw a similar mix of products, though the reaction went to completion. We isolated 51% of the reduced **5.16** and a surprisingly small 8% yield of **5.14**.



3.06 **5.14** (56%) **5.17** (33%)

Scheme 77

When the reaction is conducted in anhydrous DMSO we isolate none of the reduced product **5.16**, but 33% of the hemi-acetal **5.17** as by-product (Scheme 77). When the reaction was repeated we isolated a 64% yield of **5.14**, 6% of the reduced **5.16** and 24% of the hemi-acetal.

The presence of the hemi-acetal under the anhydrous conditions and it's absence under wet conditions is unexpected. It is clear that the intermediate α–bromo ether can yield the oxonium ion via elimination of bromide, and that in the presence of H_2O this oxonium ion can under go nucleophilic attack by water or hydroxide to give an acyclic hemi-acetal; this could then hydrolyse to the aldehyde, which after cyclisation would yield **5.17**. By this mechanism the presence of the hemi-acetal can be explained, but why it is absent in hydrous conditions is not yet explained.

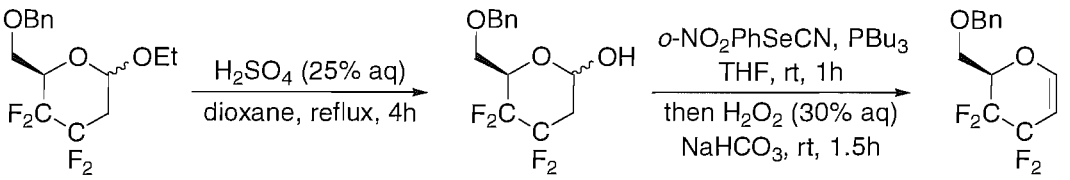
This difference in reaction profiles is of interest and so will be the subject of future investigations.

5.2.1 Functionalisation and deprotection of the tetrafluoroethylidene substituted hexoses

As the ultimate aim of is to synthesize hexapyranosides with an alcohol or amino group at C-2, research was undertaken to enable access to these structures.

One option is to use glycals as an intermediate. Glycals are extremely important in carbohydrate synthesis with great utility as glycosylation precursors. With our lack of substitution at C2 in our hexose we decided that synthesis of the glycal offered a good

opportunity to investigate glycosylations and would be a suitable method of introducing substitution at this carbon.



5.14 **5.17** (93%) **5.18** (51%)

Scheme 78

Deprotection of the ethyl acetal with H_2SO_4 (25% aq) in refluxing dioxane gave the hemi-acetal **5.17** in excellent yield after chromatography. Initial attempts to form the glycal involved the formation of the anomeric mesylate with *in situ* elimination.[208] Unfortunately this reaction only resulted in a complex mixture of products, none of which were the desired **5.18**. Castillón has developed a method for the synthesis of furanoid glycals[209,210] based on the oxidative elimination of 1-selenoglycosides and has successfully applied it to 3,3-difluoropyranoses.[63] Rather than use the two-step process outlined by Castillón, we utilised a one-pot Grieco elimination.[211] Treatment of **3.17** in THF with *ortho*-nitrophenyl selenocyanide and PBu_3 at room temperature, and subsequent addition of H_2O_2 (30% aq) gave the desired **5.18** in 51% after chromatography.

In summary, the synthesis of tetrafluorinated hexapyranosides was achieved using a tandem radical addition/intramolecular cyclisation sequence. Selective deprotection at the anomeric centre allowed the synthesis of the corresponding glycal, a precursor for the introduction of an alcohol or amino group at the C-2 position.

6.0 CONCLUSION AND FUTURE RESEARCH

In summary, we have accomplished the major aims of the project. The synthesis of tetrafluoropentoses has been developed starting from a small, commercially available fluorinated building block. In the course of their synthesis we have utilised the AD; achieving a high yield despite the unreactivity of the substrate. This AD also delivers satisfactory enantioselectivity, with the result both in terms of yield and enantioselectivity being one of the best amongst α-polyfluorinated primary alkenes. Following this AD we developed complementary methodologies for the protection of the 1,2-diol. Under basic conditions we achieve selective secondary protection, and when the chemistry of stannylene acetals is harnessed we can selectively protect the primary alcohol.

The anionic cyclisation that follows functionalisation of the protected diol is a novel process with wide scope. It can be used to produce hexoses, and pentoses both in pyanose and furanose forms in high yield. This reaction should enable the synthesis of a whole family of fluorinated carbohydrates. However, this cyclisation only allows for the synthesis of tetrafluroethylidene substituted carbohydrates where the fluorination is located next to the anomeric centre.

Alongside this methodology we have developed a useful radical addition/atom transfer/nucleophilic ring closure sequence that has enabled the synthesis of tetrafluorinated hexoses where the fluorination is distanced from the anomeric centre. Subsequent functionalisation of these compounds has led to the synthesis of a tetrafluorinated glycal; a compound expected to enable the synthesis of tetrafluorinated carbohydrates with various substrates at C-2, particularly alcohols and amino groups.

Derivatisation of the tetrafluoropentafuranose has led to the tetrafluorinated nucleoside, a compound of interest both as a challenging synthetic target and its potential biological activity.

In terms of future research, this project has an obvious successor in the synthesis of other tetrafluoromonosaccharides and there incorporation into pharmaceutical or natural products. Of particular interest will be the glycosylation chemistry of these compounds as it is likely to be unique.

Furthermore, the problem of epimerisation during basic benzylation will have to be solved. There is also further scope in further optimising the AD reaction. This could be improved both through research into different co-oxidants with a view to accelerating the reaction and through the completion of the fluorinated ligand synthesis and investigation of the AD with these new spacer molecules.

To conclude, we have synthesised several tetrafluoroethylidene carbohydrates and briefly investigated their chemistry. We have done this *via* a fluorinated building block, an enantioselective dihydroxylation and several novel cyclisations.

7.0 EXPERIMENTAL

7.1 GENERAL METHODS

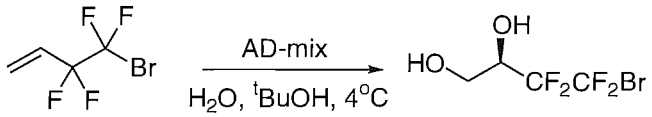
^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker DPX400 or AV300 spectrometer as indicated. Chemical shifts are quoted in ppm relative to residual solvent peaks as appropriate. ^{19}F NMR spectra were recorded on a Bruker AV300 spectrometer or a Bruker DPX400 spectrometer and are referenced to C_6F_6 and $CFCl_3$ respectively. EIMS were recorded on a Thermoquest Trace GCMS Quadrapole system. Infrared spectra were recorded as neat films on a Nicolet Impact 380 ATR spectrometer. Melting points were recorded on a Gallencamp Melting Point Apparatus and are uncorrected.

Column chromatography was performed on 230-400 mesh Matrex silica gel. Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250×22mm column eluting at 20 mL min^{-1}, connected to a Kontron 475 refractive index detector. Reactions were monitored by TLC (Merck) with detection by alkaline $KMnO_4$ oxidation.

Reaction solvents were dried before use as follows: THF and Et_2O were distilled from the sodium/benzophenone ketyl; CH_2Cl_2, m-xylene and Et_3N were distilled from CaH_2; toluene and 1,2-dimethoxyethane were distilled from sodium; pyridine was double distilled from CaH_2 and stored in a Schlenk flask for later use; DMSO was distilled under reduced pressure from CaH_2 and was stored over molecular sieves; HMPA was distilled from CaH_2 and stored over 4A molecular sieves. All reaction vessels were flame dried under vacuum and cooled under nitrogen prior to use and all experiments were carried out under a nitrogen atmosphere. All other reagents were purchased from commercial sources and used without further purification.

7.2 PROCEDURES AND CHARACTERISATION

(2*R*)-4-bromo-3,3,4,4-tetrafluorobutane-1,2-diol (1.79)



1.83 **1.79**

A single necked 1L RB flask was charged with $K_3Fe(CN)_6$ (52.7 g, 0.16 mol), K_2CO_3 (22.1 g, 0.16 mol), $K_2OsO_4.2H_2O$ (0.40 g, 1.08 mmol) and $(DHQ)_2PYR$ (0.85 g, 1.08 mmol). H_2O (270 mL) and ^tBuOH (270 mL) were added, and the reaction stirred until complete dissolution occurred. The reaction was cooled to 4°C whilst stirring and 4-bromo-3,3,4,4-tetrafluorobut-1-ene (11.2 g, 54.0 mmol) was added via syringe and the reaction stirred at 4°C for 9 days. Solid Na_2SO_3 (81.0 g) was added and the reaction allowed to warm to RT with vigorous stirring over 2 h. The reaction was diluted with H_2O (50 mL) and Et_2O (200 mL), the layers were separated and the aqueous phase extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with HCl (2M, aq, 2 × 50 mL) and brine (50 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a colourless oil. The acidic extracts were neutralised with NaOH (2M, aq) and then extracted with EtOAc (2 × 100 mL). The EtOAc extracts were dried over $MgSO_4$, filtered then concentrated to give a white solid, which, after recrystallisation from EtOAc gives pure $(DHQ)_2PYR$. The colourless oil obtained was purified by vacuum distillation (55°C, 0.1 mm Hg) to give a colourless oil which crystallised on standing to give a white deliquescent solid (12.0 g, 93%).

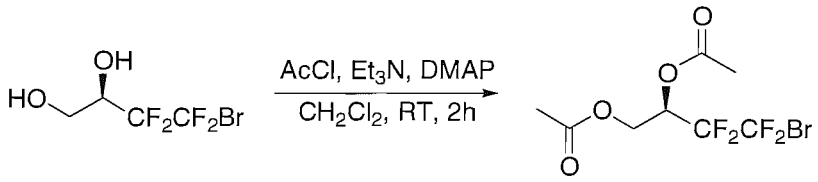
IR (neat): 3388 (br. s), 2956 (m), 2900 (w), 1414 (w), 1151 (s), 1087 (s), 919 (m).
^{1}H NMR (400 MHz, CD_3CN): δ 4.20 (1H, m, C**H**OH, simplifies upon D_2O exchange); 4.00 (1H, d, J = 7.3 Hz, CHO**H**, exchanges with D_2O); 3.78 (1H, m, **CH**HOH simplifies upon D_2O exchange); 3.66 (1H, dt, J = 11.8, 6.0 Hz, C**H**HOH) upon D_2O exchange simplifies to 1H, dd, J = 11.8, 7.0 Hz); 3.08 (1H, t, J = 6.2 Hz, CH_2O**H**, exchanges with D_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ 117.1 (tt, J = 312.5, 39.5 Hz, **C**FFBr), 114.4 (ddt, J = 262.0, 257.8, 31.0 Hz, **C**FF) (m, **C**FF and **C**FFBr); 69.4 (dd, J = 27.4, 22.1 Hz, **C**HOH); 60.4 (**C**H_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ -64.43 (2F, ddd, J = 230.5, 181.6, 5.4 Hz, C**F**$_2$Br), -116.93 (1F, dt, J = 271.9, 5.4 Hz, C**F**FCF_2Br), -123.29 (1F, ddd, J = 271.9, 17.2, 6.5 Hz, CF**F**CF_2Br).

EIMS: m/z (%): 242 and 240 (M^+, 12, 1:1 ratio), 223 and 221 (16, 1:1 ratio), 192 and 190 (16, 1:1 ratio) 141 (45), 129 (34), 111 (100).

(2*R*)-(2-Acetoxy-4-bromo-3,3,4,4-tetrafluorobutyl) ethanoate (2.22)



1.79 **2.22** (83%)

1.79 (0.1 g, 0.41mmol) was dissolved in CH_2Cl_2 (3 mL) and Et_3N (0.14 mL, 1.0 mmol), and DMAP (0.005g, 0.04 mmol) was added. Acetyl chloride (0.071 mL, 1.0 mmol) was added dropwise and the reaction stirred at RT for 2 h. The reaction was quenched by the addition of HCl (0.5M, aq, 10 mL). The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 5 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pentane / Et_2O, 80:20) gave a colourless oil (0.111 g, 83%).

IR (neat): 2974 (w), 1752 (s), 1372 (m), 1203 (s), 1143 (s), 1085 (s),1048 (m), 832 (m), 754 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.77 (1H, dtd, J = 16.4, 7.1, 3.3 Hz, C**H**OAc), 4.60 (1H, ddd, J = 12.3, 3.3, 1.7 Hz, CH**H**CH), 4.24 (1H, dd, J = 12.2, 7.4 Hz, CH**H**CH), 2.15 (3H, s, CH_3), 2.07 (3H, s, CH_3).

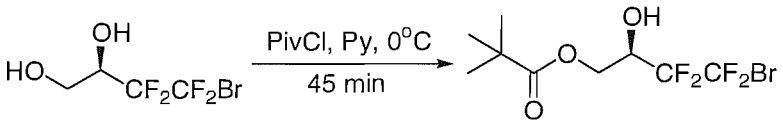
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (**C**O), 168.7 (**C**O), 66.70 (dd, J = 30.1, 22.4 Hz, **C**HCF_2), 60.1 (**C**H_2), 20.5 (**C**H_3), 20.3 (**C**H_3). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -64.70 (2F, s, CF_2Br), -114.25 (1F, d, J = 272.9 Hz, CHC**F**F), -120.21 (1F, ddt, J = 272.9, 17.2, 4.3 Hz, CHCF**F**).

CIMS: m/z (%):344 and 342 $(M+NH_4^+)^+$ (6, 1:1 ratio), 267 and 265 $(M-OAc)^+$ (30, 1:1 ratio), 203 (8), 183 (15).

HRMS (ES$^+$) for $C_8H_9O_4{}^{79}BrF_4Na$ $(M+Na)^+$ calcd 346.9513, found 346.9513.

(2*R*)-(4-bromo-2-hydroxy-3,3,4,4-tetrafluorobutyl) ethanoate (3.04)



1.79 **3.04** (81%)

To a stirred solution of **1.79** (0.444g, 1.84 mmol) in dry pyridine (3.45 mL) at 0 °C was added pivaloyl chloride (0.45 mL, 3.68 mmol) and the reaction stirred for 45 min at 0 °C. Ice (5 g) was added and the reaction stirred for 5 min. The mixture was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (pet ether / Et_2O, 8 : 2) gave a white solid (0.478 g, 81%).

m.p. 49–52°C.

IR (neat): 3045 (m), 2984 (m), 1735 (m), 1266 (s), 1156 (m), 740 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.50–4.38 (3H, m, C**H**H**O** and C**H**OH); 3.04 (1H, d, J =7.2 Hz, CHO**H**); 1.24 (9H, s, C(C**H**$_3$)$_3$).

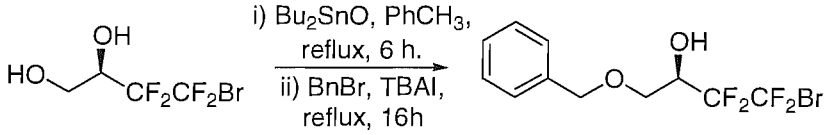
^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2 (**C**O); 68.5 (dd, J = 28.0, 23.0 Hz, **C**HOH); 62.8 (**C**HHO); 38.9 (**C**), 27.0 (3×**C**H$_3$). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -65.77–67.34 (2F, m, CF_2Br), -118.33 (1F, app. dt, J = 274.12, 4.5 Hz, CF**F**CF_2Br), -126.88 (1F, ddd, J = 271.4, 18.5, 7.6 Hz, C**F**FCF_2Br)

EIMS: m/z (%): 327 and 325 ($M+H^+$, 10, 1:1 ratio), 281 (5), 225 (8), 129 (10), 103 (52), 85 (90), 69 (50).

HRMS (EI) for $C_9H_{14}O_3{}^{79}BrF_4$ $(M+H)^+$ calcd 325.0062, found 325.0067.

(2*R*)-1-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro-butan-2-ol (3.06)



1.79 **3.06** (97%)

Diol **1.79** (5.0 g, 20.75 mmol) and Bu_2SnO (6.20 g, 24.89 mmol) were dissolved in dry toluene (75 mL). The reaction was brought to reflux and stirred under Dean and Stark conditions for 6 h. BnBr (2.96 mL, 24.89 mmol) and TBAI (1.92 g, 5.19 mmol) were added and the reaction refluxed for a further 16 h. The reaction was allowed to cool, diluted with Et_2O (100 mL), washed with KF (10 % (w/v), aq, 2 × 25 mL), dried over $MgSO_4$, filtered and then concentrated *in vacuo*. Purification by column chromatography (pet ether / Et_2O, 80:20) gave a pale yellow oil (6.64 g, 97%) which can solidify on standing to a low melting solid.

IR (neat): 3432 (br. m), 2931 (m), 2875 (m), 1497 (w), 1455 (w), 1367 (w), 1154 (s), 1094 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.32 (5H, m, Ar**H**); 4.62 (2H, s, **CH_2**Ph); 4.37 (1H, m, **C**HOH, simplifies upon D_2O exchange); 3.82–3.74 (2H, m, **C**H**H**OBn and **CH**H**O**Bn); 2.98 (1H, br. s, CHO**H**, exchanges with D_2O).

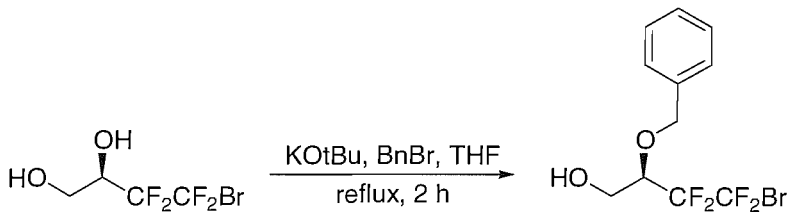
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9 (Ar**C**); 128.6 (2 × Ar**C**H); 128.2 (Ar**C**H); 127.8 (2 × Ar**C**H); 73.8 (**C**H_2Ph); 68.5 (dd, J = 28.2, 22.3 Hz, **C**HOH); 67.5 (**C**H_2CH). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -65.7–67.3 (2F, m, **C**F_2Br), -118.37 (1F, app. d, J = 270.3 Hz, **CF**FCF_2Br), -127.0 (1F, ddd, J = 270.3, 18.5, 7.6 Hz, **CF**FCF_2Br).

EIMS: m/z (%): 332 and 330 (M^+, 4, 1:1 ratio), 249 (10), 107 (24), 91 (100).

HRMS (EI) for $C_{11}H_{11}O_2{}^{79}BrF_4$ $(M)^+$ calcd 329.98785, found 329.97846.

(2*R*)-2-Benzyloxy-4-bromo-3,3,4,4-tetrafluoro-butan-1-ol (3.02)



1.79 **3.02** (47%)

To a stirred solution of **1.79** (0.25 g, 1.04 mmol) in THF (5 mL) was added KO^{t}Bu (0.116 g, 1.04 mmol). The reaction was brought to reflux and stirred for 15 min. BnBr (0.123 mL, 1.04 mmol) was added dropwise over 1 h and the reaction stirred at reflux for 2 h. The reaction was quenched with NH_4Cl (sat. aq., 2 mL), EtOAc (15 mL) was added, the layers separated. The organic phase was washed with HCl (1M, 2 × 10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant colourless oil was purified by column chromatography (pet ether / Et_2O, 90:10) to give a colourless oil (0.162 g, 47%).

IR (neat): 3407 (br. w), 2947 (w), 2887 (w), 1456 (w), 1212 (m), 1126 (s), 1086 (s), 915 (m) cm^{-1}.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 7.42–7.34 (5H, Ar**H**), 4.89 (1H, d, *J* = 11.0 Hz, C**H**HPh), 4.68 (1H, d, *J* = 11.3 Hz, C**H**HPh), 4.14 (1H, m, C**H**OBn), 3.89 (1H, dd, *J* = 12.2, 3.1 Hz, C**H**HOH), 3.83 (1H, dd, *J* = 12.4, 7.1 Hz, C**H**HOH).

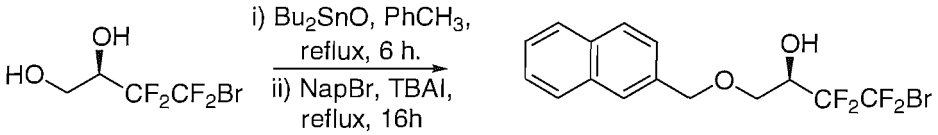
^{13}**C NMR** (100 MHz, $CDCl_3$): δ 136.6 (Ar**C**), 128.7 (2 × Ar**C**H), 128.5 (Ar**C**H), 128.2 (2 × Ar**C**H), 77.7 (dd, *J* = 25.3, 21.9 Hz, **C**HCF$_2$), 75.1 (**C**H$_2$Ph), 60.3 (**C**H$_2$OH). The CF_2CF_2 carbons were not observed.

^{19}**F NMR** (282 MHz, $CDCl_3$): δ -63.47 (2F, s, **C**F$_2$Br), -114.20 (1F, m, C**F**FCF$_2$Br), -117.87 (1F, ddt, *J* = 275.6, 14.0, 4.3 Hz).

EIMS: m/z (%): 332 and 330 (M+, 63, 1:1 ratio), 249 (19), 181 (28), 127 (27), 107 (58), 91 (100).

HRMS (ES$^+$) for $C_{11}H_{11}O_2{}^{79}BrF_4Na$ $(M+Na)^+$ calcd 352.9771, found 352.9766.

(2*R*)-4-Bromo-3,3,4,4-tetrafluoro-1-(naphth-2-ylmethyloxy)-butan-2-ol (2.25 or 3.08)



1.79 **2.25 or 3.08** (96%)

Diol **1.79** (9.5 g, 39.42 mmol) and Bu_2SnO (11.8 g, 47.31 mmol) were dissolved in dry toluene (145 mL). The reaction was brought to reflux and stirred under Dean and Stark conditions for 16 h. 2-(Bromomethyl)naphthalene (10.5 g, 47.31 mmol) and TBAI (3.64 g, 9.86 mmol) were added and the reaction refluxed for a further 24 h. The reaction was allowed to cool, diluted with Et_2O (200 mL), washed with KF (10 % (w/v), aq, 2 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pet ether / Et $_2$O, 85:15) gave a pale yellow solid (14.4 g, 96%).

m.p. 80-82°C.

IR (neat): 3386(br. m), 3061 (w), 2946 (w), 1146 (m), 1113 (s), 1091 (s), 1055 (s), 1031 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.84 (3H, m, 3 × Ar**H**), 7.79 (1H, s, Ar**H**), 7.53–7.46 (3H, m, 3 × Ar**H**), 4.78 (2H, s, **CH_2**Ar), 4.40 (1H, m, **C**HCF$_2$), 3.86–3.78 (2H, m, **CH_2**CH).

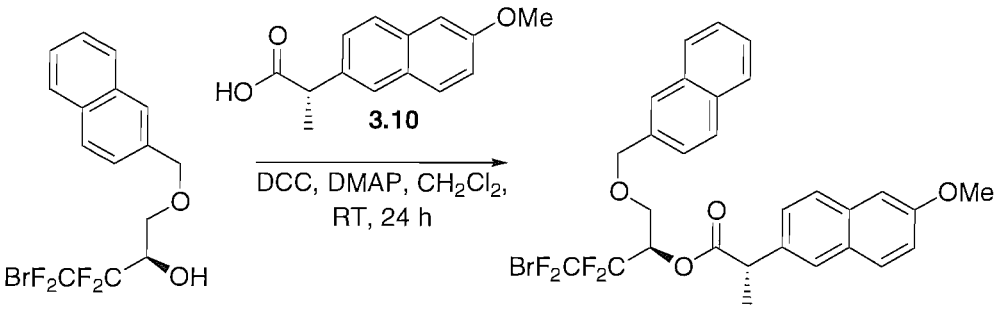
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.41 (Ar**C**CH$_2$), 133.19 (Ar**C**), 133.14 (Ar**C**), 128.49 (Ar**C**H), 127.89 (Ar**C**H), 127.73 (Ar**C**H), 126.78 (Ar**C**H), 126.32 (Ar**C**H), 126.18 (Ar**C**H), 125.52 (Ar**C**H), 73.9 (**CH_2**Ar), 68.49 (dd, *J* = 28.7, 22.4 Hz, **C**HCF$_2$), 67.52 (**CH_2**CH). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -62.96 (1F, dd, *J* = 179.5, 7.5 Hz, CF**F**Br), -63.88 (1F, m, C**F**FBr), -115.34 (1F, d, *J* = 269.3 Hz, CHCF**F**), -123.80 (1F, ddd, *J* = 282, 18.2, 7.5 Hz, CHC**F**F).

EIMS: m/z (%): 382 and 380(M^+, 8, 1:1 ratio), 207 (8), 141 (100).

HRMS (ES^+) for $C_{15}H_{13}O_2{}^{79}BrF_4Na$ $(M+Na)^+$ calcd 402.9927, found 402.9929.

(2*R*)-[4-bromo-1-(2-naphthylmethyl)-3,3,4,4-tetrafluorobut-2-yl]-(2*S*)-2-(6-methoxy-2-naphthyl) ethanoate (2.27 or 3.11)



3.08 **3.11** (67%)

To a stirred solution of **3.08** (0.5 g, 1.31 mmol) and DCC (0.3 g, 1.44 mmol) in CH_2Cl_2 (7 mL) was added DMAP (0.016 g, 0.131 mmol). The suspension was stirred until complete dissolution, upon which (*S*)-Naproxen (0.33 g, 1.44 mmol) was added and the reaction stirred overnight. The reaction was filtered to remove the white precipitate formed and the residue washed with CH_2Cl_2 (2 × 10 mL). The filtrate was concentrated *in vacuo* to give a white suspension which was directly onto a silica gel column. Elution with pet ether / acetone (90:10) gave a white solid (1.27 g, 97%). HPLC (hexane / acetone, 90:10) followed by slow evaporation of the desired fractions gave **3.11** as white needles of a single diastereomer (0.489 g, 63%).

m.p. 86–88°C.

IR (neat):2975 (w), 2936 (w), 1758 (m), 1135 (s), 1072 (s), 1027 (m), 861 (m) cm^{-1}.

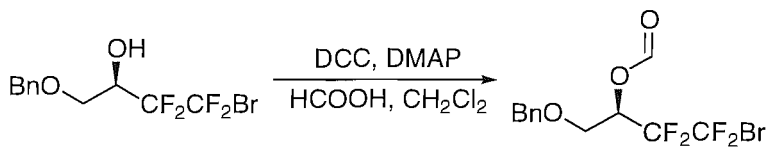
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (1H, m, Ar**H**), 7.69–7.67 (2H, m, 2 × Ar**H**), 7.60 (3H, m, 3 × Ar**H**), 7.47–7.44 (2H, m, 2 × Ar**H**), 7.39 (1H, dd, *J* = 8.4, 1.6 Hz, Ar**H**), 7.09 (1H, dd, *J* = 8.7, 1.9 Hz, Ar**H**), 7.04 (1H, d, *J* = 2.3 Hz, Ar**H**), 5.89 (1H, dtd, 15.7, 7.8, 3.0 Hz, C**H**O), 4.45 (1H, d, *J* = 12.1 Hz, **CH**HNap), 4.36 (1H, d, *J* = 12.1 Hz, C**H**HNap), 4.96 (1H, q, *J* = 7.3 Hz, CH_3C**H**), 3.90 (3H, s, OCH_3), 3.81 (1H, m, CHC**H**HO), 3.65 (1H, dd, *J* = 11.3, 7.8 Hz, CHC**H**HO), 1.62 (3H, d, *J* = 7.3 Hz, CHCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7 (**C**O), 157.7 (**C**OCH$_3$), 134.7 (Ar**C**), 134.6 (Ar**C**), 133.8 (Ar**C**), 133.1 (Ar**C**), 132.9 (Ar**C**), 129.3 (Ar**C**H), 128.9 (Ar**C**), 128.1 (Ar**C**H), 127.9 (Ar**C**H), 127.6 (Ar**C**H), 127.2 (Ar**C**H), 126.2 (Ar**C**H), 126.1 (Ar**C**H), 126.0 (Ar**C**H), 125.9 (Ar**C**H), 125.2 (Ar**C**H), 119.0 (Ar**C**H), 105.6 (Ar**C**H), 73.4 (**C**H$_2$Nap), 67.9 (dd, J = 28.7, 21.9 Hz, **C**HCF$_2$), 66.6 (CH**C**H$_2$), 55.3 (**C**HCH$_3$), 45.1 (O**C**H$_3$), 18.4 (CH**C**H$_3$). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -64.42 (2F, t, J = 4.3 Hz, **CF$_2$**Br), -114.33 (1F, app. d, J = 274.0 Hz, CH**CF**F), 119.69 (1F, ddt, J = 274.0, 16.1, 4.8 Hz, **C**HCFF)).

ESMS (**ES-**): m/z (%): 591 and 593 $(M-H)^+$ (55, 1:1 ratio), 212 (100).

(2*R*)-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobut-2-yl) formate (3.12)



3.06 **3.12** (95%)

To a stirred solution of **3.06** (8.85 g, 26.73 mmol) and DCC (6.07 g, 29.4 mmol) in CH_2Cl_2 (140 mL) was added DMAP (0.33 g, 2.67 mmol). The reaction was stirred until complete dissolution upon which formic acid (98%, 1.1 mL, 29.4 mmol) was added and the reaction stirred overnight. The reaction was diluted with hexane (100 mL), filtered to remove the white precipitate formed and the residue was washed with hexane (2 × 20 mL). The filtrate was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (pet ether / Et_2O, 90:10) gave a colourless oil (8.89 g, 93%).

IR (neat): 3033 (m), 2949 (m), 2874 (m), 1744 (s), 1369 (m), 1152 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H, s, C**H**O); 7.39–7.31 (5H, m, Ar**H**); 5.91 (1H, dtd, J = 15.4, 7.8, 3.3 Hz, C**H**CF$_2$); 4.62 (1H, d, J = 12.1 Hz, CH**H**Ph); 4.55 (1H, d, J = 11.8 Hz, CH**H**Ph); 3.89 (1H, m, C**H**HCH); 3.80 (1H, dd, J = 11.2, 7.9 Hz, CH**H**CH).

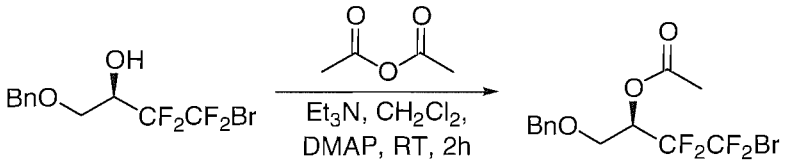
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5 (**C**HO); 137.0 (Ar**C**); 128.5 (2 × Ar**C**H); 128.0 (Ar**C**H); 127.7 (2 × Ar**C**H); 73.4 (Ph**C**H$_2$O); 66.9 (dd, J = 29.2, 22.4, **C**HCF$_2$); 66.2 (**C**H$_2$CH). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -67.18 (2F, s, **C<u>F</u>$_2$Br**), -117.24 (1F, d, J = 272.5 Hz, J = **CF<u>F</u>CF$_2$Br**), -122.52 (1H, dd, J = 274.7, 15.5 Hz, **CF<u>F</u>CF$_2$Br**).

EIMS: m/z (%): 360 and 358 (M^+, 10, 1:1 ratio), 253 and 251 (26, 1:1 ratio), 181 (12), 107 (66), 91 (100).

HRMS (EI) for $C_{12}H_{11}O_3{}^{79}BrF_4$ $(M)^+$ calcd 357.98277, found 357.98311.

(2*R*)-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobut-2-yl) ethanoate (3.23)



3.06 **3.23** (95%)

To a stirred solution of **3.06** (0.25 g, 0.76 mmol) in CH_2Cl_2 (1 mL) was added Et_3N (0.127 mL, 0.91 mmol) and DMAP (0.005 g, 0.04 mmol). The solution was stirred at RT for 5 min and then acetic anhydride (0.085 mL, 0.91 mmol) was added dropwise. The reaction was stirred at RT for 2 h. The reaction was quenched with H_2O (1 mL), diluted with CH_2Cl_2 (10 mL) the layers separated and the organic layer, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (pet ether / Et_2O, 90:10) to give a colourless oil (0.268 g, 95%).

IR (neat): 2877 (w), 1763 (s), 1373 (m), 1212 (s), 1143 (s), 1083 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.28 (5H, m, Ar**<u>H</u>**), 5.82 (1H, dtd, J = 16.4, 7.4, 3.4 Hz, **<u>H</u>CF$_2$**), 4.62 (1H, d, J = 12.1 Hz, **C<u>H</u>HPh**), 4.53 (1H, d, J = 11.8 Hz, **CH<u>H</u>Ph**), 3.86 (1H, ddd, J = 11.3, 3.3, 2.0 Hz, **C<u>H</u>HCH**), 3.77 (1H, dd, J = 11.0, 7.5 Hz, **CH<u>H</u>CH**), 2.15 (3H, s, **C<u>H</u>$_3$**).

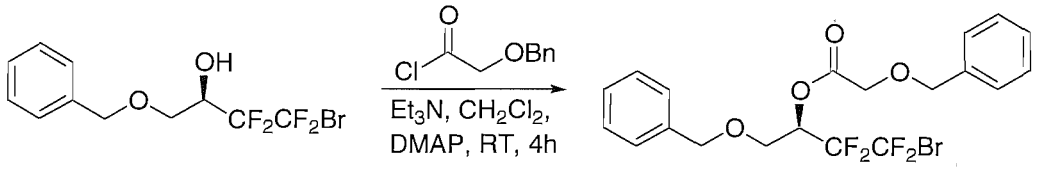
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.85 (**<u>C</u>O**), 137.19 (Ar**<u>C</u>**), 128.49 (2 × Ar**<u>C</u>H**), 127.94 (Ar**<u>C</u>H**), 127.63 (2 × Ar**<u>C</u>H**), 73.32 (**<u>C</u>H$_2$Ph**), 67.39 (dd, J = 30.1, 22.4 Hz, **<u>C</u>HCF$_2$**), 66.41 (**<u>C</u>H$_2$CH**), 20.43 (**<u>C</u>H$_3$**). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -64.29 (2F, t, J = 3.8 Hz, **<u>C</u>F$_2$Br**), 114.10 (1F, d, J = 274.0 Hz, **CF<u>F</u>CF$_2$Br**), 119.72 (1F, ddt, J = 274.0, 16.1, 4.8 Hz, **CF<u>F</u>CF$_2$Br**).

EIMS: m/z (%): 374 ($M(^{81}Br))^+$ (15), 372 ($M(^{79}Br))^+$ (15), 331 (32), 329 (29), 267 (68), 265 (58), 181 (46), 153 (15), 107 (84), 91 (100).

HRMS (EI) for $C_{13}H_{13}O_3{}^{79}BrF_4$ $(M)^+$ calcd 371.9984, found 371.9987.

(2*R*)-(1-benzyloxy-4-bromo-3,3,4,4-tetrafluorobut-2-yl)-2-benzyloxyethanoate (3.25)



3.06 **3.25** (98%)

To a stirred solution of **3.06** (0.5 g, 1.5 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (0.23 mL, 1.65 mmol) and DMAP (0.018 g, 0.15 mmol). The solution was stirred at RT for 5 min and then benzyloxyacetyl chloride (0.36 mL, 2.25 mmol) was added dropwise. The reaction was stirred at RT for 4 h. The reaction was diluted with CH_2Cl_2 (10 mL) then washed with HCl (1M, aq., 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (pet ether / acetone, 90:10) to give a colourless oil (0.703 g, 98%).

IR (neat): 2881 (w), 1777 (m), 1122 (s), 1079.8 (m), 908 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (10H, m, Ar**H**), 5.92 (1H, dtd, *J* = 15.6, 7.8, 3.2 Hz, **CH**O), 4.66–4.60 (3H, m, **CH$_2$**Ph + **CHH**CO_2), 4.52 (1H, d, *J* = 11.9 Hz, **CHH**CO_2), 4.21 (1H, d, *J* = 16.9 Hz, **CHH**Ph), 4.16 (1H, d, *J* = 16.9 Hz, **CHH**Ph), 3.88 (1H, dt, *J* = 11.1, 2.5 Hz, CHCH**H**), 3.78 (1H, dd, *J* = 11.0, 8.0 Hz, CHC**H**H).

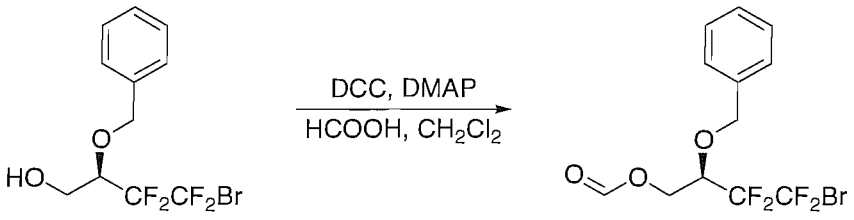
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.61 (**C**O), 137.05 (Ar**C**), 136.78 (Ar**C**), 128.52 (4 × Ar**C**H), 128.09 (2 × Ar**C**H), 127.99 (2 × Ar**C**H), 127.66 (2 × Ar**C**H), 73.34 (2 × Ph**C**H_2), 67.61 (dd, *J* = 29.2, 22.4 Hz, **C**HCF_2), 66.64 (**C**H_2CO_2), 66.19 (**C**H_2CH). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -67.3 (2F, s, **CF$_2$**Br), -117.2 (1F, app. d, *J* = 269.2 Hz, **CF**FCF_2Br), -122.4 (1F, ddt, *J* = 273.6, 16.6, 4.8 Hz, **CF**FCF_2Br).

EIMS: m/z (%):389 and 387($M-CH_2Ph$)$^+$ (8), 283 (21), 281 (21), 165 (11), 132 (14), 107 (32), 91 (100).

HRMS (ES+) for $C_{20}H_{19}O_4{}^{79}BrF_4$ $(M+Na)^+$ calcd 501.0295, found 501.0305.

(2*R*)-(2-benzyloxy-4-bromo-3,3,4,4-tetrafluorobut-1-yl) formate ester (3.37)



3.02 **3.37** (98%)

To a stirred solution of **3.02** (0.60 g, 1.8 mmol) and DCC (0.41 g, 1.99 mmol) in CH_2Cl_2 (9.6 mL) was added DMAP (0.022 g, 0.18 mmol). The reaction was stirred until complete dissolution upon which formic acid (98%, 0.075 mL, 1.99 mmol) was added and the reaction stirred overnight. The reaction was diluted with hexane (10 mL), then filtered to remove the white precipitate formed and the residue washed with hexane (2 × 5 mL). The filtrate was concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (pet ether / Et_2O, 90:10) gave a colourless oil (0.633 g, 98%).

IR (neat): 3035 (w), 2944 (w), 1728 (s), 1134 (s), 1079 (s), 1027 (m), 907 (m).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (1H, s, OC**H**O), 7.42–7.31 (5H, m, Ar**H**), 4.80 (1H, d, J = 11.2 Hz, PhC**H**H), 4.72 (1H, d, J = 11.2 Hz, PhC**H**H), 4.57 (1H, dd, J = 12.0, 3.4 Hz, OC**H**HCH), 4.39 (1H, m, OCH**H**CH), 4.29 (1H, dtd, J = 14.2, 7.1, 3.4 Hz, C**H**CF_2).

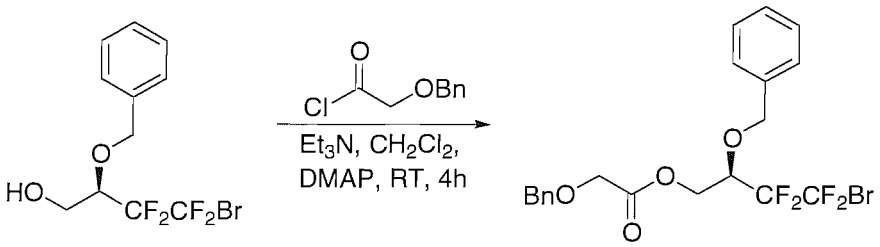
^{13}C NMR (75 MHz, $CDCl_3$): δ 160.07 (**C**O), 136.1 (Ar**C**), 128.5 (2 × Ar**C**H), 128.4 (Ar**C**H), 128.3 (2 × Ar**C**H), 74.7 (dd, J = 27.1, 22.3 Hz, **C**HCF_2), 74.6 (**C**H_2Ph), 60.9 (**C**H_2CH). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -63.13 (2F, m, C**F**$_2$Br), -112.75 (1F, d, J = 272.9 Hz, CHC**F**F), -119.64 (1F, m, CHCF**F**).

EIMS: m/z (%): 360 and 358 (M^+, 26, 1:1 ratio), 253 and 251 (6, 1:1 ratio), 107 (70), 106 (52), 105 (70), 91 (100).

HRMS (ES^+) for $C_{12}H_{11}O_3{}^{79}BrF_4Na$ $(M+Na)^+$ calcd 380.9720, found 380.9719.

(2*R*)-(2-benzyloxy-4-bromo-3,3,4,4-tetrafluorobut-1-yl)-1-benzyloxyethanoate (3.39)



3.02 **3.39** (95%)

To a stirred solution of **3.02** (0.5 g, 1.5 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.25 mL, 1.81 mmol) and DMAP (0.018 g, 0.15 mmol). The solution was stirred at RT for 5 min and then benzyloxyacetyl chloride (0.29 mL, 1.81 mmol) was added dropwise. The reaction was stirred at RT for 4 h. The reaction was diluted with CH_2Cl_2 (10 mL) then washed with HCl (1M, aq., 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by column chromatography (pet ether / acetone, 90:10) to give a colourless oil (0.683 g, 95%).

IR (neat): 2877 (w), 1760 (m), 1455 (m), 1120 (s), 1027 (m), 906 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.33 (10H, m, Ar**H**), 4.78 (1H, d, J = 11.3 Hz, OCH**H**Ph), 4.69 (1H, d, J = 11.3 Hz, OC**H**HPh), 4.62 (2H, s, C**H$_2$**Ph), 4.58 (1H, dd, J = 12.1, 3.5 Hz, CHCH**H**), 4.38 (1H, dd, J = 12.1, 6.8 Hz, CHC**H**H), 4.27 (1H, dtd, J = 14.2, 7.3, 3.6 Hz, C**H**OBn), 4.07 (2H, s, C**H$_2$**CO_2).

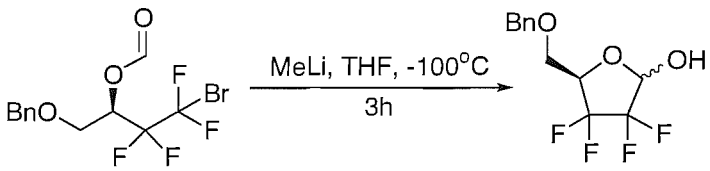
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (**C**O), 136.9 (Ar**C**), 136.2 (Ar**C**), 128.5 (4 × Ar**C**H), 128.4 (Ar**C**H), 128.3 (Ar**C**H), 128.1 (2 × Ar**C**H), 128.0 (2 x Ar**C**H), 74.8 (dd, J = 27.0, 22.7 Hz, **C**HHOBn), 74.5 (**C**H$_2$Ph), 73.4 (**C**H$_2$Ph), 66.8 (**C**H$_2$$CO_2$), 61.6 (CH**C**H$_2$). The CF_2CF_2 carbons were not observed.

^{19}F NMR (282 MHz, $CDCl_3$): δ -63.51 (2F, m, C**F$_2$**Br), -113.21 (1F, app. d, J = 274.7 Hz, CHCF**F**), -120.05 (1F, ddd, J = 274.7, 12.9, 6.4 Hz, CHC**F**F).

EIMS: m/z (%): 389 and 387 (M-PhCH$_2^+$, 29, 1:1 ratio), 331 and 329 (18, 1:1 ratio), 283 and 281 (13, 1:1 ratio), 181 (24), 132 (28), 107 (72), 91 (100).

HRMS (EI) for $C_{20}H_{19}O_4{}^{79}BrF_4Na$ (M+Na)$^+$ calcd 501.0295, found 501.0298.

(5*R*)-5-Benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydrofuran-2-ol (3.14)



3.12 **3.14** (85%)

A stirred solution of **3.12** (1.11g, 3.09 mmol) in THF (33 mL) was cooled to -100°C. MeLi (1.93 mL of a 1.6M solution in Et_2O) was added dropwise and the reaction stirred at -100°C for 3 hours. NH_4Cl (10 mL, sat. aq.) was added, the reaction warmed to RT and stirred for 5 min. H_2O (5 mL) and EtOAc (100 mL) were added and the layers separated. The aqueous phase was extracted with EtOAc (3 × 100 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant colourless oil was purified by column chromatography (hexane/acetone, 85:15) to give **3.14** as a colourless oil (0.734 g, 85%). The 1.4:1 mixture of anomers was inseparable by column chromatography and by HPLC.

IR (neat): 3388 (br. m), 3034 (w), 2928 (w), 1621 (br. w), 1497 (w), 1455 (m), 1239 (m), 1146 (s), 1023(s).

^{1}H NMR (400 MHz, $CDCl_3$): 7.42–7.31 (10H, m, Ar**H**), 5.37 (1H, br. s, C**H**OH, minor isomer, simplifies upon D_2O exchange), 5.28 (1H, t, J = 8.9 Hz, C**H**OH, major isomer, simplifies upon D_2O exchange), 4.74 (1H, d, J = 11.04 Hz, CHO**H**, major isomer, exchanges with D_2O), 4.67–4.52 (5H, m, 2 × C**H$_2$**Ph + 2 × C**H$_2$**OBn + **C**HCH$_2$), 4.39

(1H, m, **C**HCH$_2$, major isomer), 3.88 (1H, m, CHO**H**, minor isomer, exchanges with D$_2$O), 3.88–3.67, (4H, m, 2 × CH$_2$C**H**O + CHO**H**).

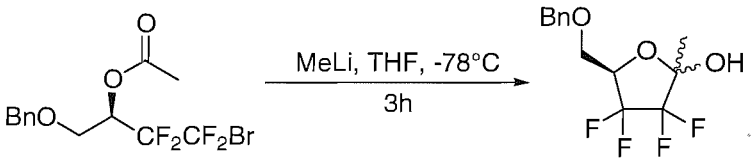
^{13}C NMR (100 MHz, CDCl$_3$): 136.87 (Ar**C**), 135.87 (Ar**C**), 128.72 (Ar**C**H), 128.55 (Ar**C**H), 128.51 (Ar**C**H), 128.13 (Ar**C**H), 128.08 (Ar**C**H), 127.94 (Ar**C**H), 96.12 (dd, *J* = 22.8, 40.3 Hz, **C**HOH), 94.72 (dd, *J* = 21.4, 38.9 Hz, **C**HOH), 79.34 (dd, *J* = 24.3, 28.2 Hz, **C**HCH$_2$), 77.07 (m, **C**HCH$_2$), 74.22 (Ph**C**H$_2$), 73.87 (Ph**C**H$_2$), 66.36–66.24 (m, 2 × **C**H$_2$OBn).

^{19}F NMR (376 MHz, CDCl$_3$): -116.84 (1F, dd, *J* = 245.0, 6.5 Hz, HOCHCF**F**), -119.24 (1F, dd, *J* = 248.0, 13.0 Hz , HOCHCF**F**), -124.83 (1F, d, *J* = 247.0 Hz, CH$_2$CHC**F**F), -125.65 (1F, dd, *J* = 250.0, 8.0 Hz, HOCHC**F**F), -127.67 (1F, dd, *J* = 247.0, 7.0 Hz, HOCHC**F**F), -128.11 (1F, m, CH$_2$CHC**F**F), -130.82 (1F, d, *J* = 249.0 Hz, CH$_2$CHC**F**F), -134.06 (1F, dd, *J* = 246.0, 15.0 Hz, CH$_2$CHC**F**F).

EIMS: m/z (%): 280 (M$^+$, 46), 232 (5), 153 (4), 107 (61), 91 (100).

HRMS (EI) for C$_{12}$H$_{12}$O$_3$F$_4$ (M)$^+$: calcd 280.07226, found 280.07206.

(5*R*)-5-Benzyloxymethyl-3,3,4,4-tetrafluoro-2-methyl-tetrahydrofuran-2-ol (3.28)



3.23 **3.28** (63%)

A stirred solution of **3.23** (0.10g, 0.268 mmol) in THF (2.9 mL) was cooled to -78°C. MeLi (1.6M in Et$_2$O, 0.17 mL, 0.268 mmol) was added slowly dropwise and the reaction stirred at -78 °C for 3 hours. NH$_4$Cl (sat. aq., 2.5 mL) was added, the reaction warmed to RT and stirred for 5 min. H$_2$O (5 mL) and Et$_2$O (10 mL) were added and the layers separated. The aqueous phase was extracted with Et$_2$O (3 × 10 mL), the organic layers combined, dried over MgSO$_4$, filtered and concentrated *in vacuo*. The resultant colourless oil was purified by column chromatography (hexane/acetone, 80:20) to give a mixture of compounds as a colourless oil. Purification by HPLC gave a colourless oil (0.05 g, 63%) found to be impure **3.28** as an inseparable 1.5:1 mixture of anomers.

IR (neat): 3362 (br. w), 2931 (w), 2859 (w), 1791 (w), 1455 (m), 1376 (m), 1257 (m), 1152 (s), 1104 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42–7.29 (10H, m, Ar**H**), 4.66–4.60 (4H, m, 2 × **C**$\underline{\mathbf{H}}_2$Ph), 4.51 (1H, m, **C**$\underline{\mathbf{H}}$), 4.37 (1H, m, **C**$\underline{\mathbf{H}}$), 3.80–3.74 (3H, m, **C**$\underline{\mathbf{H}}_2$OBn + **C**$\underline{\mathbf{H}}$**H**OBn), 3.65 (1H, dd, J = 10.2, 7.5 Hz, **CH**$\underline{\mathbf{H}}$OBn), 3.27 (1H, br. s, **O**$\underline{\mathbf{H}}$), 2.41 (1H, d, J = 1.6 Hz, **O**$\underline{\mathbf{H}}$), 1.58 (3H, dd, J = 3.1, 0.7 Hz, **C**$\underline{\mathbf{H}}_3$), 1.54 (3H, d, J = 3.66 Hz, **C**$\underline{\mathbf{H}}_3$).

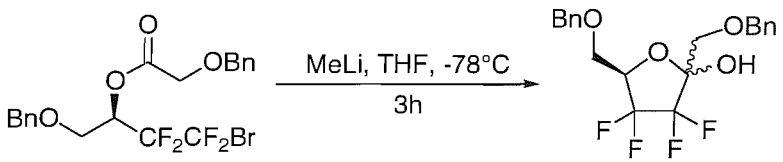
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2 (Ar**C**), 136.2 (Ar**C**), 128.7 (Ar**C**H), 128.5 (2 x Ar**C**H), 128.37 (Ar**C**H), 128.0 (4 × Ar**C**H), 127.9 (2 × Ar**C**H), 77.00 (m, 2 × CF_2**C**), 74.2 (**C**$\underline{\mathbf{H}}_2$Ph), , 73.78 (**C**$\underline{\mathbf{H}}_2$Ph), 66.4 (**C**$\underline{\mathbf{H}}_2$OBn), 66.3 (**C**$\underline{\mathbf{H}}_2$OBn), 20.4 (d, J = 3.3 Hz, **C**$\underline{\mathbf{H}}_3$), 20.0 (J = 3.5 Hz, **C**$\underline{\mathbf{H}}_3$).

^{19}F NMR (282 MHz, $CDCl_3$): δ -112.7 (1F, ddd, J = 244.4, 11.8, 5.9 Hz, CC**F**$\underline{\mathbf{F}}$), -119.0 (1F, ddt, J = 247.2, 15.0, 4.3 Hz, CC**F**$\underline{\mathbf{F}}$), -122.4 (1F, dt, J = 247.1, 8.1 Hz, CHC**F**$\underline{\mathbf{F}}$), -127.72 (1F, d, J = 240.7 Hz, CC**F**$\underline{\mathbf{F}}$), -128.77 (1F, d, J = 238.6 Hz, CC**F**$\underline{\mathbf{F}}$), -131.60 (1F, dt, J = 239.6, 6.4 Hz, CHC**F**$\underline{\mathbf{F}}$), -132.36 (1F, dt, J = 239.6, 5.6 Hz, CHC**F**$\underline{\mathbf{F}}$), -133.69 (1F, ddd, J = 244.5, 14.0, 4.8 Hz, CHC**F**$\underline{\mathbf{F}}$).

EIMS: m/z (%): 294 (M^+, 23), 276 (8), 253 (23), 168 (32), 153 (16), 107 (34), 91 (100).

HRMS (EI) for $C_{13}H_{14}O_3F_4$ $(M)^+$ calcd 294.08791, found 294.08802.

(5*R*)-2,5-Bisbenzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydrofuran-2-ol (3.29)



3.25 **3.29** (75%)

A stirred solution of **3.25** (0.134g, 0.28 mmol) in THF (3.0 mL) was cooled to -78°C. MeLi (1.6M in Et_2O, 0.175 mL, 0.28 mmol) was added slowly dropwise and the reaction stirred at -78°C for 3 hours. NH_4Cl (sat. aq., 2 mL) was added, the reaction warmed to RT and stirred for 5 min. H_2O (5 mL) and Et_2O(10 mL) were added and the layers

separated. The aqueous phase was extracted with Et_2O (3 × 10 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by column chromatography (hexane/acetone, 80:20) to give a mixture of compounds. Purification by HPLC gave a colourless oil (0.084 g, 75%) found to be **3.31** as an inseparable 2.1:1mixture of anomers.

IR (neat): 3398 (w), 3067 (w), 3032 (w), 2935 (w), 2876 (w), 1497 (w), 1454 (m), 1366 (w), 1298 (m), 1259 (m), 1208 (w), 1148 (s), 1101 (s), 1028 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.10 (20H, m, Ar**H**), 4.51 – 4.21 (10H, m), 4.07 (1H, br. s), 3.66 – 3.45 (8H, m).

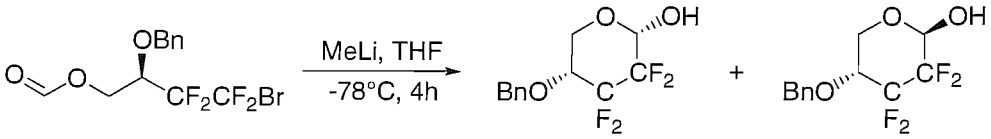
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.31 (C), 136.94 (C), 136.84 (C), 136.59 (C), 128.59 (2 × CH), 128.52 (2 × CH), 128.51 (2 × CH), 128.44 (2 × CH), 128.25 (CH), 128.11 (CH), 128.04 (CH), 127.94 (2 × CH), 127.88 (3 × CH), 127.85 (2 × CH), 127.72 (2 × CH), 99.32 (t, *J* = 24.8 Hz, C), 98.71 (dd, *J* = 31.1, 21.4 Hz, C), 78.20 (dd, *J* = 29.1, 24.3 Hz, CH), 77.22 (dd, *J* = 28.0, 23.2 Hz, CH), 74.10 (CH_2), 74.03 (CH_2), 73.79 (CH_2), 73.64 (CH_2), 68.59 (CH_2), 68.08 (d, *J* = 4.9 Hz, CH_2), 67.32 (m, CH_2), 66.12 (d, *J* = 7.8 Hz, CH_2).

^{19}F NMR (282 MHz, $CDCl_3$): δ 111.1 (1F, dddd, *J* = 243.0, 11.7, 4.2, 2.7 Hz, **CF**F**C**), 122.35 (1F, ddt, *J* = 245.5, 13.8, 5.4 Hz, **CF**F**C**), 123.49 (1F, m, **CF**F**C**), 129.4 (1F, dt, *J* = 239.4, 5.0 Hz, **CHCF**F), 130.81 (1F, d, *J* = 185.7 Hz, **CHCF**F), 131.45 (1F, d, *J* = 184.5, **CHCF**F), 131.90 (1F, dt, *J* = 241.0, 6.3 Hz, **CHCF**F), 134.10 (1F, dd, *j* = 243.5, 13.9, 5.4 Hz, **CF**F**C**)

CIMS: m/z (%): 418 $(M+NH_4)^+$ (8), 309 (2), 181 (6), 106 (100), 91 (65) (m/z).

HRMS (ES+) for $C_{20}H_{20}O_4F_4$ $(M)^+$ calcd 423.1190, found 423.1186.

(2*S*, 5*R*)-5-Benzyloxy-3,3,4,4,-tetrafluoro-tetrahydro-pyran-2ol (3.38a) and (2*R*, 5*R*)-5-benzyloxy-3,3,4,4,-tetrafluoro-tetrahydro-pyran-2ol (3.38b)



3.37 **3.38a** (17%) **3.38b** (51%)

A solution of **3.37** (0.2 g, 0.56 mmol) in dry CH_2Cl_2 (2.5 mL) was filtered through a plug of $MgSO_4$ into a 10 mL 2-neck RB flask. The CH_2Cl_2 was removed under a stream of dry nitrogen, followed by drying under high vacuum for 16 h. The resulting oil was taken up in THF (5.6 mL) and cooled, whilst stirring, to -78 °C. MeLi (1.6M in Et_2O, 0.35 mL, 0.56 mmol) was added, slowly, dropwise. The reaction was stirred for 4 h at -78 °C before quenching with NH_4Cl (sat. aq., 2.5 mL), the resulting suspension was allowed tio warm to RT and then diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The organic phases where combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (pet ether / acetone, 80:20) gave a mixture of two compounds which were separated by preparative HPLC (hexane / acetone, 85:15) giving **3.38a** (0.028 g, 18%) and **3.38b** (0.08 g, 51%) as white solids.

Data for **3.38a**:

m.p. 85–88°C

I.R. 3380 (m), 1216 (m), 1134 (s), 1115 (m), 1067 (s), 1053 (s), 1028 (m), 988 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.33 (5H, m, Ar**H**), 5.09 (1H, br. s, **CH**OH), 4.89 (1H, d, *J* = 11.8 Hz, **CHH**Ph), 4.68 (1H, d, *J* = 12.1 Hz, **CHH**Ph), 4.05 (1H, m, CHCH**H**), 3.89 (1H, m, **CH**CHH), 3.72 (1H, dt, *J* = 11.9, 4.1 Hz, CHC**H**H), 3.56 (1H, m, **OH**).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (Ar**C**), 128.7 (2 × Ar**C**H), 128.4 (Ar**C**H), 128.1 (2 × Ar**C**H), 92.0 (dd, *J* = 35.2, 25.1 Hz, **C**HOH), 74.1 (**C**H_2Ph), 73.1 (dd, *J* = 20.4, 19.0 Hz, **C**HOBn), 60.5 (**C**HCH_2).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -124.28 (1F, br. d, J = 135.4 Hz, **CF<u>F</u>**CHOH), -125.22 (1F, br. d, J = -129.0 Hz, **C<u>F</u>F**CHOH), -130.76 (1F, dt, J = 264.3, 15.0 Hz, **C<u>F</u>F**CHOBn), -136.24 (1F, dd, J = 269.7, 15.0 Hz, **CF<u>F</u>**CHOBn).

EIMS: m/z (%): 280 $(M)^+$ (50), 262 (8), 107 (49), 91 (100) 65 (46).

HRMS (ES^+) for $C_{12}H_{12}O_3F_4Na$ $(M+Na)^+$ calcd 303.0615, found 303.0614.

Data for **3.38b**:

m.p. 86–88°C.

IR (neat): 3356 (br. m), 2893 (w), 1346 (w), 1231 (m), 1136 (m), 1117 (m), 1066 (s), 975 (s), 949 (m).

^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.35 (5H, m, Ar**<u>H</u>**), 4.94 (1H, br. s, **C<u>H</u>**OH), 4.89 (1H, d, J = 12.0 Hz, **C<u>H</u>H**Ph), 4.67 (1H, d, J = 12.0 Hz, **CH<u>H</u>**Ph), 3.99 (1H, dt, J = 12.1, 4.7 Hz, CHC**<u>H</u>H**), 3.90 (1H, m, **C<u>H</u>**OBn), 3.57 (1H, m, CHC**H<u>H</u>**), 3.36 (1H, br. s, **O<u>H</u>**).

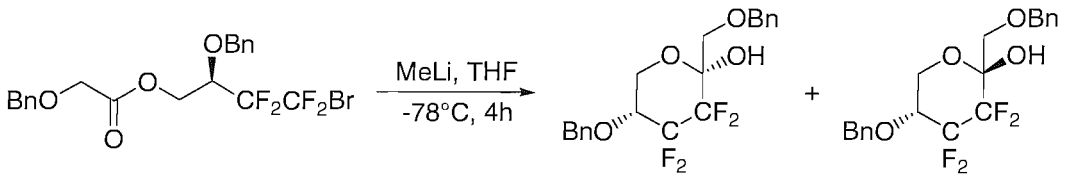
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (Ar**<u>C</u>**), 128.7 (2 × Ar**<u>C</u>H**), 128.5 (Ar**<u>C</u>H**), 128.1 (2 × Ar**<u>C</u>H**), 92.1 (m, **<u>C</u>H**OH), 74.2 (**<u>C</u>H$_2$**Ph), 73.0 (t, J = 19.2 Hz, **<u>C</u>H**OBn), 61.7 (dd, J = 6.1, 1.7 Hz, CH**<u>C</u>H$_2$**)

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -127.99 (1F, d, J = 263.3 Hz, **C<u>F</u>F**CHOH), -265.82 (1F, dt, J = 261.1, 16.1 Hz, **C<u>F</u>F**CHOBn), -134.18 (1F, d, J = 263.3 Hz, **CF<u>F</u>**CHOH), -139.27 (1F, m, J = 262.2 Hz can be observed, **CF<u>F</u>**CHOBn).

EIMS: m/z (%): 280 $(M)^+$ (19), 262 (3), 107 (22), 91 (100).

HRMS (ES^+) for $C_{12}H_{12}O_3F_4Na$ $(M+Na)^+$ calcd 303.0615, found 303.0615.

(2*S*, 2*R*)-5-Benzyloxy-2-benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydro-pyran-2-ol (3.40a)



3.39 **3.40a** (65%) **3.40b** (10%)

A solution of **3.39** (0.20 g, 0.42 mmol) in dry CH_2Cl_2 (2.5 mL) was filtered through a plug of $MgSO_4$ into a 10 mL 2-neck RB flask. The CH_2Cl_2 was removed under a stream of dry nitrogen, followed by drying under high vacuum for 16 h. The resulting oil was taken up in THF (4.2mL) and cooled, whilst stirring, to -78 °C. MeLi (1.6M in Et_2O, 0.26 mL, 0.42 mmol) was added, slowly, dropwise. The reaction was stirred for 4 h at -78 °C before quenching with NH_4Cl (sat. aq., 2.5 mL), the resulting suspension was allowed tio warm to RT and then diluted with H_2O (10 mL) and Et_2O (10 mL). The layers were separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The organic phases where combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography (pet ether / acetone, 80:20) gave a mixture of compounds which were separated by preparative HPLC (hexane / acetone, 85:15) giving **3.40a** as a single anomer (0.11 g, 65%) and mixed fractions containing both **3.40a** and **3.40b** (0.017 g, 10%). The data below is for the major isomer as a pure sample of the minor anomer could not be obtained. The configuration at the anomeric centre is assumed to be as shown, though this is only a tentative assignment.

Data for **3.40a**:

IR (neat): 3489 (br. w), 3033 (w), 2879 (w), 1455 (m), 1303 (m), 1214 (m), 1104 (s), 1062 (s), 926 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.31 (10H, m, Ar**H**), 4.90 (1H, d, J = 12.1 Hz, CHOC**H**HPh), 4.70 (1H, d, J = 12.0 Hz, CH_2OC**H**HPh), 4.68–4.62 (2H, m, CH_2OCH**H**Ph + CHOCH**H**Ph), 4.20 (1H, t, J = 2.8 Hz, O**H**), 4.04 (1H, t, J = 11.2 Hz,

CHC**H**H), 3.90 (1H, m, C**H**OBn), 3.75 (1H, d, *J* = 10.7 Hz, C**H**HOBn), 3.72 (1H, m, CHCH**H**), 3.62 (1H, d, *J* = 10.6 Hz, CH**H**OBn).

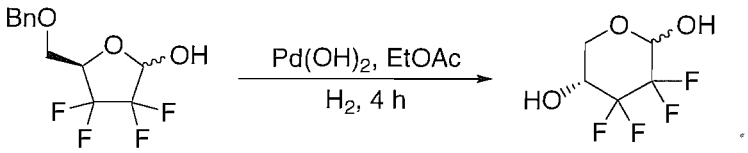
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8 (Ar**C**), 136.6 (Ar**C**), 128.63 (2 × Ar**C**H), 128.61 (2 × Ar**C**H), 128.33 (Ar**C**H), 128.30 (Ar**C**H), 127.98 (2 × Ar**C**H), 127.92 (2 × Ar**C**H), 95.5 (dd, *J* = 28.2, 25.3 Hz, **C**CF_2), 74.4 (**C**H_2Ph), 74.2 (**C**H_2Ph), 72.7 (t, *J* = 18.5 Hz, **C**HCF_2), 68.4 (d, *J* = 3.9 Hz, **C**H_2OBn), 59.3 (d, *J* = 7.8 Hz, CH**C**H_2).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -127.41 (1F, dddd, *J* = 254.7, 19.9, 9.7, 5.4 Hz, CF**F**COH), -127.92 (1F, m, *J* = 264.0 Hz can be observed, C**F**FCOH), -130.39 (1F, dtd, *J* = 255.8, 17.2, 7.5 Hz, CHCF**F**), -135.71 (1F, ddd, *J* = 266.5, 17.3, 9.9 Hz, CHC**F**F).

EIMS: m/z (%): 418 $(M+NH_4)^+$ (12), 181 (21), 106 (100), 91 (60) (m/z)

HRMS (ES+) for $C_{20}H_{20}O_4F_4Na$ $(M+Na)^+$ calcd 423.1190, found 423.1192.

(5*R*)-3,3,4,4-Tetrafluorotetrahydropyran-2,5-diol (3.31)



3.14 **3.31** (98%)

To a stirred solution of **3.14** (0.1 g, 0.36 mmol) in EtOAc (2.9 mL) was added $Pd(OH)_2/C$ (10% Pd/C, 0.12 g). The flask was evacuated and purged with H_2. This sequence was repeated twice more and then the reaction allowed to stir for 4 h. The reaction was diluted with EtOAc (10 mL) and then filtered through celite. The residue was washed with EtOAc (2 × 10 mL) and the combined filtrates concentrated *in vacuo*. The resulting oil was purified by column chromatography (pet ether / acetone, 70:30) to give a colourless oil (0.067 g, 98%) which solidified on standing, which was found to be **3.33** as a inseparable 2.8:1 β:α mixture of anomers (anomers assigned from coupling constants obtained from a D_2O exchanged ^{1}H NMR).

m.p. 87-89°C.

IR (neat): 3313 (br. m), 2968 (w), 1635 (br. w), 1264 (m), 1206 (m), 1111 (s), 1065 (s), 1040 (s), 997 (s) cm^{-1}.

^{1}H NMR (400 MHz, d^6-DMSO): δ 7.87 (1H, d, *J* = 6.52 Hz, OCH**O**<u>**H**</u>, major isomer, exchanges with D_2O), 7.69 (1H, d, *J* = 4.02 Hz, OCH**O**<u>**H**</u>, minor isomer, exchanges with D_2O), 6.18 (1H, d, *J* = 5.77 Hz, CH_2CH**O**<u>**H**</u>, major isomer, exchanges with D_2O), 6.13 (1H, d, *J* = 6.53 Hz CH_2CH**O**<u>**H**</u>, minor isomer, exchanges with D_2O), 5.14 (1H, m, O**C**<u>**H**</u>OH, minor isomer, simplifies to ddd, *J* = 7.0, 5.2, 1.7 Hz upon D_2O exchange), 4.90 (1H, m, O**C**<u>**H**</u>OH, major isomer, simplifies to app. dd, *J* = 14.7, 3.9 Hz), 3.40–3.89 (3H, m, 2 × CF_2**C**<u>**H**</u> + **C**<u>**H**</u>**H**), 3.81 (1H, t, *J* = 10.4 Hz, **C**<u>**H**</u>**H**, minor isomer), 3.66 (1H, m, **CH**<u>**H**</u>, minor isomer), 3.42 (1H, t, *J* = 10.3 Hz, **C**<u>**H**</u>**H**, major isomer).

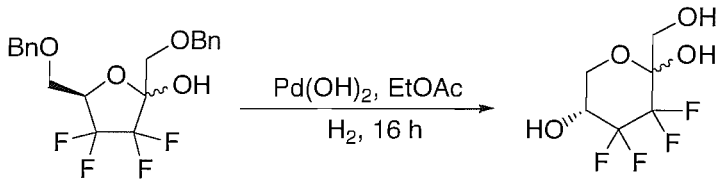
^{13}C NMR (100 MHz, d^6-DMSO): δ 91.4 (m, O<u>**C**</u>**H**OH, major isomer), 90.9 (dd, *J* = 35.1, 24.3 Hz, O<u>**C**</u>**H**OH, minor isomer), 66.6–66.1 (m, 2 × CH_2<u>**C**</u>**H**), 62.7 (d, *J* = 6.8 Hz, <u>**C**</u>H_2, major isomer), 60.0 (<u>**C**</u>H_2, minor isomer).

^{19}F NMR (376 MHz, d^6-DMSO referenced to $CFCl_3$): δ -120.97 (1F, m, CF_2**C**<u>**F**</u>**F**CH), –127.27 (1F, br. d, *J* = 253.9 Hz, CF_2**CF**<u>**F**</u>CH), -129.0 (1F, br. d, *J* = 259.0, CF_2**C**<u>**F**</u>**F**CH), –130.78 (1F, ddd, *J* = 252.2, 17.0, 6.0 Hz, CH**C**<u>**F**</u>**F**CF_2), –132.44 (1F, m, CF_2**CF**<u>**F**</u>CH), –132.68 (1F, d, *J* = 173.2 Hz, CH**C**<u>**F**</u>**F**CF_2), -133.36 (1F, d, *J* = 180.7 Hz, CH**CF**<u>**F**</u>CF_2), –136.82 (1F, d, *J* = 259.8 Hz, CH**CF**<u>**F**</u>CF_2)

ESMS (ES-): m/z (%): 189 ($M-H^+$, 100), 161 (12), 149 (8), 129 (22).

HRMS (ES^+) for $C_5H_6O_3F_4Na$ $(M+Na)^+$ calcd 213.0145, found 213.0148.

(2S)-3,3,4,4-Tetrafluoro-2-hydroymethyl-tetrahydro-pyran-2,5-diol (3.36)



3.29 **3.36** (96%)

To a stirred solution of **3.29** (0.50 g, 1.25 mmol) in EtOAc (10 mL) was added $Pd(OH)_2/C$ (10% Pd/C, 0.40 g). The flask was evacuated and purged with H_2. This sequence was repeated twice more and then the reaction allowed to stir for 16 h. The reaction was diluted with EtOAc (30 mL) and then filtered through celite. The residue was washed with EtOAc (2 × 30 mL) and the combined filtrates concentrated *in vacuo*. The resulting oil was purified by column chromatography (pet ether / acetone, 60:40) to give a colourless oil (0.26 g, 96%), which was found to be **3.36** as a inseparable 7:1 mixture of anomers.

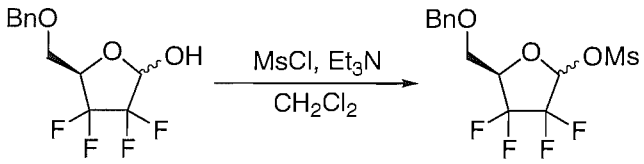
IR (neat): 3354 (br. m), 1698 (m), 1150 (s), 1094 (s), 1046 (s), 870 (s) cm^{-1}.
^{1}H NMR (400 MHz, d^6-DMSO): δ 6.83 (1H, br. s, **OH**), 6.70 (1H, br. s, **OH**), 6.10 (1H, br. s, **OH**), 5.96 (1H, br. s, **OH**), 5.13 (2H, m, 2 × CH_2**OH**), 4.09 (1H, d, *J* = 12.8 Hz, **CH**H**O**H, minor isomer), 3.90 (2H, m, 2 × **C**H**O**H), 3.77 (2H, t, *J* = 10.4 Hz, CH**CH**H), 3.65 (2H, m, CH**C**H**H**), 3.58 (1H, d, *J* = 12.1 Hz, **C**H**H**OH, major isomer), 3.53 (1H, app. s, **CH**H**O**H, minor isomer), 3.48 (1H, d, *J* = 11.8, **CH**H**O**H, major isomer).
^{13}C NMR (100 MHz, d^6-DMSO): δ 95.6 (dd, *J* = 29.2, 21.9 Hz, **C**CF_2, major isomer), 67.9 (m, **C**HCF_2, minor isomer), 66.0 (t, *J* = 18.95 Hz, **C**HCF_2, major isomer), 61.7 (**C**H_2OH, major isomer), 61.6 (**C**H_2OH, minor isomer), 59.4 (d, *J* = 7.3 Hz, 2 × **C**H_2OC).
^{19}F NMR (282 MHz, d^6-DMSO referenced to $CFCl_3$): δ -115.83 (1F, ddt, *J* = 260.0, 15.0, 7.5 Hz, **CF**F**C**OH, minor isomer), -123.80 (1F, ddd, *J* = 261.8, 17.2, 7.5 Hz, **C**F**F**COH, minor isomer), -124.51 (1F, m, *J* = 262.2 can be observed, **C**F**F**COH, major isomer), -128.06 (1F, m, **CF**F**C**HOH, major isomer), -128.27 (1F, m, **CF**F**C**OH, minor

isomer), -129.39 (1F, m, **CFFCHOH**, major isomer), -132.32 (1F, m, **CFFCHOH**, minor isomer), -133.88 (1F, m, **CFFCHOH**, major isomer).

ESMS (ES+): m/z (%): 243 $(M+Na)^+$ (55), 139 (100).

HRMS (ES^+) for $C_6H_8O_4F_4Na$ $(M+Na)^+$ calcd 243.0257, found 243.0251.

(5*R*)-Methanesulfonic acid 5-benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydro-furan-2-yl ester (4.09)



3.14 **4.09** (92%)

To a solution of **3.14** (0.147 g, 0.52 mmol) in CH_2Cl_2 (2.3 mL) was added Et_3N (0.10 mL, 0.73 mmol). The reaction was cooled to -100°C and stirred for 1h. A pre-cooled solution of methanesulfonyl chloride (0.049 mL, 0.63 mmol) in CH_2Cl_2 was added *via* cannula. The reaction was stirred for 2 h, then allowed to warm slowly to RT. The reaction was transferred to a separating funnel and washed with HCl (5 mL, 1M aq.), $NaHCO_3$ (5 mL, 5% aq.). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resultant yellow oil was purified by column chromatography (hexane/acetone 85:15) to give a colourless oil (0.171g, 92%) as an inseparable mixture of anomers in a 3.5:1 diastereomeric ratio.

IR (neat): 3033 (w), 2940 (w), 2873 (w), 1497 (w), 1376 (s), 1275 (m), 1187 (s), 1155, 1093 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.31 (10H, m, Ar**H**), 6.07 (1H, dd, J = 6.5, 2.4 Hz, C**H**OH), 6.00 (1H, dt, J = 7.3, 1.0 Hz, C**H**OH), 4.65–4.57 (6H, m, 2 × C**H$_2$**Ph + C**H**HCH), 3.86–3.70 (4H, m, 2 × CH**H**CH +C**H**OMs), 3.17 (3H, s, $SO_2C\underline{H}_3$), 3.05 (3H, s, $SO_2C\underline{H}_3$).

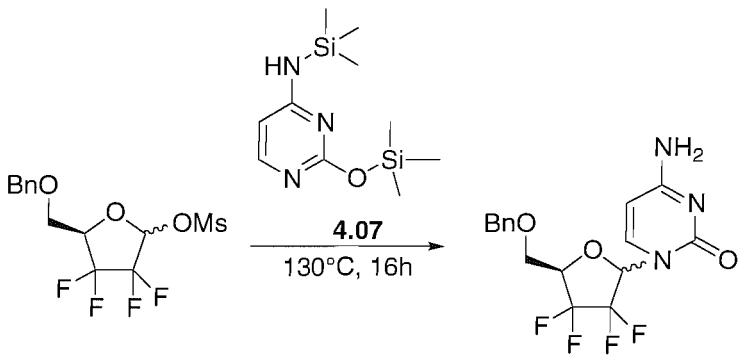
^{13}C NMR (100 MHz, $CDCl_3$): δ 136.93 (Ar**C**), 136.89 (Ar**C**), 128.59 (Ar**CH**), 128.56 (Ar**CH**), 128.17 (Ar**CH**), 128.11 (Ar**CH**), 128.85 (Ar**CH**), 127.74 (Ar**CH**), 97.81–96.87 (m, 2× **C**HOMs), 80.03–79.34 (m, CH_2**C**H signal from other anomer obscured by solvent peaks), 7.87 (**C**H_2Ph), 73.78 (**C**H_2Ph), 66.57 (d, J = 6.8 Hz, CH**C**H_2O), 65.78 (d, J = 6.8 Hz, CH**C**H_2O), 40.29 (2× **C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$ relative to $CFCl_3$): 115.03 (1F, dddd, J = 247.4, 11.5, 4.9, 2.6 Hz, C**F**FCHOMs), 124.6 (1F, ddd, J = 249.4, 6.62, 1.9 Hz, C**F**FCHOMs), 125.69 (1F, ddt, j = 251.5, 8.0, 1.8 Hz, CF**F**CHOMs), 250.83 (1F, ddd, J = 250.8, 13.9, 8.2, CH_2CHC**F**F), 127.62 (1F, dt, J = 249.8, 5.2, CH_2CHC**F**F), 128.96 (1F, m, CH_2CHC**F**F), 133.93 (1F, ddd, J = 251.2, 8.7, 6.3 Hz, CH_2CHC**F**F), 134.57 (1F, m, C**F**FCHOMs).

EIMS: m/z (%): 358 (3, M^+), 262 (6), 172 (6), 106 (58), 91 (100), 79 (42), 65 (39).

HRMS (EI) for $C_{13}H_{14}O_5F_4S$ $(M)^+$: calcd 358.04981, found 358.04951.

4-Amino-1-((5*R*)-5-benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one (4.10)



4.09 **4.10** (73%)

Cytosine (2.0 g, 18 mmol) and NH_4SO_4 (4.3 mg, 0.032 mmol) were weighed into a 25 mL flame dried RB flask. The flask was evacuated and purged with N_2. HMDS (13.68 mL, 64.84 mmol) was added and the reaction warmed to reflux. The reaction was stirred at reflux for 2 h, then allowed to cool to RT. The HMDS was removed *in vacuo* to give a white solid. To ensure that no trace of HMDS remained the solid was suspended in dry

toluene (15 mL) and the solvent then removed *in vacuo*, this was repeated twice and the solid then dried under high vacuum to yield 2,4-bis(trimethylsilyl)cytosine **4.07**.

A flame dried 10 mL RB flask was charged with **4.07** (3.58 g, 14.0 mmol) and the apparatus flushed with N_2. The flask was placed into a 130°C oil bath and the solid stirred very slowly until molten. **4.09** (0.482 g, 1.35 mmol) was added dropwise *via* pipette, the flask purged with N_2 and the reaction stirred at 130°C for 20h. The reaction was allowed to cool before dilution with EtOAc (100 mL). The resulting solution was washed with $NaHCO_3$ (sat. aq., 50 mL). The organic phase was dried over Na_2SO_4 and then filtered. Silica (2 g) was added to the solution and the solvent removed *in vacuo*, pre-absorbing the compound onto the silica. Subsequent column chromatography (CH_2Cl_2 / MeOH, 95:5 + 0.5% (v/v) NH_4OH) gave a white solid (0.368 g, 73%) found to be **4.10** as an inseparable 2.2:1 mixture of anomers.

m.p. 176–180°C

IR (neat): 3409 (w), 3107 (w), 3030 (w), 2970 (w), 2911 (w), 1645 (s), 1516 (m), 1491 (s), 1287 (m), 1368 (m), 1278 (s), 1145 (s) 1109 (s), 1066 (s), 1017 (s), 969 (m) cm^{-1}.

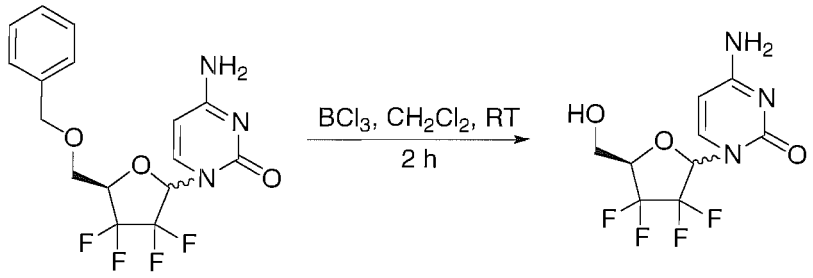
^{1}H NMR (400 MHz, d^6-DMSO): δ 7.60–7.55 (5H, m, 2 × **N<u>H</u>$_2$** + **C<u>H</u>**CNH$_2$), 7.43 (1H, d, *J* = 7.5 Hz, **C<u>H</u>**CNH$_2$), 7.39–7.29 (10H, m, Ar**<u>H</u>**), 6.56–6.50 (2H, m, 2 × OC**<u>H</u>**N), 5.85 (1H, d, *J* = 7.7 Hz, CHC**<u>H</u>**N), 5.83 (1H, d, *J* = 7.7 Hz, CHC**<u>H</u>**N), 5.08 (1H, m, CH$_2$C**<u>H</u>**O), 4.81 (1H, m, CH$_2$C**<u>H</u>**O), 4.59 (4H, s, 2 × PhC**<u>H</u>$_2$**), 3.95–3.77 (4H, m, 2 × OC**<u>H</u>$_2$**CH).

^{19}F NMR (376 MHz, d^6-DMSO referenced to $CFCl_3$): δ -118.22 (1F, dd, *J* = 240.6, 3.7 Hz, C**<u>F</u>**FCHN), -122.3 (1F, m, CF**<u>F</u>**CHN), -122.4 (1F, d, *J* = 244.7 Hz, C**<u>F</u>**FCHN), -124.6 (2F, br. s, CF**<u>F</u>**CHN + C**<u>F</u>**FCHCH$_2$), -128.4 (1F, d, *J* = 240.9 Hz, CF**<u>F</u>**CHCH$_2$), -128.9 (1F, d, *J* = 240.9 Hz, C**<u>F</u>**FCHCH$_2$), -131.97 (1F, d, *J* = 240.9 Hz, CF**<u>F</u>**CHCH$_2$).

ESMS (ES+): m/z (%): 747 ($2M+H^+$, 3), 374 ($M+H^+$, 100)

HRMS (ES+) for $C_{16}H_{15}O_3F_4N_3$ $(M+H)^+$: calcd 374.1123, found 374.1123.

4-Amino-1-((5*R*)3,3,4,4-tetrafluoro-5-hydroxymethyl-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one (4.11)



4.10 **4.11** (92%)

A suspension of **4.10** (0.235 g, 0.63 mmol) in CH_2Cl_2 (7 mL) was stirred at RT. BCl_3 (1.0 M in CH_2Cl_2, 2.52 mL, 2.52 mmol) was added *via* syringe and the reaction was stirred for 2h. The reaction was then concentrated, and the resulting solid dissolved in MeOH and pre-absorbed onto silica. Column chromatography (CH_2Cl_2 / MeOH, 90:10) gave **4.11** as a white solid (0.164 g, 92%) found to be a 2.2:1 mixture of anomers.

m.p. 197-205°C.

I.R. (neat): 3355 (w), 3207 (m), 1645 (s), 1627 (s), 1504 (s), 1460 (m), 1415 (w), 1361 (m), 1332 (w), 1289 (m), 1170 (m), 1129 (m), 1053 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.44 (6H, m, 2 × C**H**CNH$_2$ + 2 × N**H**$_2$), 6.53–6.46 (2H, m, 2 × OC**H**N), 5.86 (1H, d, *J* = 7.5 Hz, NC**H**CH), 5.35 (1H, d, *J* = 7.5 Hz, NC**H**CH), 5.39 (1H, t, *J* = 5.4 Hz, O**H**), 5.35 (1H, t, *J* = 5.7 Hz, O**H**), 4.79 (1H, m, C**H**CH$_2$), 4.50 (1H, m, C**H**CH$_2$), 3.88–3.76 (4H, m, 2× C**H**$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.83 (**C**NH$_2$), 165.74 (**C**NH$_2$), 154.48 (**C**O), 154.34 (**C**O), 140.55 (**C**HCNH$_2$), 140.26 (**C**HCNH$_2$), 95.44 (N**C**HCH), 95.22 (N**C**HCH), 83.06 (m, O**C**HN), 82.07 (dd, *J* = 37.7, 19.2 Hz, O**C**HN), 78.89 (t, *J* = 23.8 Hz, CH$_2$**C**H), 76.86 (t , *J* = 24.5 Hz, CH$_2$**C**H), 57.94 (**C**H$_2$), 56.81 (d, *J* = 5.83, **C**H$_2$).

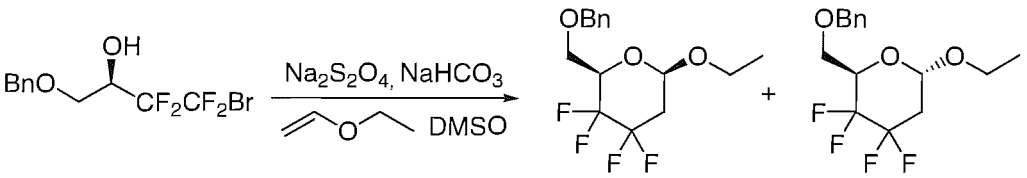
^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -119.14 (1F, dt, *J* = 241.4, 7.5 Hz, C**F**FCHCH$_2$), -122.16 (2F, m, C**F**FCHCH$_2$ +CF**F**CHCH$_2$), -125.25 (2F, br. s,

CF<u>F</u>CHCH$_2$ + **CF<u>F</u>**CHN), -129.39 (1F, dd, *J* = 245.0, 12.9 Hz, **C<u>F</u>F**CHN), -129.87 (1F, d, *J* = -240.7 Hz, **C<u>F</u>F**CHN), -133.22 (1F, dd, *J* = 240.7, 19.4 Hz, **CF<u>F</u>**CHN).

ESMS (**ES+**): m/z (%): 589 ((2M)+Na)$^+$ (32), 306 (M+Na)$^+$ (100), 284 (M+H)$^+$ (40), 217 (50).

HRMS (ES+) for $C_9H_{10}O_3F_4N_3$ (M+H)$^+$: calcd 284.0653, found 284.0652

(2*R*)-2-Benzyloxymethyl-6-ethoxy-3,3,4,4-tetrafluoro-tetrahydropuran (5.14)



3.06 **5.14a** **5.14b**

To a stirred solution of **3.06** (0.1 g, 0.3 mmol) in dry DMSO (1.5 mL) was added ethyl vinyl ether (0.29 mL, 3.0 mmol). $Na_2S_2O_4$ (0.078 g, 0.45 mmol) and $NaHCO_3$ (0.038 g, 0.45 mmol) were added simultaneously and the reaction stirred at RT for 17 hours. H_2O (5 mL) was added, the aqueous phase extracted with Et_2O (3 × 10 ml). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (pet ether / Et_2O, 80:20) gives a colourless oil (0.059 g, 61%) as a 50:50 mixture of anomers. Analytical samples of the pure anomers were obtained by HPLC.

Data for **5.14a**:

IR (neat): 3032 (w), 2981 (m), 2883 (m), 2817 (w), 1497 (w), 1456 (m), 1381 (m), 1185 (s), 1058 (s).

^{1}H NMR (300 MHz, $CDCl_3$): 7.40–7.30 (5H, m, Ar**<u>H</u>**), 4.76 (1H, d, *J* = 9.5 Hz, **C<u>H</u>**OEt), 4.65 (1H, d, *J* = 12.1 Hz, **CH<u>H</u>**Ph), 4.59 (1H, d, *J* = 12.1 Hz, **C<u>H</u>H**Ph), 4.04–3.93 (3H, m, **C<u>H</u>H**OBn, CF_2C**<u>H</u>**, CH_3C**<u>H</u>H**), 3.77 (1H, dd, *J* = 11.2, 7.4 Hz, **CH<u>H</u>**OBn), 3.62 (1H, dq, *J* = 9.3, 7.0 Hz, CH_3C**H<u>H</u>**), 2.56–2.47 (1H, m, CF_2C**<u>H</u>H**), 2.28 (1H, dddd, *J* = 35.8, 17.9, 9.4, 4.5 Hz, CF_2C**<u>H</u>H**), 1.27 (3H, t, *J* = 7.0 Hz, **C<u>H</u>$_3$**).

^{13}C NMR (100 MHz, $CDCl_3$):137.59 (Ar**C**), 128.48 (Ar**C**H), 127.87 (Ar**C**H), 127.65 (Ar**C**H), 97.87 (d, *J* = 12.6 Hz, **C**HOEt), 73.77 (**C**H_2Ph), 72.7 (dd, *J* = 25.3, 22.4, Hz, CF_2**C**H), 66.35 (**C**H_2OBn), 65.56 (**C**H_2CH_3), 38.85 (t, *J* = 20.9, CF_2**C**H_2), 14.97 (**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -113.62 (1F, m, C**F**FCH_2); -120.06 (1F, m, CHC**F**F); -132.59 (1F, m, CF**F**CH_2); -140.24 (1F, m, CHCF**F**).

EIMS: m/z (%): 322 (M^+, 3), 293 (9), 276 (12), 248 (23), 216 (8), 201 (13), 173 (25), 153 (59), 107 (71), 91 (100).

HRMS (EI) for $C_{15}H_{18}O_3F_4$ $(M)^+$: calcd 322.1192, found 322.1188

Data for **5.14b**:

IR (neat): 3033 (w), 2975 (m), 2891 (m), 2817 (w), 1499 (w), 1457 (m), 1388 (m), 1185 (s), 1057 (s).

^{1}H NMR (300 MHz, $CDCl_3$): 7.39–7.29 (5H, m, Ar**H**), 5.07 (1H, t, *J* = 3.9 Hz, C**H**OEt), 4.65 (1H, d, *J* = 12.1 Hz, C**H**HPh), 4.59 (1H, d, *J* = 12.3 Hz, CH**H**Ph), 4.36 (1H, ddt, *J* = 22.7, 7.3, 3.7 Hz, CF_2C**H**), 3.91 (1H, ddd, *J* = 11.0, 2.3, 1.1 Hz, C**H**HOBn), 3.80 (1H, dq, *J* = 9.8, 7.0 Hz, CH_3C**H**H), 3.75 (1H, dd, *J* = 11.0, 7.5 Hz, CH**H**OBn), 3.53 (1H, dq, *J* = 9.8, 7.0 Hz, CH_3CH**H**), 2.51–2.3 (2H, m, CF_2CH**H** + CF_2C**H**H), 14.79 (3H, t, *J* = 7.0 Hz, CH_3).

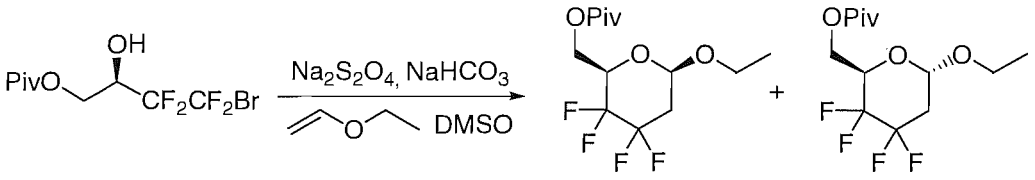
^{13}C NMR (100 MHz, $CDCl_3$): 137.7 (Ar**C**), 128.4 (Ar**C**H), 127.8 (Ar**C**H), 127.5 (Ar**C**H), 95.2 (d, *J* = 12.6 Hz, **C**HOEt), 73.6 (**C**H_2Ph), 67.9 (dd, *J* = 24.8, 21.9 Hz, CF_2**C**H), 66.0 (**C**H_2OBn), 63.8 (CH_3**C**H_2), 37.1 (t, *J* = 20.9 Hz, CF_2**C**H_2), 14.8 (**C**H_3).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): -110.6 (1F, m, C**F**FCH_2); -118.9 (1F, m, CHC**F**F); -133.5 (1F, m, CF**F**CH_2); -137.9 (1F, m, CHCF**F**.)

EIMS: m/z (%): 322 (4, M_+), 293 (14), 276 (13), 248 (31), 216 (10), 201 (17), 173 (36), 153 (69), 107 (67), 91 (100).

HRMS (EI) for $C_{15}H_{18}O_3F_4$ $(M)^+$: calcd 322.1192, found 322.1193

2,2-Dimethyl-propionic acid (2*R*)-6-ethoxy-3,3,4,4-tetrafluorotetrahydro-pyran-2-methyl ester (5.13)



3.04 **3.14a** **3.14b**

To a stirred solution of **3.04** (0.1 g, 0.3 mmol) in dry DMSO (1.5 mL) was added ethyl vinyl ether (0.3 mL, 3.14 mmol). $Na_2S_2O_4$ (0.078 g, 0.45 mmol) and $NaHCO_3$ (0.038 g, 0.45 mmol) were added simultaneously and the reaction stirred at RT for 16 h. H_2O (5 mL) was added, the aqueous phase extracted with Et_2O (3 × 10 ml). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (pet ether / Et_2O, 80:20) gave a colourless oil (0.057 g, 60%). Analytical samples of the pure anomers were obtained by HPLC.

Data for **5.13a**:

IR (neat): 2979 (s0, 2938 (m), 2904 (m), 2877 (m), 1736 (s), 1482 (m), 1427 (m), 1361 (m), 1132 (s), 1062 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (1H, dt, *J* = 9.8, 1.0 Hz, **C<u>H</u>**OEt); 4.46 (1H, dd, *J* = 11.8, 4.5 Hz, **CH<u>H</u>**OPiv); 4.36 (1H, dd, *J* = 11.9, 7.2 Hz, **C<u>H</u>H**OPiv); 4.0 (1H, m, **C<u>H</u>**CF_2); 3.93 (1H, dq, *J* = 9.6, 7.0 Hz, **C<u>H</u>H**CH_3); 3.59 (1H, dq, *J* = 9.5, 7.0 Hz, **CH<u>H</u>**CH_3); 2.51 (1H, m, CF_2**C<u>H</u>H**CH); 2.28 (1H, dddd, *J* = 35.6, 18.8, 8.5, 3.8 Hz, CF_2**CH<u>H</u>**CH); 1.25 (3H, t, *J* = 7.2 Hz, CH_2**C<u>H</u>$_3$**); 1.22 (9H, s, C(**C<u>H</u>$_3$**)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9 (**<u>C</u>**O); 98.1 (d, *J* = 13.5 Hz, **<u>C</u>**HOEt); 70.4 (dd, *J* = 25.3, 21.4 Hz, **<u>C</u>**HCF_2); 65.5 (**<u>C</u>H$_2$**CH_3); 59.7 (**<u>C</u>H$_2$**OPiv); 38.82 (t, *J* = 20.4 Hz, CF_2**<u>C</u>H$_2$**); 38.78 (**<u>C</u>**$(CH_3)_3$); 27.0 (C(**<u>C</u>H$_3$**)$_3$); 15.0 (CH_2**<u>C</u>H$_3$**).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -113.5 (1F, ddddd, *J* = 259, 36, 27, 11.4, 3.1 Hz, **C<u>F</u>F**CH_2); -120.1 (1F, dddd, *J* = 258.3, 12.5, 8.8, 3.8 Hz, CH**C<u>F</u>F**); -132.7 (1F, m, **CF<u>F</u>**CH_2); -140.3 (1F, dddd, *J* = 258, 13.5, 9.3, 4.6 Hz, CH**CF<u>F</u>**).

EIMS: m/z (%): 315 ($M\text{-}H^+$, 2), 271 (4), 214 (8), 201 (12), 173 (14), 153 (16), 121 (14), 85 (30), 57 (100).

HRMS (EI) for $C_{13}H_{20}O_4F_4$ $(M)^+$: calcd 316.1298, found 316.1285.

Data for **5.13**:

IR (neat): 2978 (s), 2936 (m), 2877 (w), 1736 (s), 1482 (m), 1373 (m), 1354 (m), 1284 (m), 1129 (s), 1096 (s).

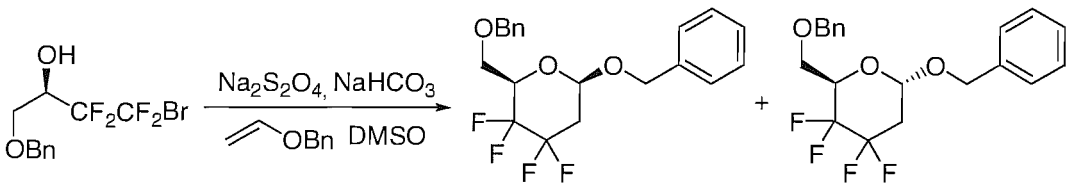
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (1H, t, J = 4.0 Hz, C**H**OEt); 4.46 (1H, m, C**H**HOPiv); 4.39 (1H, m, C**H**CF_2); 4.32 (1H, m, CH**H**OPiv); 3.76 (1H. dq, J = 9.8, 7.0 Hz, C**H**HCH_3); 3.52 (1H, dq, J = 9.8, 7.0Hz, C**H**HCH_3); 2.51–2.30 (2H, m, CF_2C**H**H and CF_2CH**H**); 1.25 (3H, t, J = 7.0, CH_2C**H**$_3$); 1.22 (9H, s, C(C**H**$_3$)$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 117.9 (**C**O); 95.1 (d, J = 12.6 Hz, **C**HOEt); 66.6 (dd, J = 25.3, 23.3 Hz, **C**HCF_2); 63.8 (**C**H$_2$$CH_3$); 59.89 (**C**H$_2$OPiv); 38.8 (**C**$(CH_3)_3$); 37.0 (t, J = 21.4 Hz, CF_2**C**H$_2$); 27.1 (C(**C**H$_3$)$_3$); 14.7 (CH_2**C**H$_3$).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -110.61 (1F, m, C**F**FCH_2); -119.03 (1F, m, CHC**F**F); -133.76 (1F, ddddd, J = 258, 24, 15.5, 12.5, 3 Hz, CF**F**CH_2); -137.92 (1F, m, CHCF**F**).

EIMS: m/z (%): 315 ($M\text{-}H^+$, 1), 271 (2), 214 (4), 201 (6), 173 (3), 153 (5), 121 (8), 85 (10), 77 (10), 57 (100).

(2*R*)-6-Benzyloxy-2-benzyloxymethyl-3,3,4,4-tetrafluoro-tetrahydro-pyran (5.15)



3.06 **5.15a** **5.15b**

To a stirred solution of **3.06** (0.25 g, 0.756 mmol) in dry DMSO (3 mL) was added benzyl vinyl ether (0.15 g, 1.13 mmol). $Na_2S_2O_4$ (0.197 g, 1.13 mmol) and $NaHCO_3$ (0.095 g, 1.13 mmol) were added simultaneously and the reaction stirred at RT for 17 hours. H_2O (5 mL) was added, the aqueous phase extracted with Et_2O (3 × 20 ml). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (pet ether / Et_2O, 85:15) gives a colourless oil (0.174 g, 60%) as a mixture of anomers. Analytical samples of the pure anomers were obtained by HPLC.

Data for **5.15a**:

IR (neat): 3032 (w), 2921 (w), 2882 (w), 1497 (w), 1366 (w), 1229 (w), 1172 (m), 1121 (s), 1063 (s), 1016 (s), 954 (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (10H, m, Ar**H**), 4.95 (1H, d, *J* = 11.8 Hz, CHOC**H**HPh), 4.82 (1H, dt, *J* = 9.5, 1.0 Hz, **OCHOBn**), 4.68 (1H. d, *J* = 7.3 Hz, CH_2OC**H**HPh), 4.65 (1H. d, *J* = 8.0 Hz, CH_2OCH**H**Ph), 4.62 (1H. d, *J* = 12.1 Hz, CHOCH**H**Ph), 4.03-3.95 (2H, m, C**H**HOBn + CF_2C**H**), 3.82 (1H, dd, *J* = 11.2, 7.3 Hz, **CH**HOBn), 2.59-2.50 (1H, m, C**H**HCHO), 2.35 (1H, dddd, *J* = 35.8, 18.0, 9.3, 4.5 Hz, **CH**HCHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.61 (Ar**C**), 136.34 (Ar**C**), 128.55 (Ar**C**H), 128.51 (Ar**C**H), 128.2 (Ar**C**H), 128.12 (Ar**C**H), 127.89 (Ar**C**H), 127.63 (Ar**C**H), 96.80 (d, *J* = 13.6 Hz, **C**HOBn), 73.77 (O**C**H_2Ph), 72.65 (dd, *J* = 26.3, 22.4 Hz, **C**HCF_2), 71.02 (O**C**H_2Ph), 66.33 (**C**H_2OBn), 38.76 (t, *J* = 20.1 Hz, CF_2**C**H_2).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -113.42 (1F, m, C**F**FCO), -120.02 (1F, dddd, *J* = 259.2, 20.7, 10.0, 5.1 Hz, CF**F**CO), -132.45 (1F, m, C**F**FCH_2), -140.10 (1F, dddd, *J* = 257.9, 13.9, 9.4, 4.3 Hz, CF**F**CH_2)

CIMS: m/z (%): 402 $(M+NH_4)^+$ (14), 293 (64), 181 (26), 167 (20), 107 (57), 91 (100).

HRMS (EI) for $C_{20}H_{20}O_3F_4$ $(M)^+$: calcd 384.13486, found 384.13462.

Data for **5.15b**:

IR (neat): 3032 (w), 2920 (w), 2882 (w), 1497 (w), 1366 (w), 1350 (w), 1315 (w), 1172 (m), 1121 (s), 1063 (s), 1016 (s), 954 (w).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.12 (1H, t, J = 3.9 Hz, C**H**OBn), 4.81 (1H, d, J = 12.0 Hz, CHOC**H**HOPh), 4.66 (1H. d. J = 12.0 Hz, CH_2OC**H**HOPh), 4.61 (1H, d, J = 12.0 Hz, CH_2OCH**H**OPh), 4.55 (1H, d, J = 12.0 Hz, CHOC**H**HOPh), 4.43 (1H, m, CF_2C**H**), 3.91 (1H, ddd, J = 11.0, 2.8, 1.1 Hz, C**H**HOBn), 3.77 (1H, dd, J = 10.9, 7.3 Hz, CH**H**OBn), 2.56-2.32 (2H, m, CF_2CH**H**CHOBn + CF_2C**H**H).

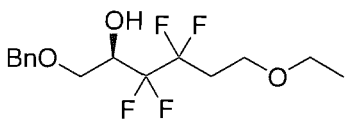
^{13}C NMR (100 MHz, $CDCl_3$): δ 137.65 (Ar**C**), 136.53 (Ar**C**), 128.52 (Ar**C**H), 128.45 (Ar**C**H), 127.99 (2 × Ar**C**H), 127.91 (Ar**C**H), 127.79(2 × Ar**C**H), 127.52 (Ar**C**H), 94.13 (d, J = 12.6 Hz, **C**HOBn), 73.59 (**C**H_2Ph), 69.27 (**C**H_2Ph), 68.12 (dd, J = 24.3, 21.6 Hz, CF_2**C**H), 65.92 (**C**H_2OBn), 36.73 (t, J = 21.9 Hz, CF_2**C**H_2).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -110.4 (1F, dddd, J = 255.2, 33.4, 26.0, 12.9 Hz, C**F**FCO), -119.1 (1F, m CF**F**CO), -133.46 (1F, ddd, J = 257.09, 52.9, 13.3 Hz, CF**F**CH_2), -137.9 (1F, m, C**F**FCH_2).

CIMS: m/z (%): 402 $(M+NH_4)^+$ (5), 293 (64), 181 (11), 107 (30), 91 (100).

HRMS (EI) for $C_{20}H_{20}O_3F_4$ $(M)^+$: calcd 384.13486, found 384.13455.

Data for **5.16**



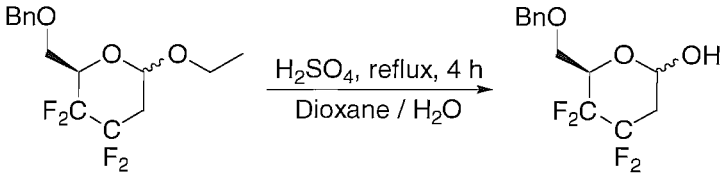
5.16

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.417.29 (5H, m, Ar**H**), 4.61 (2H, app. t, J = 12.3 Hz, CH_2Ph), 4.30 (1H, m, C**H**OH), 3.80 (1H, dt, J = 10.1, 2.7 Hz, C**H**HOBn), 3.74 (1H, m, CH**H**OBn), 3.70 (2H, t, J = 7.1 Hz, CH_2CH_2O), 3.52 (2H, q, J = 7.0 Hz, CH_2CH_3), 2.96 (H, br. s, O**H**), 2.592.31 (2H, m, CF_2CH_2), 1.22 (3H, t, J = 7.1 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.31, 128.54, 128.1, 127.78, 73.68, 68.1 (dd, J = 28.2, 22.8 Hz), 67.89 (m), 66.46, 62.93 (m), 32.03 (app. t, J = 22.3 Hz), 15.03.

CIMS: m/z (%): 342 $(M+NH_4)^+$ (35), 325 $(M+H)^+$ (26), 108 (48), 91 (100).

(6*R*)-6-Benzyloxymethyl-4,4,5,5-tetrafluoro-tetrahydro-pyran-2-ol (5.17)



5.14 **5.17** (91%)

To a stirred solution of **5.14** (0.408 g, 1.27 mmol) in dioxane (6.5 mL) was added H_2SO_4 (25% (v/v) aq, 6.5 mL) and the reaction warmed to reflux. The reaction was stirred at reflux for 4 h before cooling to RT. The reaction mixture was extracted with EtOAc (3 × 50 mL), the organic layers combined, dried over Na_2SO_4, filtered then concentrated. The resulting oil was purified by column chromatography (pet ether / acetone, 70:30) to give a white solid (0.333g, 91 %), found to be **5.17** as a 3.5:1 mixture of anomers.

m.p. 106-108°C.

IR (neat): 3415 (w), 1453 (w), 1433 (w), 1365 (m), 1252 (w), 1210 (m), 1184 (m), 1154 (m), 1130 (m), 1110 (s), 1090 (s), 1060 (m), 1019 (s), 881 (m), 809 (m).

^{1}**H NMR** (400 MHz, $CDCl_3$): 7.40–7.31 (10H, m, Ar**H**), 5.41 (1H, br. s, C**H**OH), 4.87 (1H, d, J = 9.3 Hz, C**H**OH), 4.63–4.54 (5H, m, 2 × C**H**$_2$Ph + CF_2C**H**), 4.31 (1H, br. s, O**H**), 3.95 (1H, m, CF_2C**H**), 3.89–3.85 (2H, m, 2 × CH**H**OBn), 3.79 (1H, br. s, O**H**), 3.75 (2H, dd, J = 10.5, 8.3 Hz, 2 × CH**H**OBn), 2.47–2.08 (4H, m, 2 × CF_2C**H**$_2$).

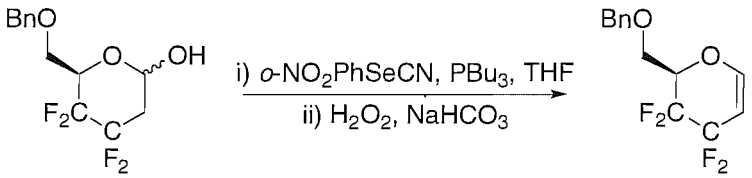
^{13}**C NMR** (100 MHz, $CDCl_3$): 137.1 (2 × Ar**C**), 128.5 (4 × Ar**C**H), 128.1 (2 x Ar**C**H), 128.1 (2 × Ar**C**H), 128.0 (2 × Ar**C**H), 92.6 (d, J = 13.1 Hz, **C**HOH), 90.2 (d, J = 12.6 Hz, **C**HOH), 73.9 (**C**H$_2$OBn), 73.8 (**C**H$_2$OBn), 72.2 (dd, J = 26.7, 23.3 Hz, CF_2**C**H), 67.7 (dd, J = 25.3, 22.8 Hz, CF_2**C**H), 66.1 (br. s, O**C**H$_2$Ph), 65.9 (br. s, O**C**H$_2$Ph), 39.2 (t, J = 20.9 Hz, CF_2**C**H$_2$), 37.0 (t, J = 20.9 Hz, CF_2**C**H$_2$).

^{19}**F NMR** (282 MHz, $CDCl_3$ referenced to $CFCl_3$): -110.25 (1F, dddd, J = 257.9, 34.4, 25.8, 12.9 Hz, C**F**FCH2), -113.84 (1F, m, C**F**FCH2), -118.90 (1F, m, CF**F**CH2), -120.30 (1F, CF**F**CH2), -132.46 (1F, m, CF**F**CH) -133.86 (1F, m, CF**F**CH), -137.96 (1F, m, CF**F**CH), -140.59 (1F, m, CF**F**CH).

CIMS: m/z (%): 312 ($M+NH_4^+$, 4), 272 (20), 255 (28), 237 (16), 168 (8), 108 (42), 91 (100).

HRMS (ES+) for $C_{13}H_{14}O_3F_4Na$ $(M+Na)^+$: calcd 317.0771, found 317.0768

(2R)-2-Benzyloxymethyl-3,3,4,4-tetrafluoro-3,4-dihydro-2H-pyran (5.18)



5.17 **5.18** (51%)

A 5 mL flame dried RB flask was charged with **5.17** (0.05 g, 0.17 mmol) and 2-nitrophenyl selenocyanate (0.057 g, 0.25 mmol). The solids were dissolved in THF (1 mL) and stirred at RT. PBu_3 (0.077 mL, 0.31 mmol) was added dropwise *via* syringe and the reaction stirred for 1 h at RT. $NaHCO_3$ (0.016 g, 0.19 mmol) and H_2O_2 (30 % aq., 0.42 mL, 0.37 mmol) were added and the reaction stirred for 90 min. The reaction was poured into H_2O (5 mL) then the aqueous mixture was extracted with Et_2O (3 × 10 mL), the organic layers combined, dried over Na_2SO_4, filtered then concentrated *in vacuo* giving a brown solid. Purification by column chromatography (pet ether / acetone, 90:10) gave a colourless oil (0.024 g, 51%).

IR (neat): 3026 (w), 2923 (w), 2862 (w), 1645 (m), 1602 (w), 1493 (w), 1453 (m), 1406 (m), 1304 (w), 1282 (m), 1218 (m), 1155 (s), 1129 (s), 1072 (s), 1048 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 7.41–7.31 (5H, m, Ar**H**), 6.68 (1H, d, J = 6.3 Hz, OC**H**CH), 5.14 (1H, dd, J = 13.1, 6.5 Hz, C**H**CF_2), 4.66 (1H, d, J = 12.1 Hz, PhC**H**H), 4.62 (1H, d, J = 11.8 Hz, PhCH**H**), 4.49 (1H, m, CH_2C**H**O), 3.97 (1H, m, OC**H**H), 3.87 (1H, dd, J = 11.2, 7.7 Hz, OCH**H**).

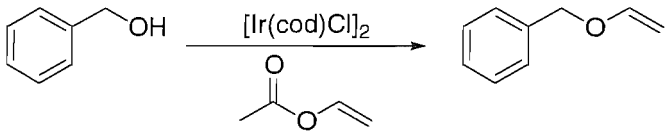
^{13}C NMR (100 MHz, $CDCl_3$): 150.5 (dd, J = 10.7, 7.8 Hz, O**C**HCH), 137.1 (Ar**C**), 128.6 (2 × Ar**C**H), 128.0 (Ar**C**H), 127.8 (2 × Ar**C**H), 96.9 (dd, J = 29.6, 24.8 Hz, **C**HCF_2), 75.44 (dd, J = 27.2, 24.3 Hz, CH_2**C**H), 73.9 (Ph**C**H_2), 65.4 (O**C**H_2).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): 97.17 (1F, ddd, J = 269, 12, 6 Hz, C**F**FCHCH), -126.19 (1F, ddt, J = 270, 16, 8 Hz, CF**F**CHCH), -132.07 (1F, ddd, J = 259, 26, 16 Hz, C**F**FCHO), -136.14 (1F, dt, J = 258, 6 Hz, CF**F**CHO)

EIMS: m/z (%): 276 (M+) (10), 248 (70), 218 (8), 181 (16), 121 (11) 105 (58), 91 (100).

HRMS (EI) for $C_{13}H_{12}O_2F_4$ $(M)^+$: calcd 276.07734, found 276.07699.

Benzyl vinyl ether

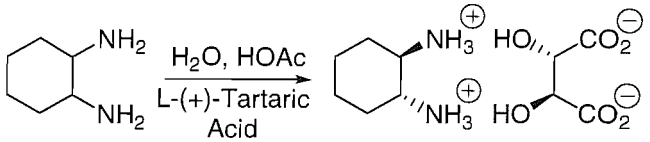


(81%)

$[Ir(cod)Cl]_2$ (0.324 g, 0.483 mmol) and Na_2CO_3 (3.07 g, 28.99 mmol) were weighed into a flame dried 100 mL RB and dissolved in toluene (48 mL). Benzyl alcohol (5.0 mL, 48.31 mmol) and vinyl acetate (8.91 mL, 0.096 mol) were added, the reaction warmed to 100°C and stirred for 2 h. The reaction was cooled to RT and wet Et_2O (20 mL) was added. The reaction was carefully concentrated *in vacuo* and the residue purified by column chromatography (pentane) to give a colourless oil which was further purified by distillation (b.p. 90°C, 25 mmHg) to give the title compound as a colourless oil (5.27 g, 81%)

The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values.[212]

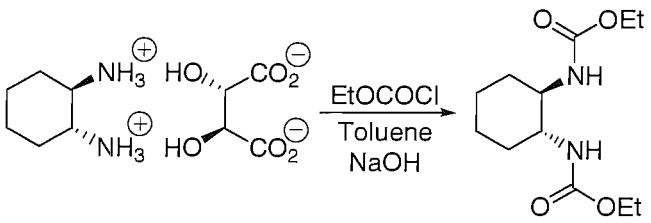
(*R*,*R*)-1,2-Diammoniumcyclohexane mono-(+)-tartrate (2.34)[122]



2.33 **2.34**

A 1L, 3-necked RB flask equipped with a mechanical overhead stirrer and a thermometer is charged with distilled water (250 mL). L-(+)-Tartaric acid (150 g, 0.99 mol) is added with stirring in one portion. The solution is stirred until complete dissolution, at which point a mixture of *cis*- and *trans*-1,2-diaminocyclohexane (240 mL, 1.94 mol was added at a rate such that the reaction temperature reached 70°C. To the resulting solution was added glacial acetic acid (100 mL, 1.75 mol) at a rate such that the reaction temperature just reached 90°C. A white precipitate formed immediately upon addition of the acid, and the slurry was vigorously stirred as it was cooled to RT over 2 h. The mixture was then cooled to ≤5°C in an ice bath for 2 h and the precipitate was collected by filtration. The wet cake was washed with 5°C water (100 mL) and then rinsed with methanol (5 × 100 mL). The solid was dried by drawing air through the filter cake for 1 h. The product was then dried under high vacuum overnight to yield **2.34** as a white solid (160.2 g).

(*R*,*R*)-1,2-Diaminocyclohexane-*N*,*N*'-diethyl carbamate (2.35)[213]



2.34 **2.35** (82%)

A 3L 3-necked RB flask equipped with an overhead mechanical stirrer and thermometer was charged with **2.34** (160.2 g, 0.61 mol). The solid was taken up in toluene (1.6 L) and stirred at 0°C. NaOH (101 g dissolved in 130 mL of H_2O) and ethyl chloroformate (126 mL, 1.32 mol) were added simultaneously at a rate such that the reaction temperature did not exceed 10°C. The reaction was then stirred for 30 minutes at 0°C before warming to RT at which time an observed exotherm raised the internal temperature to 50°C. After the reaction had been allowed to cool to RT over 3 h a white precipitate was filtered off, washing with hexane. The filtrate was then concentrated *in vacuo* to give a white solid, dissolved in CH_2Cl_2 (100 mL) and water (100 mL), the layers separated, the organic phase washed with water (100 mL) and then set aside. The precipitate that had

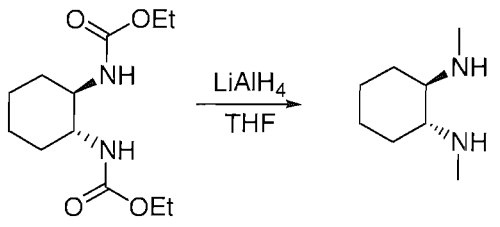
previously been filtered off was dissolved in CH_2Cl_2 (1300 mL) and washed with water (600 mL). The organic phases were combined and then washed with $NaHCO_3$ (sat. aq. 300 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid. Recrystallization from ethanol gave **2.35** as fluffy white needles (128.6g, 82%).

m.p. 165–167°C, lit. 166.5–168.5°C.[123]

$[\alpha]_D$ = +46.5° (*c* 0.95, $CHCl_3$, 24°C), lit. +45.5° (*c* 1.0, $CHCl_3$).[123]

The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values.[123]

(*R*,*R*)-*N*,*N*'-Dimethyl-1,2-diaminocyclohexane (2.36)[213]

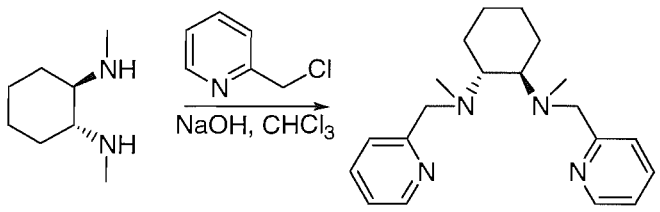


2.35 **2.36** (76%)

$LiAlH_4$ (200 mL of a 1M soln. in THF, 0.2 mol) was transferred, *via* cannula, to a flame dried 3-necked RB and cooled to 0°C. Whilst stirring, **2.35** (4.90 g, 19.0 mmol) was added in portions under a flow of N_2 and the reaction stirred at 0°C for 1h. The reaction was allowed to warm to room temperature and then stirred for a further 1h. The reaction was then heated to reflux and stirred for a further 2h. The reaction was cooled to RT, and then to 0°C. Water (5.5 mL) was added carefully dropwise, then NaOH (5.5 mL, 4M aq.), followed by a further portion of water (16 mL). The resulting slurry was stirring vigorously for 45 minutes at RT and then filtered. The residue was resuspended in THF and heated to reflux for 10 minutes before being refiltered. The filtrates were combined, concentrated *in vacuo* and then dissolved in NaOH (40 mL, 4M aq.). The aqueous solution was extracted with CH_2Cl_2 (4 × 30 mL), the organic phases combined, dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield **2.36** as a white solid (2.04 g, 76%).

$[\alpha]_D$ = -141.7° (*c* 1.0, $CHCl_3$, 24°C), lit. -144.2° (*c* 1.15, $CHCl_3$).[123]
The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values.[123]

(*R*,*R*)-mcp (2.32)



2.36 **2.32** (82%)

To a solution of K_2CO_3 (6.74 g, 48.8 mmol) in H_2O (20 mL) was added 2-picolyl chloride hydrochloride (4.0 g, 24.4 mmol) and the solution was shaken for 5 minutes. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL), the organics combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. **2.36** (1.5 g, 10.6 mmol) was dissolved in $CHCl_3$ (30 mL), NaOH (35 mL, 1M aq.) was added. The free-based 2-picolyl chloride (2.69 g, 21.1 mmol) was added dropwise, the reaction warmed to 70°C and stirred for 48h. The reaction was cooled to RT, diluted with NaOH (20 mL, 1 aq.), the layers separated and the aqueous phase extracted with $CHCl_3$ (3 × 75 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated in vacuo to give a brown oil. Purification by chromatography (CH_2Cl_2/MeOH, 9:1, 0.5 % NH_4OH) to give **2.27** as a brown oil (2.80 g, 82 %).

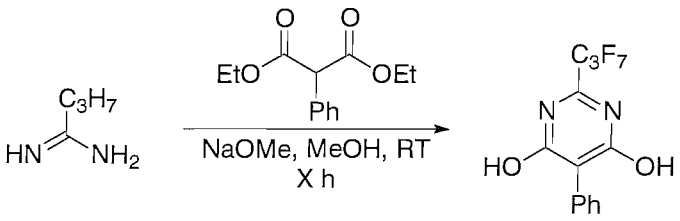
IR (neat): 3415 (m), 3050 (w), 3007 (w), 2930 (m), 2854 (m), 2788 (m), 1590 (s), 1568 (m), 1473 (s), 1448 (m), 1433 (s), 1355 (m), 1145 (m), 1047 (m), 1029 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (2H, dt, *J* = 4.9, 1.4 Hz, 2 ×Ar**H**); 7.60–7.58 (4H, m, 4 × Ar**H**); 7.12 (2H, td, *J* = 4.9, 3.5 Hz, 2 × Ar**H**); 3.93 (2H, d, *J* = 14.6 Hz, 2 × **CHH**Py); 3.81 (2H, d, *J* = 14.6 Hz, 2 × **CHH**Py); 2.71–2.64 (2H, m, 2 × CH_2**CH**N); 2.30 (6H, s, 2 × N**CH$_3$**); 2.01–1.98 (2H, m, **CHH**CHN); 1.79–1.76 (2H, m, **CHH**CHN); 1.34-1.11 (4H, m, 2× **CHH**CH_2CH and 2× **CHH**CH_2CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2 (2 × Ar**C**); 148.5 (2 × Ar**C**H); 136.2 (2 × Ar**C**H); 122.8 (2 × Ar**C**H); 121.5 (2 × Ar**C**H); 64.5 (2 × CH_2**C**HN); 60.3 (2 × N**C**H_2); 36.6 (2 × N**C**H_3); 25.74 (2 × **C**H_2CHN); 25.72 (2 × **C**H_2CH_2CH).

ESMS (ES+): m/z (%): 325 ($M+H^+$, 100).

HRMS (ES+) for $C_{20}H_{28}N_4$ $(M+H)^+$: calcd 325.2387, found 325.2386.

2-Heptafluoro-5-phenyl-4,6-dihydroxypyrimidine(2.46)



2.45 **2.46** (84%)

To a stirred solution of **2.45** (2.14 g, 10.07 mmol) in MeOH (17 mL) was added NaOMe (1.36 g, 25.18 mmol). The reaction was stirred for 10 min at RT then diethylphenylmalonate (2.17 mL, 10.07 mmol) was added. The reaction was stirred at RT for 16 h before being concentrated *in vacuo*. The residue was taken up in H_2O (20 mL) and the solution neutralised with HCl (5M, aq.) giving a white precipitate. The precipitate was collected by filtration and washed with H_2O (4 × 5 mL), then dried under high vacuum for 16 h to give a white solid (2.99 g, 84%).

m.p. Sample decomposed before melting

IR (neat): 3043 (w), 2903 (w), 2651 (w), 2577 (w), 1586(w), 1493 (w), 1429 (m), 1343 (m), 1238 (s), 1204 (s), 1181 (s), 1083 (s), 1067 (s), 1015 (w) cm^{-1}.

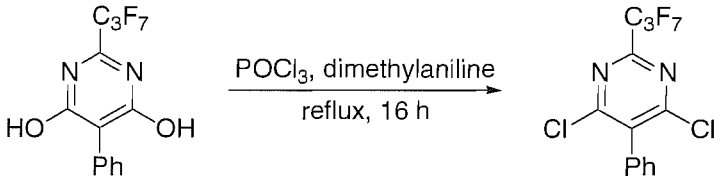
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.46 (2H, m, Ar**H**), 7.39–7.26 (3H, m, Ar**H**).

^{13}C NMR (75 MHz, $CDCl_3$): δ 131.5 (2 × Ar**C**H), 128.7 (2 × Ar**C**H), 128.4 (Ar**C**H).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -82.32 (3F, t, J = 9.1 Hz, **C**F_3), -117.7 (2F, m, **C**F_2CF_3), 127.7 (1F, s, **C**F_2CF_2).

ESMS (ES-): m/z (%): 355 $(M-H)^+$ (100)

2-Heptafluoro-5-phenyl-4,6-dichloroypyrimidine (2.47)



2.46 **2.47** (87%)

A 25 mL RB flask was charged with **2.46** (2.95 g, 8.28 mmol). $POCl_3$ (17.5 mL, 0.19 mol) was added and the suspension stirred at RT. Dimethylaniline (2.6 mL, 20.5 mmol) was added *via* syringe, with the solids dissolving upon completion of addition. The reaction was brought to reflux and then stirred for 16h. The reaction was allowed to cool then concentrated *in vacuo*. The residue was poured into NaOH (1M, aq., 50 mL), the mixture stirred for 10 min at RT. The resulting solution was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic phases were washed with HCl (0.5 M, aq., 2× 50 mL), dried over $MgSO_4$, filtered and concentrated to give a dark red solid. This solid was passed through a silica plug, eluting with CH_2Cl_2 to give a pale red solid (2.82 g, 87%).

m.p. 64-66°C.

IR (neat): 1539 (w), 1514 (m), 1446 (w), 1345 (m), 1303 (m), 1224 (s), 1209 (s), 1142 (s), 1113 (s), 1003 (m) cm^{-1}.

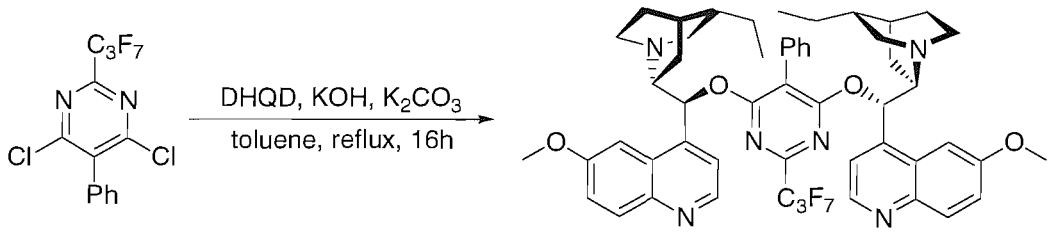
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.55 (3H, m, Ar**H**), 7.36–7.33 (2H, m,. Ar**H**).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (2 × **C**Cl), 131.7 (**C**Ph), 130.0 (Ar**C**H), 129.7 (CH**C**CH), 129.0 (2 × Ar**C**H), 128.9 (2 × Ar**C**H).

^{19}F NMR (376 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -80.32 (3F, t, J = 8.6 Hz, **CF_3**), -115.32 (2F, q, J = 9.7 Hz, **CF_2**CF_3), -125.65 (2F, s, **CF_2**C).

CIMS: m/z (%): 392 $(M-H)^+$ (100), 273 (19), 127 (44).

2-Heptafluoro-5-phenyl-4,6-bis-(9-O-dihydroquinidyl)pyrimidine (2.40)



2.47 **2.40** (57%)

A 25 mL RB flask was charged with **2.47** (0.5 g, 1.27 mmol), K_2CO_3 (0.527 g, 3.82 mmol) and dihydroquinidine (0.83 g, 2.54 mmol). Toluene (10 mL) was added, the flask equipped with a Dean and Stark condenser and the mixture stirred at reflux for 2 h. The suspension was allowed to cool to RT, then KOH (0.243 g, 4.32 mmol) added and the reaction refluxed under Dean and Stark conditions for 16 h. After cooling to RT the reaction was diluted with H_2O (50 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown solid. This was purified by column chromatography (CH_2Cl_2 / MeOH, 90:10) to give the desired compounds as a pale brown solid (0.704 g, 57%)

m.p. Sample decomposed before melting.

IR (neat): 2935 (w), 2870 (w), 1621 (m), 1567 (m), 1508 (m), 1474 (w), 1433 (w), 1355 (m), 1226 (s), 1110 (s), 1031 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (2H, d, *J* = 4.5 Hz, 2 × ArC**H**N), 7.90 (2H, d, *J* = 9.3 Hz, 2 × ArNCC**H**), 7.51–7.42 (3H, m, ArC**H**C**H**C**H**), 7.36 (2H, br. d, ArC**H**CC**H**), 7.27–7.24 (4H, m, 2 × ArNCCHC**H** + 2 × MeOCC**H**), 7.18 (2H, d, *J* = 4.5 Hz, 2 × ArNCHC**H**), 3.69 (6H, s, 2 × C**H**$_3$), 3.11 (2H, m, 2 × C**H**), 2.75–2.44 (8H, 4 × C**H**$_2$), 1.62–1.56 (4H, m, 4 × C**H**), 1.401.18 (8H, m, 4 × C**H**$_2$), 0.95 (4H, br. s, 2 × C**H**$_2$CH$_3$), 0.66 (6H, t, *J* = 7.2 Hz, 2 × CH$_2$C**H**$_3$).

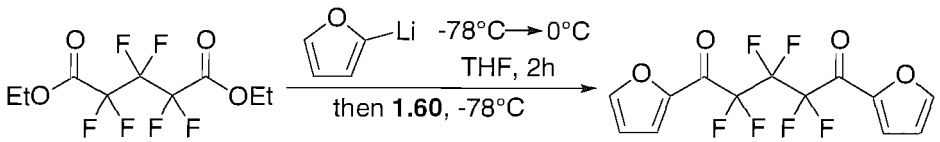
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9 (2 × ArN**C**O), 157.9 (2 × ArN**C**CH), 152.7 (t, *J* = 26.0 Hz, CF$_2$**C**), 147.0 (2 × ArN**C**H), 144.7 (2 × **C**OMe), 143.5 (2 × OCH**C**), 131.5 (2 ×

ArNC**C**H), 130.0 (**C**H**C**H**C**H), 129.4 (CH**C**CH), 128.6 (**C**HC**C**H), 126.8 (**C**Ph), 122.1 (2 × C**C**HCOMe), 118.9 (2 × ArNCH**C**H), 108.4 (2 × ArC**C**C), 101.2 (2 × ArNCCH**C**H), 59.5 (2 × O**C**H), 55.3 (2 × O**C**H_3), 50.7 (2 × **C**H_2), 49.7 (2 × **C**H_2), 37.0 (2 × **C**H), 26.7 (2 × **C**H_2), 25.8 (4 × **C**H), 24.7 (2 × **C**$H_2$$CH_3$), 23.1 (2 × **C**$H_2$), 11.89 (2 × CH_2**C**H_3).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -81.21 (3F, m, **C**F_3), -116.50 (2F, m, CF_3**C**F_2), -126.99 (2F, s, CF_2**C**F_2).

ESMS (ES+): m/z (%): 974 $(M+H)^+$ (12), 973 $(M)^+$ (20), 508.2 (36), 488 (100).

1,5-di(2-furanyl)-2,2,3,3,4,4,-hexafluoropentane-1,5-dione (2.41)



1.60 **2.41** (81%)

Furan (1.23 mL, 16.9 mmol) was dissolved in THF (60 mL) and the solution cooled to -78°C. *n*-BuLi (1.6 M in hexanes, 11.1 mL, 17.7 mmol) was added slowly dropwise keeping the temperature of the reaction below -65°C. Upon complete addition the reaction was allowed to warm to 0°C and stirred for 2 h. The reaction was then recooled to -78°C prior to dropwise addition of a solution of diethyl hexafluoroglutarate (2.5 g, 8.4 mmol) in THF (5 mL) over 30 min. The reaction was stirred for 5 min at -78°C then quenched with HCl (2M, aq., 30 mL) and warmed to RT. The solution was extracted with Et_2O (3 × 50 mL), the organic layers combined, washed with $NaHCO_3$ (sat. aq., 30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a green solid. Purification by column chromatography (cyclohexane / EtOAc, 85:15) gave a white solid (2.32 g, 81%).

m.p. 60-63°C.

IR (neat): 3130 (w), 1658 (s), 1456 (s), 1399 (m), 1271 (w), 1207 (s), 1188 (s), 1162 (s), 1127 (s), 1039 (m), 990 (m), 941 (m) cm^{-1}.

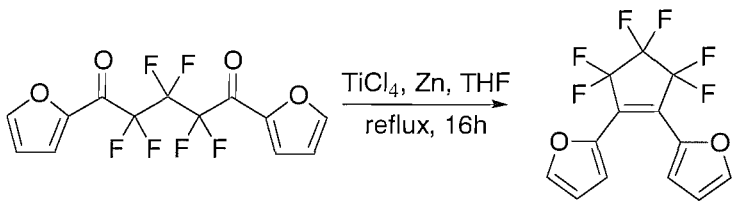
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (2H, d, *J* = 1.1 Hz, 2 × C**H**O), 7.53 (2H, d, *J* = 3.1 Hz, 2 × C**H**C) 6.67 (2H, dd, *J* = 3.8, 1.6 Hz, 2 × CHC**H**CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (m, 2 × **C**=O), 150.2 (2 × **C**HO), 148.1 (2 × Ar**C**), 124.8 (2 × **C**HC), 113.3 (2 × CH**C**HCH).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -116.11 (4F, s, 2 × CO**C**F_2), -121.61 (2F, s, CF_2**C**$F_2$$CF_2$).

CIMS: m/z (%): 358 $(M+NH_4)^+$ (8), 341 $(M+H)^+$ (8), 95 (100).

1,2-di-(2-furanyl)-3,3,4,4,5,5-hexafluorocyclopentene (2.42)



2.41 **2.42** (83%)

A vigorously stirred suspension of zinc powder (3.84 g, 58.8 mmol) in THF (65 mL) was cooled to -10°C. $TiCl_4$ (1.93 mL, 17.64 mmol) was added slowly dropwise, the reaction warmed to reflux and stirred for 1 h. After cooling to -10°C a solution of **2.36** (1.0 g, 2.94 mmol) in THF (10 mL) was added dropwise. The reaction was warmed to reflux and stirred for 24 h. The reaction was allowed to cool, K_2CO_3 (10% aq (w/v), 50 mL) was added and the resulting slurry stirred for 30 min. The reaction was filtered through celite washing with Et_2O (2 × 25 mL), the layers separated and the aqueous phase extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a brown oil. Column chromatography (cyclohexane) gave a colourless oil (0.753 g, 83%).

I.R. 1483 (m), 1340 (m), 1274 (s), 1221 (m), 1191 (s), 1123 (s), 1094 (m).

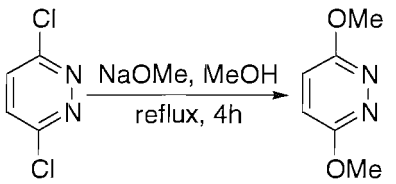
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (2H, d, *J* = 1.1 Hz, 2 × C**H**O), 7.18 (2H, d, *J* = 3.5 Hz, 2 × C**H**C), 6.62 (2H, dd, *J* = 3.7, 1.8 Hz, 2 × CHC**H**CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (2 × **C**HO), 143.5 (2 × CH**C**C), 117.2 (2 × **C**HC), 112.4 (2 × CH**C**HCH).

^{19}F NMR (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -109.24 (4F, m, **C**F_2CF2**C**F_2), -131.71 (2F, m, CF_2**C**$F_2$$CF_2$).

CIMS: m/z (%): 308 $(M)^+$ (100), 290 (14), 279 (20), 151 (22).

3,6-Dimethoxypyridizine (2.50)



2.49 **2.50** (89%)

2.49 (5.0 g, 33.6 mmol) was dissolved in MeOH (50 mL). NaOMe (7.26 g, 0.134 mol) was added portion-wise, the reaction warmed to reflux and stirred for 4 h. The reaction was cooled to RT, diluted with EtOAc (250 mL) then washed with H_2O (2 × 100 mL). The organic layer was dried over Na_2SO_4, filtered then concentrated to give a white crystalline solid (4.19 g, 89%).

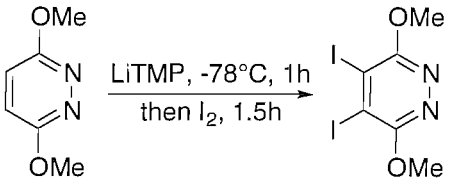
m.p. 107–109°C, lit. 106–108°C[214]

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (2H, s, 2 × Ar**H**), 3.97 (6H, s, 2 × O**C**H_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5 (2 × Ar**C**), 120.9 (2 × Ar**C**H), 54.1 (2 × **C**H_3)

The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values[214]

4,5-Diiodo-3,6-dimethoxy-pyridazine (2.51)



2.50 **2.51** (87%)

THF (280 mL) was cooled to -78°C and BuLi (1.6 M in hexanes, 25.2 mL) was added. TMPH (6.81 mL, 40.38 mmol) was added, the reaction warmed to 0°C and stirred for 20 min. The reaction was cooled to -78°C and a solution of **2.50** (2.46 g, 17.55 mmol) in THF (20 mL) was added dropwise. The reaction was stirred at -78°C for 1 h, I_2 (10.51 g, 41.43 mmol) was added in one portion and the reaction stirred for a further 90 min. The reaction was quenched at -78°C with EtOH (20 mL) in THF (35 mL), then warmed to RT. The reaction was concentrated *in vacuo* and the residue taken up in CH_2Cl_2 (150 mL). The solution was washed with NaS_2O_3 (1M, aq., 150 mL), then H_2O (150 mL), the organic layer was dried over $MgSO_4$, filtered and concentrated to give a yellow solid. Column chromatography (pet ether / EtOAc, 90:10) gave a pale yellow solid (6.02 g, 87%).

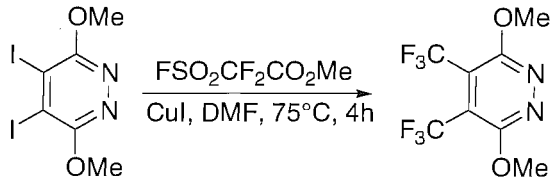
m.p. 188-190°C, lit. 192°C[136]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08 (2H, s, 2 × O<u>C</u>H$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2 (2 × Ar<u>C</u>), 109.8 (2 × Ar<u>C</u>), 56.5 (2 × O<u>C</u>H$_3$).

The **^{1}H** and **^{13}C NMR** spectra corresponded to the literature values[136]

4,5-Di-trifluoromethyl-3,6-dimethoxy-pyridazine (2.52)



2.51 **2.52** (81%)

A 50 mL RB flask was charged with **2.51** (2.5 g, 6.38 mmol) and CuI (0.243 g, 1.28 mmol). DMF (25 mL) was added and the solution warmed to 75°C. $FSO_2CF_2CO_2Me$ (3.25 mL, 25.51 mmol) was added dropwise over 10 min and the reaction stirred for 4 h. The reaction was cooled to RT then H_2O (25 mL) and celite (5 g) were added and stirred for 10 min. The mixture was filtered through celite, washing with Et_2O (2 × 10 mL). The aqueous phase was neutralised with NaOH (2M, aq.), then Et_2O (100 mL) was added. The layers were separated, and the organic phase washed with H_2O (2 × 50 mL), brine (50 mL) then dried over $MgSO_4$, filtered and concentrated. Column chromatography (pet ether / EtOAc 90:10) gave a yellow oil (1.422 g, 81 %) which crystallised on standing.

m.p. 166-169°C

IR (neat): 1472 (s), 1457 (m), 1371 (s), 1299 (m), 1248 (s), 1153 (s), 1095 (m), 1011 (s), 912 (w), 849 (w) cm^{-1}.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 4.20 (6H, s, 2 × O**C**$\underline{\mathbf{H}}_3$).

^{13}**C NMR** (75 MHz, $CDCl_3$): δ 157.8 (**C**OMe), 56.1 (O**C**$\underline{\mathbf{H}}_3$).

^{19}**F NMR** (282 MHz, $CDCl_3$ referenced to $CFCl_3$): δ -57.74 (6F, s, 2 × **C**$\underline{\mathbf{F}}_3$).

CIMS: m/z (%): 277 $(M+H)^+$ (100), 276 (62), 247 (10), 205 (12), 143 (10), 121 (16).

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APPENDIX

Departmental Single Crystal X-Ray Diffraction Service
School of Chemistry - University of Southampton
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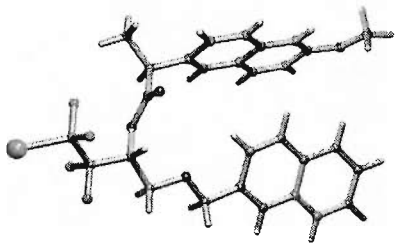
Table 1. Crystal data and structure refinement details.



Identification code	**05sot0066 (JB/4271/13)**
Empirical formula	$C_{29}H_{25}BrF_4O_4$
Formula weight	593.40
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.1963(6) Å
	b = 14.5597(15) Å
	c = 29.452(4) Å
Volume	2657.1(5) Å^3
Z	4
Density (calculated)	1.483 Mg / m^3
Absorption coefficient	1.609 mm^{-1}
F(000)	1208
Crystal	Slab; Colourless
Crystal size	0.4 × 0.3 × 0.04 mm^3
θ range for data collection	3.57 – 27.47°
Index ranges	$-8 \le h \le 6$, $-18 \le k \le 18$, $-26 \le l \le 38$
Reflections collected	19046
Independent reflections	5856 [R_{int} = 0.0579]
Completeness to θ = 27.47°	99.1 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9385 and 0.5655
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5856 / 0 / 346
Goodness-of-fit on F^2	1.005
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0420, $wR2$ = 0.0723
R indices (all data)	$R1$ = 0.0713, $wR2$ = 0.0810
Absolute structure parameter	0.025(7)
Extinction coefficient	0.0015(2)
Largest diff. peak and hole	0.338 and –0.493 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. C12 = S, C15 = R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	4782(1)	3279(1)	1898(1)	29(1)	1
F1	6001(4)	2556(1)	2853(1)	52(1)	1
F2	6661(3)	4017(1)	2782(1)	38(1)	1
F3	2473(4)	4269(1)	2489(1)	46(1)	1
F4	1947(4)	2821(2)	2551(1)	57(1)	1
O1	–2312(3)	6569(1)	6073(1)	22(1)	1
O2	174(4)	4208(1)	3426(1)	40(1)	1
O3	3718(3)	4521(1)	3396(1)	17(1)	1
O4	4540(3)	3421(1)	4135(1)	21(1)	1
C1	–4360(5)	6169(2)	6184(1)	29(1)	1
C2	–1601(5)	6465(2)	5634(1)	18(1)	1
C3	–2708(5)	6061(2)	5288(1)	19(1)	1
C4	–1791(5)	6011(2)	4850(1)	17(1)	1
C5	317(5)	6366(2)	4775(1)	15(1)	1
C6	1417(5)	6776(2)	5143(1)	17(1)	1
C7	485(4)	6839(2)	5560(1)	17(1)	1
C8	–2887(5)	5635(2)	4472(1)	17(1)	1
C9	–1949(5)	5585(2)	4054(1)	21(1)	1
C10	190(5)	5897(2)	3981(1)	18(1)	1
C11	1259(5)	6293(2)	4342(1)	18(1)	1
C12	1311(5)	5774(2)	3530(1)	22(1)	1
C13	78(6)	6187(2)	3128(1)	37(1)	1
C14	1604(5)	4751(2)	3445(1)	21(1)	1
C15	4150(5)	3553(2)	3346(1)	17(1)	1
C16	5089(5)	3408(2)	2871(1)	21(1)	1
C17	3470(5)	3449(2)	2486(1)	26(1)	1
C18	5671(5)	3260(2)	3721(1)	20(1)	1
C19	5884(4)	3275(2)	4520(1)	20(1)	1
C20	4725(5)	3570(2)	4946(1)	17(1)	1
C21	5649(5)	3390(2)	5357(1)	19(1)	1
C22	4677(5)	3666(2)	5770(1)	17(1)	1
C23	2659(5)	4127(2)	5752(1)	18(1)	1
C24	1721(5)	4296(2)	5319(1)	22(1)	1
C25	2722(5)	4023(2)	4930(1)	18(1)	1
C26	5615(5)	3492(2)	6197(1)	24(1)	1
C27	4605(6)	3762(2)	6592(1)	27(1)	1
C28	2605(5)	4216(2)	6576(1)	26(1)	1
C29	1664(5)	4402(2)	6165(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

Br1–C17	1.927(3)	C9–C10	1.417(5)
F1–C16	1.365(3)	C10–C11	1.380(4)
F2–C16	1.342(3)	C10–C12	1.509(4)
F3–C17	1.343(4)	C12–C14	1.522(4)
F4–C17	1.328(4)	C12–C13	1.532(4)
O1–C2	1.373(3)	C15–C18	1.512(4)
O1–C1	1.434(3)	C15–C16	1.530(4)
O2–C14	1.188(3)	C16–C17	1.515(4)
O3–C14	1.360(4)	C19–C20	1.507(4)
O3–C15	1.443(3)	C20–C21	1.366(4)
O4–C19	1.423(3)	C20–C25	1.406(4)
O4–C18	1.427(3)	C21–C22	1.415(4)
C2–C3	1.363(4)	C22–C26	1.409(4)
C2–C7	1.420(4)	C22–C23	1.420(4)
C3–C4	1.412(4)	C23–C29	1.420(4)
C4–C8	1.415(4)	C23–C24	1.422(4)
C4–C5	1.422(4)	C24–C25	1.363(4)
C5–C11	1.405(4)	C26–C27	1.377(4)
C5–C6	1.414(4)	C27–C28	1.405(4)
C6–C7	1.360(4)	C28–C29	1.372(5)
C8–C9	1.364(4)		

C2–O1–C1	117.0(2)	C10–C12–C14	108.4(2)
C14–O3–C15	115.5(2)	C10–C12–C13	113.8(3)
C19–O4–C18	111.7(2)	C14–C12–C13	108.5(3)
C3–C2–O1	126.1(3)	O2–C14–O3	123.3(3)
C3–C2–C7	120.6(3)	O2–C14–C12	124.8(3)
O1–C2–C7	113.3(3)	O3–C14–C12	111.9(3)
C2–C3–C4	120.2(3)	O3–C15–C18	108.5(2)
C3–C4–C8	123.1(3)	O3–C15–C16	107.3(2)
C3–C4–C5	119.6(3)	C18–C15–C16	113.1(2)
C8–C4–C5	117.3(3)	F2–C16–F1	107.0(3)
C11–C5–C6	121.8(3)	F2–C16–C17	108.0(2)
C11–C5–C4	119.7(3)	F1–C16–C17	106.3(2)
C6–C5–C4	118.5(3)	F2–C16–C15	111.3(2)
C7–C6–C5	121.1(3)	F1–C16–C15	108.5(2)
C6–C7–C2	120.0(3)	C17–C16–C15	115.3(3)
C9–C8–C4	121.8(3)	F4–C17–F3	106.5(3)
C8–C9–C10	121.2(3)	F4–C17–C16	109.6(3)
C11–C10–C9	117.8(3)	F3–C17–C16	109.5(3)
C11–C10–C12	120.5(3)	F4–C17–Br1	109.9(2)
C9–C10–C12	121.7(3)	F3–C17–Br1	108.3(2)
C10–C11–C5	122.1(3)	C16–C17–Br1	112.8(2)

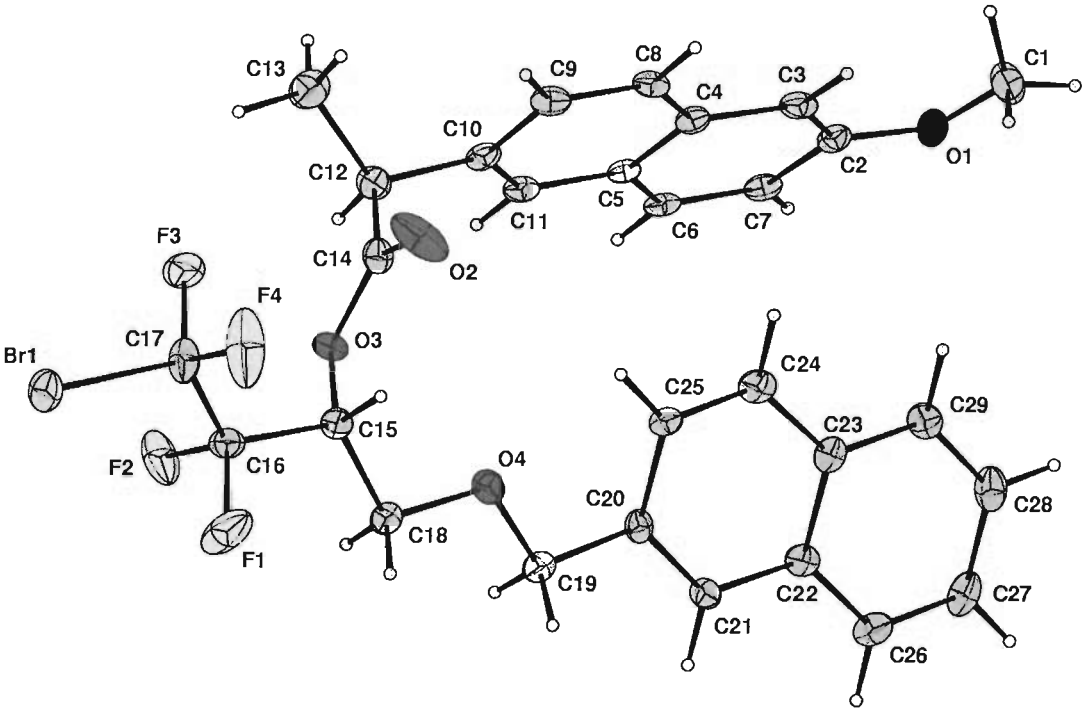
O4–C18–C15	105.8(2)	C29–C23–C22	118.9(3)
O4–C19–C20	110.0(2)	C29–C23–C24	122.7(3)
C21–C20–C25	119.3(3)	C22–C23–C24	118.3(3)
C21–C20–C19	118.9(3)	C25–C24–C23	121.2(3)
C25–C20–C19	121.8(3)	C24–C25–C20	120.7(3)
C20–C21–C22	122.0(3)	C27–C26–C22	121.0(3)
C26–C22–C21	122.7(3)	C26–C27–C28	120.5(3)
C26–C22–C23	118.8(3)	C29–C28–C27	119.8(3)
C21–C22–C23	118.5(3)	C28–C29–C23	121.0(3)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	33(1)	40(1)	16(1)	−1(1)	1(1)	2(1)
F1	94(2)	40(1)	24(1)	0(1)	−1(1)	39(1)
F2	22(1)	65(2)	28(1)	−9(1)	5(1)	−14(1)
F3	49(1)	70(2)	20(1)	5(1)	1(1)	34(1)
F4	59(2)	89(2)	24(1)	−11(1)	4(1)	−48(1)
O1	23(1)	28(1)	16(1)	2(1)	1(1)	−1(1)
O2	21(1)	30(1)	68(2)	−22(1)	10(2)	−8(1)
O3	13(1)	16(1)	23(1)	−2(1)	1(1)	2(1)
O4	18(1)	30(1)	16(1)	−2(1)	−1(1)	2(1)
C1	23(2)	41(2)	24(2)	−1(2)	6(2)	−1(2)
C2	21(2)	14(2)	18(2)	2(1)	−1(2)	3(1)
C3	14(2)	14(2)	28(2)	4(1)	−1(2)	1(1)
C4	20(2)	11(1)	20(2)	1(1)	−2(2)	3(1)
C5	17(2)	10(1)	19(2)	2(1)	−2(2)	4(1)
C6	14(2)	11(1)	25(2)	3(2)	−5(1)	2(1)
C7	17(2)	14(2)	21(2)	−1(1)	−7(1)	1(1)
C8	13(2)	13(2)	26(2)	−1(1)	−2(2)	1(1)
C9	21(2)	15(2)	27(2)	−3(1)	−4(2)	3(2)
C10	22(2)	12(1)	21(2)	3(1)	−2(2)	4(2)
C11	16(2)	13(2)	26(2)	2(1)	−3(2)	2(1)
C12	20(2)	22(2)	23(2)	0(1)	1(2)	1(1)
C13	44(2)	41(2)	26(2)	4(2)	2(2)	16(2)
C14	23(2)	26(2)	14(2)	−2(1)	2(2)	2(2)
C15	20(2)	14(2)	18(2)	−1(1)	1(1)	1(1)
C16	20(2)	21(2)	22(2)	0(1)	−1(2)	4(2)
C17	26(2)	33(2)	20(2)	2(2)	3(2)	−10(2)
C18	23(2)	21(2)	17(2)	2(2)	1(1)	4(2)
C19	20(2)	21(2)	18(2)	2(2)	−2(1)	2(2)
C20	18(2)	15(1)	18(2)	1(1)	3(2)	−3(1)
C21	18(2)	18(2)	20(2)	1(1)	3(1)	2(1)
C22	17(2)	13(1)	22(2)	1(1)	0(2)	−3(1)
C23	23(2)	13(2)	19(2)	1(1)	0(2)	−6(1)
C24	23(2)	12(2)	30(2)	3(1)	1(2)	−1(1)
C25	20(2)	16(2)	20(2)	2(1)	−2(2)	3(1)
C26	27(2)	23(2)	23(2)	1(1)	−5(2)	3(1)
C27	38(2)	25(2)	17(2)	2(1)	−2(2)	−5(2)
C28	35(2)	20(2)	23(2)	−1(2)	8(2)	−5(2)
C29	26(2)	14(2)	27(2)	−1(1)	5(2)	1(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	–5504	6486	6016	44	1
H1B	–4621	6231	6511	44	1
H1C	–4354	5517	6102	44	1
H3	–4101	5811	5342	22	1
H6	2831	7012	5099	20	1
H7	1230	7134	5801	21	1
H8	–4316	5412	4510	21	1
H9	–2744	5337	3807	25	1
H11	2677	6524	4298	21	1
H12	2767	6068	3547	26	1
H13A	–1315	5876	3096	55	1
H13B	923	6107	2850	55	1
H13C	–161	6844	3182	55	1
H15	2768	3203	3374	21	1
H18A	6042	2601	3690	25	1
H18B	7018	3625	3710	25	1
H19A	7234	3632	4486	24	1
H19B	6268	2617	4541	24	1
H21	6984	3070	5367	22	1
H24	374	4606	5301	26	1
H25	2058	4139	4645	22	1
H26	6964	3183	6213	29	1
H27	5266	3640	6876	32	1
H28	1908	4394	6850	31	1
H29	326	4720	6156	27	1



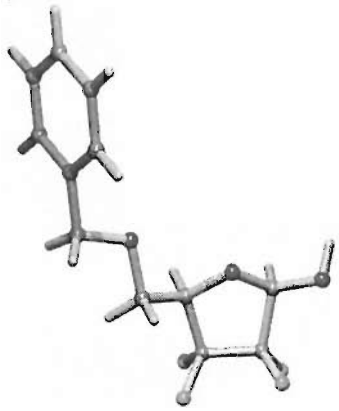
Thermal ellipsoids drawn at the 50% probability level

Departmental Single Crystal X-Ray Diffraction Service

School of Chemistry - University of Southampton

Contact: Dr Mark E Light, light@soton.ac.uk, ex 26722

Table 1. Crystal data and structure refinement details.



Identification code	**05sot0148 (4082/23–44)**
Empirical formula	$C_{12}H_{12}F_4O_3$
Formula weight	280.22
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.1009(8) Å
	b = 10.8873(11) Å
	c = 18.2277(18) Å
Volume	1210.7(2) Å^3
Z	4
Density (calculated)	1.537 Mg / m^3
Absorption coefficient	0.148 mm^{-1}
F(000)	576
Crystal	Shard; Colourless
Crystal size	0.4 × 0.06 × 0.04 mm^3
θ range for data collection	2.91 – 27.48°
Index ranges	$-7 \le h \le 7$, $-14 \le k \le 12$, $-23 \le l \le 22$
Reflections collected	11758
Independent reflections	1616 [R_{int} = 0.0658]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9941 and 0.9430
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1616 / 0 / 173
Goodness-of-fit on F^2	1.019
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0712, $wR2$ = 0.1869
R indices (all data)	$R1$ = 0.1071, $wR2$ = 0.2142
Largest diff. peak and hole	0.638 and –0.392 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. C9=R (from previous structure), C10=R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–4389(9)	–443(5)	5169(3)	32(1)	1
C2	–4972(9)	–830(5)	5866(3)	36(1)	1
C3	–3564(10)	–1555(5)	6268(3)	38(1)	1
C4	–1560(10)	–1905(5)	5982(3)	36(1)	1
C5	–965(9)	–1531(5)	5282(3)	31(1)	1
C6	–2379(8)	–790(4)	4874(3)	27(1)	1
C7	–1685(10)	–363(5)	4125(2)	33(1)	1
C8	770(9)	982(5)	3528(3)	34(1)	1
C9	1707(10)	2238(5)	3638(3)	36(1)	1
C10	4687(12)	3274(6)	4043(3)	47(2)	1
C11	4907(10)	3332(5)	3214(3)	39(1)	1
C12	2735(9)	2800(5)	2958(3)	36(1)	1
O1	–118(6)	602(3)	4209(2)	33(1)	1
O2	3460(8)	2176(4)	4146(2)	47(1)	1
O3	6647(10)	3200(6)	4376(3)	74(2)	1
F1	6563(6)	2613(5)	2979(2)	78(2)	1
F2	5342(9)	4448(4)	2956(2)	77(2)	1
F3	2962(6)	2013(3)	2396(2)	48(1)	1
F4	1466(6)	3727(4)	2676(2)	61(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.384(8)	C9–O2	1.416(7)
C1–C6	1.392(7)	C9–C12	1.518(7)
C2–C3	1.378(8)	C10–O3	1.344(9)
C3–C4	1.383(8)	C10–O2	1.423(7)
C4–C5	1.387(7)	C10–C11	1.519(7)
C5–C6	1.396(7)	C11–F2	1.330(7)
C6–C7	1.503(7)	C11–F1	1.347(7)
C7–O1	1.428(6)	C11–C12	1.519(8)
C8–O1	1.415(6)	C12–F3	1.343(6)
C8–C9	1.495(7)	C12–F4	1.372(6)
C2–C1–C6	120.0(5)	O2–C10–C11	102.3(4)
C3–C2–C1	120.2(5)	F2–C11–F1	105.6(5)
C2–C3–C4	120.5(5)	F2–C11–C10	114.0(5)
C3–C4–C5	119.8(5)	F1–C11–C10	111.0(5)
C4–C5–C6	119.9(5)	F2–C11–C12	114.5(5)
C1–C6–C5	119.6(5)	F1–C11–C12	109.6(4)
C1–C6–C7	121.1(5)	C10–C11–C12	102.3(5)
C5–C6–C7	119.3(5)	F3–C12–F4	104.0(4)
O1–C7–C6	108.6(4)	F3–C12–C9	114.1(4)
O1–C8–C9	107.2(4)	F4–C12–C9	111.7(5)
O2–C9–C8	109.5(4)	F3–C12–C11	112.8(5)
O2–C9–C12	103.9(5)	F4–C12–C11	109.1(5)
C8–C9–C12	114.6(4)	C9–C12–C11	105.3(4)
O3–C10–O2	111.0(6)	C8–O1–C7	112.2(4)
O3–C10–C11	111.9(6)	C9–O2–C10	105.8(4)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	28(3)	32(2)	37(3)	0(2)	0(2)	4(2)
C2	27(3)	43(3)	39(3)	−5(2)	5(2)	−2(2)
C3	42(3)	46(3)	26(3)	2(2)	6(2)	−6(3)
C4	38(3)	40(3)	28(2)	5(2)	−8(2)	0(3)
C5	30(2)	35(3)	28(2)	−4(2)	−1(2)	−1(2)
C6	30(2)	25(2)	26(2)	−1(2)	−3(2)	−4(2)
C7	38(3)	36(3)	25(2)	−1(2)	−4(2)	−8(2)
C8	40(3)	43(3)	20(2)	0(2)	0(2)	−7(2)
C9	46(3)	33(3)	29(2)	3(2)	4(3)	0(3)
C10	57(4)	56(3)	27(3)	−1(2)	7(3)	−26(3)
C11	41(3)	48(3)	29(3)	−5(2)	4(2)	−8(3)
C12	42(3)	39(3)	26(2)	5(2)	−4(2)	2(2)
O1	40(2)	36(2)	24(2)	2(1)	−1(2)	−14(2)
O2	65(3)	48(2)	28(2)	7(2)	−10(2)	−24(2)
O3	76(4)	103(4)	43(2)	11(3)	−19(3)	−42(3)
F1	40(2)	142(4)	51(2)	−22(3)	−5(2)	22(3)
F2	107(4)	74(3)	52(2)	26(2)	−11(2)	−51(3)
F3	58(2)	60(2)	27(1)	−13(1)	9(2)	−18(2)
F4	58(2)	67(2)	58(2)	30(2)	0(2)	11(2)

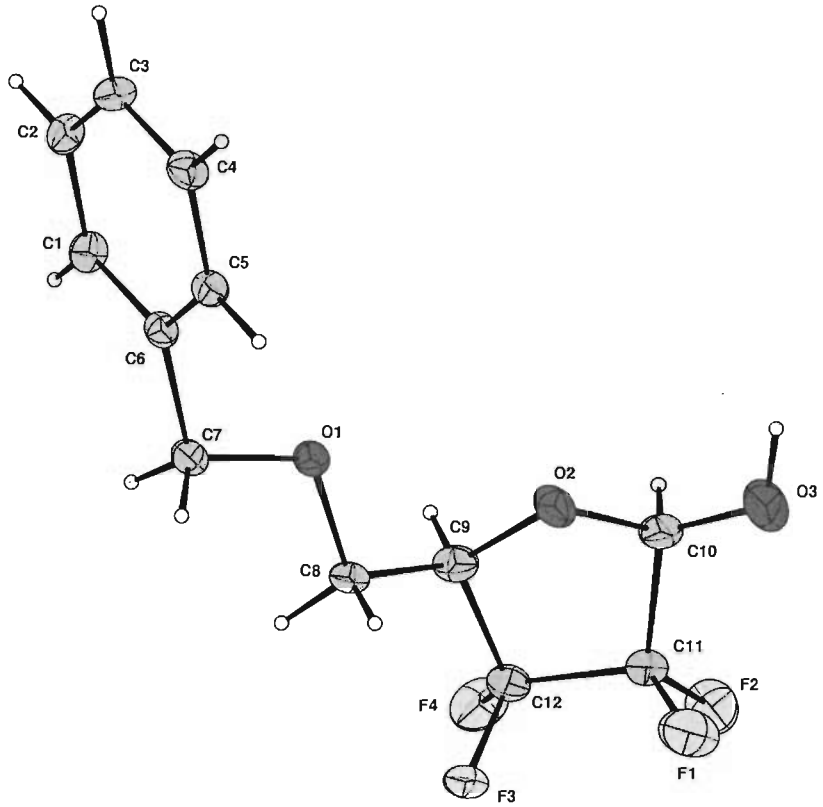
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	−5361	58	4893	39	1
H2	−6345	−595	6068	43	1
H3	−3973	−1817	6746	45	1
H4	−592	−2401	6263	43	1
H5	402	−1778	5081	37	1
H7A	−1027	−1053	3849	40	1
H7B	−2973	−61	3849	40	1
H8A	−389	1003	3148	41	1
H8B	1929	405	3368	41	1
H9	545	2799	3832	43	1
H10	3848	3999	4229	56	1
H3A	6482	3283	4831	111	1

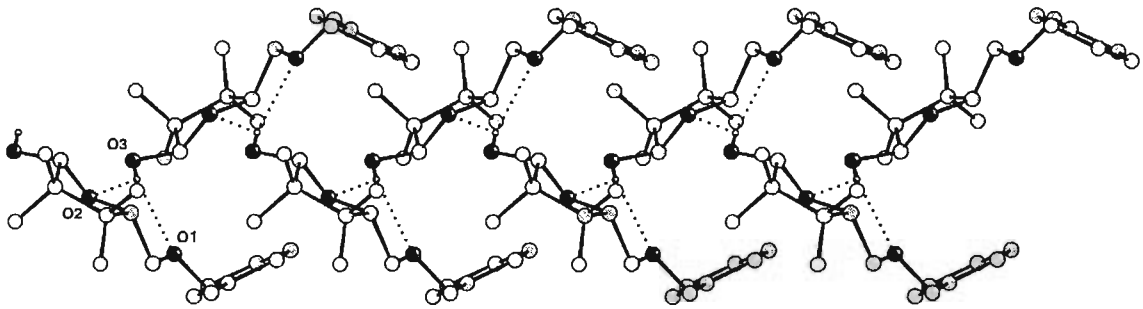
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O3–H3A···O2^{i}	0.84	2.28	2.941(6)	136.2
O3–H3A···O1^{i}	0.84	2.34	3.084(7)	147.4

Symmetry transformations used to generate equivalent atoms:
(i) x+1/2,−y+1/2,−z+1



Thermal ellipsoids drawn at the 35% probability level



Hydrogen bonded chains extend along *a*

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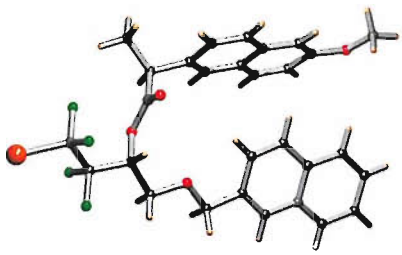
Table 1. Crystal data and structure refinement details.



Identification code	**05sot0066 (JB/4271/13)**
Empirical formula	$C_{29}H_{25}BrF_4O_4$
Formula weight	593.40
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.1963(6) Å
	b = 14.5597(15) Å
	c = 29.452(4) Å
Volume	2657.1(5) Å^3
Z	4
Density (calculated)	1.483 Mg / m^3
Absorption coefficient	1.609 mm^{-1}
$F(000)$	1208
Crystal	Slab; Colourless
Crystal size	0.4 × 0.3 × 0.04 mm^3
θ range for data collection	3.57 – 27.47°
Index ranges	$-8 \le h \le 6$, $-18 \le k \le 18$, $-26 \le l \le 38$
Reflections collected	19046
Independent reflections	5856 [R_{int} = 0.0579]
Completeness to θ = 27.47°	99.1 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9385 and 0.5655
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5856 / 0 / 346
Goodness-of-fit on F^2	1.005
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0420, $wR2$ = 0.0723
R indices (all data)	$R1$ = 0.0713, $wR2$ = 0.0810
Absolute structure parameter	0.025(7)
Extinction coefficient	0.0015(2)
Largest diff. peak and hole	0.338 and –0.493 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. C12 = S, C15 = R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
Br1	4782(1)	3279(1)	1898(1)	29(1)	1
F1	6001(4)	2556(1)	2853(1)	52(1)	1
F2	6661(3)	4017(1)	2782(1)	38(1)	1
F3	2473(4)	4269(1)	2489(1)	46(1)	1
F4	1947(4)	2821(2)	2551(1)	57(1)	1
O1	–2312(3)	6569(1)	6073(1)	22(1)	1
O2	174(4)	4208(1)	3426(1)	40(1)	1
O3	3718(3)	4521(1)	3396(1)	17(1)	1
O4	4540(3)	3421(1)	4135(1)	21(1)	1
C1	–4360(5)	6169(2)	6184(1)	29(1)	1
C2	–1601(5)	6465(2)	5634(1)	18(1)	1
C3	–2708(5)	6061(2)	5288(1)	19(1)	1
C4	–1791(5)	6011(2)	4850(1)	17(1)	1
C5	317(5)	6366(2)	4775(1)	15(1)	1
C6	1417(5)	6776(2)	5143(1)	17(1)	1
C7	485(4)	6839(2)	5560(1)	17(1)	1
C8	–2887(5)	5635(2)	4472(1)	17(1)	1
C9	–1949(5)	5585(2)	4054(1)	21(1)	1
C10	190(5)	5897(2)	3981(1)	18(1)	1
C11	1259(5)	6293(2)	4342(1)	18(1)	1
C12	1311(5)	5774(2)	3530(1)	22(1)	1
C13	78(6)	6187(2)	3128(1)	37(1)	1
C14	1604(5)	4751(2)	3445(1)	21(1)	1
C15	4150(5)	3553(2)	3346(1)	17(1)	1
C16	5089(5)	3408(2)	2871(1)	21(1)	1
C17	3470(5)	3449(2)	2486(1)	26(1)	1
C18	5671(5)	3260(2)	3721(1)	20(1)	1
C19	5884(4)	3275(2)	4520(1)	20(1)	1
C20	4725(5)	3570(2)	4946(1)	17(1)	1
C21	5649(5)	3390(2)	5357(1)	19(1)	1
C22	4677(5)	3666(2)	5770(1)	17(1)	1
C23	2659(5)	4127(2)	5752(1)	18(1)	1
C24	1721(5)	4296(2)	5319(1)	22(1)	1
C25	2722(5)	4023(2)	4930(1)	18(1)	1
C26	5615(5)	3492(2)	6197(1)	24(1)	1
C27	4605(6)	3762(2)	6592(1)	27(1)	1
C28	2605(5)	4216(2)	6576(1)	26(1)	1
C29	1664(5)	4402(2)	6165(1)	23(1)	1

Table 3. Bond lengths [Å] and angles [°].

Br1–C17	1.927(3)	C9–C10	1.417(5)
F1–C16	1.365(3)	C10–C11	1.380(4)
F2–C16	1.342(3)	C10–C12	1.509(4)
F3–C17	1.343(4)	C12–C14	1.522(4)
F4–C17	1.328(4)	C12–C13	1.532(4)
O1–C2	1.373(3)	C15–C18	1.512(4)
O1–C1	1.434(3)	C15–C16	1.530(4)
O2–C14	1.188(3)	C16–C17	1.515(4)
O3–C14	1.360(4)	C19–C20	1.507(4)
O3–C15	1.443(3)	C20–C21	1.366(4)
O4–C19	1.423(3)	C20–C25	1.406(4)
O4–C18	1.427(3)	C21–C22	1.415(4)
C2–C3	1.363(4)	C22–C26	1.409(4)
C2–C7	1.420(4)	C22–C23	1.420(4)
C3–C4	1.412(4)	C23–C29	1.420(4)
C4–C8	1.415(4)	C23–C24	1.422(4)
C4–C5	1.422(4)	C24–C25	1.363(4)
C5–C11	1.405(4)	C26–C27	1.377(4)
C5–C6	1.414(4)	C27–C28	1.405(4)
C6–C7	1.360(4)	C28–C29	1.372(5)
C8–C9	1.364(4)		

C2–O1–C1	117.0(2)	C10–C12–C14	108.4(2)
C14–O3–C15	115.5(2)	C10–C12–C13	113.8(3)
C19–O4–C18	111.7(2)	C14–C12–C13	108.5(3)
C3–C2–O1	126.1(3)	O2–C14–O3	123.3(3)
C3–C2–C7	120.6(3)	O2–C14–C12	124.8(3)
O1–C2–C7	113.3(3)	O3–C14–C12	111.9(3)
C2–C3–C4	120.2(3)	O3–C15–C18	108.5(2)
C3–C4–C8	123.1(3)	O3–C15–C16	107.3(2)
C3–C4–C5	119.6(3)	C18–C15–C16	113.1(2)
C8–C4–C5	117.3(3)	F2–C16–F1	107.0(3)
C11–C5–C6	121.8(3)	F2–C16–C17	108.0(2)
C11–C5–C4	119.7(3)	F1–C16–C17	106.3(2)
C6–C5–C4	118.5(3)	F2–C16–C15	111.3(2)
C7–C6–C5	121.1(3)	F1–C16–C15	108.5(2)
C6–C7–C2	120.0(3)	C17–C16–C15	115.3(3)
C9–C8–C4	121.8(3)	F4–C17–F3	106.5(3)
C8–C9–C10	121.2(3)	F4–C17–C16	109.6(3)
C11–C10–C9	117.8(3)	F3–C17–C16	109.5(3)
C11–C10–C12	120.5(3)	F4–C17–Br1	109.9(2)
C9–C10–C12	121.7(3)	F3–C17–Br1	108.3(2)
C10–C11–C5	122.1(3)	C16–C17–Br1	112.8(2)

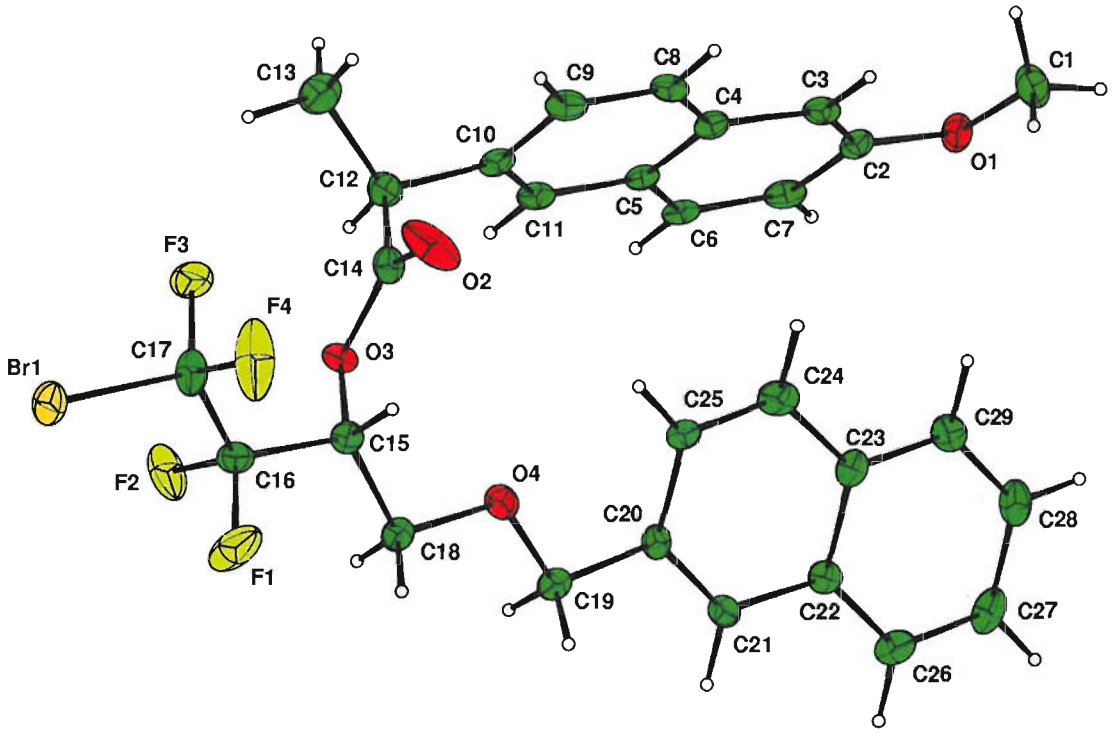
O4–C18–C15	105.8(2)	C29–C23–C22	118.9(3)
O4–C19–C20	110.0(2)	C29–C23–C24	122.7(3)
C21–C20–C25	119.3(3)	C22–C23–C24	118.3(3)
C21–C20–C19	118.9(3)	C25–C24–C23	121.2(3)
C25–C20–C19	121.8(3)	C24–C25–C20	120.7(3)
C20–C21–C22	122.0(3)	C27–C26–C22	121.0(3)
C26–C22–C21	122.7(3)	C26–C27–C28	120.5(3)
C26–C22–C23	118.8(3)	C29–C28–C27	119.8(3)
C21–C22–C23	118.5(3)	C28–C29–C23	121.0(3)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br1	33(1)	40(1)	16(1)	−1(1)	1(1)	2(1)
F1	94(2)	40(1)	24(1)	0(1)	−1(1)	39(1)
F2	22(1)	65(2)	28(1)	−9(1)	5(1)	−14(1)
F3	49(1)	70(2)	20(1)	5(1)	1(1)	34(1)
F4	59(2)	89(2)	24(1)	−11(1)	4(1)	−48(1)
O1	23(1)	28(1)	16(1)	2(1)	1(1)	−1(1)
O2	21(1)	30(1)	68(2)	−22(1)	10(2)	−8(1)
O3	13(1)	16(1)	23(1)	−2(1)	1(1)	2(1)
O4	18(1)	30(1)	16(1)	−2(1)	−1(1)	2(1)
C1	23(2)	41(2)	24(2)	−1(2)	6(2)	−1(2)
C2	21(2)	14(2)	18(2)	2(1)	−1(2)	3(1)
C3	14(2)	14(2)	28(2)	4(1)	−1(2)	1(1)
C4	20(2)	11(1)	20(2)	1(1)	−2(2)	3(1)
C5	17(2)	10(1)	19(2)	2(1)	−2(2)	4(1)
C6	14(2)	11(1)	25(2)	3(2)	−5(1)	2(1)
C7	17(2)	14(2)	21(2)	−1(1)	−7(1)	1(1)
C8	13(2)	13(2)	26(2)	−1(1)	−2(2)	1(1)
C9	21(2)	15(2)	27(2)	−3(1)	−4(2)	3(2)
C10	22(2)	12(1)	21(2)	3(1)	−2(2)	4(2)
C11	16(2)	13(2)	26(2)	2(1)	−3(2)	2(1)
C12	20(2)	22(2)	23(2)	0(1)	1(2)	1(1)
C13	44(2)	41(2)	26(2)	4(2)	2(2)	16(2)
C14	23(2)	26(2)	14(2)	−2(1)	2(2)	2(2)
C15	20(2)	14(2)	18(2)	−1(1)	1(1)	1(1)
C16	20(2)	21(2)	22(2)	0(1)	−1(2)	4(2)
C17	26(2)	33(2)	20(2)	2(2)	3(2)	−10(2)
C18	23(2)	21(2)	17(2)	2(2)	1(1)	4(2)
C19	20(2)	21(2)	18(2)	2(2)	−2(1)	2(2)
C20	18(2)	15(1)	18(2)	1(1)	3(2)	−3(1)
C21	18(2)	18(2)	20(2)	1(1)	3(1)	2(1)
C22	17(2)	13(1)	22(2)	1(1)	0(2)	−3(1)
C23	23(2)	13(2)	19(2)	1(1)	0(2)	−6(1)
C24	23(2)	12(2)	30(2)	3(1)	1(2)	−1(1)
C25	20(2)	16(2)	20(2)	2(1)	−2(2)	3(1)
C26	27(2)	23(2)	23(2)	1(1)	−5(2)	3(1)
C27	38(2)	25(2)	17(2)	2(1)	−2(2)	−5(2)
C28	35(2)	20(2)	23(2)	−1(2)	8(2)	−5(2)
C29	26(2)	14(2)	27(2)	−1(1)	5(2)	1(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	–5504	6486	6016	44	1
H1B	–4621	6231	6511	44	1
H1C	–4354	5517	6102	44	1
H3	–4101	5811	5342	22	1
H6	2831	7012	5099	20	1
H7	1230	7134	5801	21	1
H8	–4316	5412	4510	21	1
H9	–2744	5337	3807	25	1
H11	2677	6524	4298	21	1
H12	2767	6068	3547	26	1
H13A	–1315	5876	3096	55	1
H13B	923	6107	2850	55	1
H13C	–161	6844	3182	55	1
H15	2768	3203	3374	21	1
H18A	6042	2601	3690	25	1
H18B	7018	3625	3710	25	1
H19A	7234	3632	4486	24	1
H19B	6268	2617	4541	24	1
H21	6984	3070	5367	22	1
H24	374	4606	5301	26	1
H25	2058	4139	4645	22	1
H26	6964	3183	6213	29	1
H27	5266	3640	6876	32	1
H28	1908	4394	6850	31	1
H29	326	4720	6156	27	1



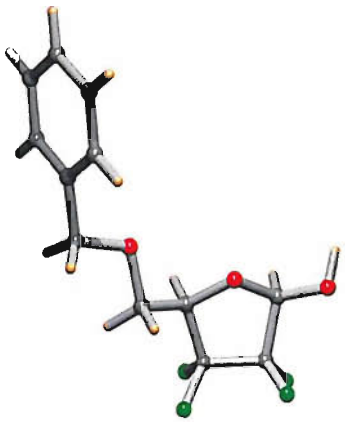
Thermal ellipsoids drawn at the 50% probability level

Departmental Single Crystal X-Ray Diffraction Service

School of Chemistry - University of Southampton

Contact: Dr Mark E Light, light@soton.ac.uk, ex 26722

Table 1. Crystal data and structure refinement details.



Identification code	**05sot0148 (4082/23–44)**
Empirical formula	$C_{12}H_{12}F_4O_3$
Formula weight	280.22
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.1009(8) Å
	b = 10.8873(11) Å
	c = 18.2277(18) Å
Volume	1210.7(2) Å^3
Z	4
Density (calculated)	1.537 Mg / m^3
Absorption coefficient	0.148 mm^{-1}
F(000)	576
Crystal	Shard; Colourless
Crystal size	0.4 × 0.06 × 0.04 mm^3
θ range for data collection	2.91 – 27.48°
Index ranges	$-7 \le h \le 7$, $-14 \le k \le 12$, $-23 \le l \le 22$
Reflections collected	11758
Independent reflections	1616 [R_{int} = 0.0658]
Completeness to θ = 27.48°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9941 and 0.9430
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1616 / 0 / 173
Goodness-of-fit on F^2	1.019
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0712, $wR2$ = 0.1869
R indices (all data)	$R1$ = 0.1071, $wR2$ = 0.2142
Largest diff. peak and hole	0.638 and –0.392 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model. C9=R (from previous structure), C10=R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–4389(9)	–443(5)	5169(3)	32(1)	1
C2	–4972(9)	–830(5)	5866(3)	36(1)	1
C3	–3564(10)	–1555(5)	6268(3)	38(1)	1
C4	–1560(10)	–1905(5)	5982(3)	36(1)	1
C5	–965(9)	–1531(5)	5282(3)	31(1)	1
C6	–2379(8)	–790(4)	4874(3)	27(1)	1
C7	–1685(10)	–363(5)	4125(2)	33(1)	1
C8	770(9)	982(5)	3528(3)	34(1)	1
C9	1707(10)	2238(5)	3638(3)	36(1)	1
C10	4687(12)	3274(6)	4043(3)	47(2)	1
C11	4907(10)	3332(5)	3214(3)	39(1)	1
C12	2735(9)	2800(5)	2958(3)	36(1)	1
O1	–118(6)	602(3)	4209(2)	33(1)	1
O2	3460(8)	2176(4)	4146(2)	47(1)	1
O3	6647(10)	3200(6)	4376(3)	74(2)	1
F1	6563(6)	2613(5)	2979(2)	78(2)	1
F2	5342(9)	4448(4)	2956(2)	77(2)	1
F3	2962(6)	2013(3)	2396(2)	48(1)	1
F4	1466(6)	3727(4)	2676(2)	61(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C2	1.384(8)	C9–O2	1.416(7)
C1–C6	1.392(7)	C9–C12	1.518(7)
C2–C3	1.378(8)	C10–O3	1.344(9)
C3–C4	1.383(8)	C10–O2	1.423(7)
C4–C5	1.387(7)	C10–C11	1.519(7)
C5–C6	1.396(7)	C11–F2	1.330(7)
C6–C7	1.503(7)	C11–F1	1.347(7)
C7–O1	1.428(6)	C11–C12	1.519(8)
C8–O1	1.415(6)	C12–F3	1.343(6)
C8–C9	1.495(7)	C12–F4	1.372(6)

C2–C1–C6	120.0(5)	O2–C10–C11	102.3(4)
C3–C2–C1	120.2(5)	F2–C11–F1	105.6(5)
C2–C3–C4	120.5(5)	F2–C11–C10	114.0(5)
C3–C4–C5	119.8(5)	F1–C11–C10	111.0(5)
C4–C5–C6	119.9(5)	F2–C11–C12	114.5(5)
C1–C6–C5	119.6(5)	F1–C11–C12	109.6(4)
C1–C6–C7	121.1(5)	C10–C11–C12	102.3(5)
C5–C6–C7	119.3(5)	F3–C12–F4	104.0(4)
O1–C7–C6	108.6(4)	F3–C12–C9	114.1(4)
O1–C8–C9	107.2(4)	F4–C12–C9	111.7(5)
O2–C9–C8	109.5(4)	F3–C12–C11	112.8(5)
O2–C9–C12	103.9(5)	F4–C12–C11	109.1(5)
C8–C9–C12	114.6(4)	C9–C12–C11	105.3(4)
O3–C10–O2	111.0(6)	C8–O1–C7	112.2(4)
O3–C10–C11	111.9(6)	C9–O2–C10	105.8(4)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	28(3)	32(2)	37(3)	0(2)	0(2)	4(2)
C2	27(3)	43(3)	39(3)	–5(2)	5(2)	–2(2)
C3	42(3)	46(3)	26(3)	2(2)	6(2)	–6(3)
C4	38(3)	40(3)	28(2)	5(2)	–8(2)	0(3)
C5	30(2)	35(3)	28(2)	–4(2)	–1(2)	–1(2)
C6	30(2)	25(2)	26(2)	–1(2)	–3(2)	–4(2)
C7	38(3)	36(3)	25(2)	–1(2)	–4(2)	–8(2)
C8	40(3)	43(3)	20(2)	0(2)	0(2)	–7(2)
C9	46(3)	33(3)	29(2)	3(2)	4(3)	0(3)
C10	57(4)	56(3)	27(3)	–1(2)	7(3)	–26(3)
C11	41(3)	48(3)	29(3)	–5(2)	4(2)	–8(3)
C12	42(3)	39(3)	26(2)	5(2)	–4(2)	2(2)
O1	40(2)	36(2)	24(2)	2(1)	–1(2)	–14(2)
O2	65(3)	48(2)	28(2)	7(2)	–10(2)	–24(2)
O3	76(4)	103(4)	43(2)	11(3)	–19(3)	–42(3)
F1	40(2)	142(4)	51(2)	–22(3)	–5(2)	22(3)
F2	107(4)	74(3)	52(2)	26(2)	–11(2)	–51(3)
F3	58(2)	60(2)	27(1)	–13(1)	9(2)	–18(2)
F4	58(2)	67(2)	58(2)	30(2)	0(2)	11(2)

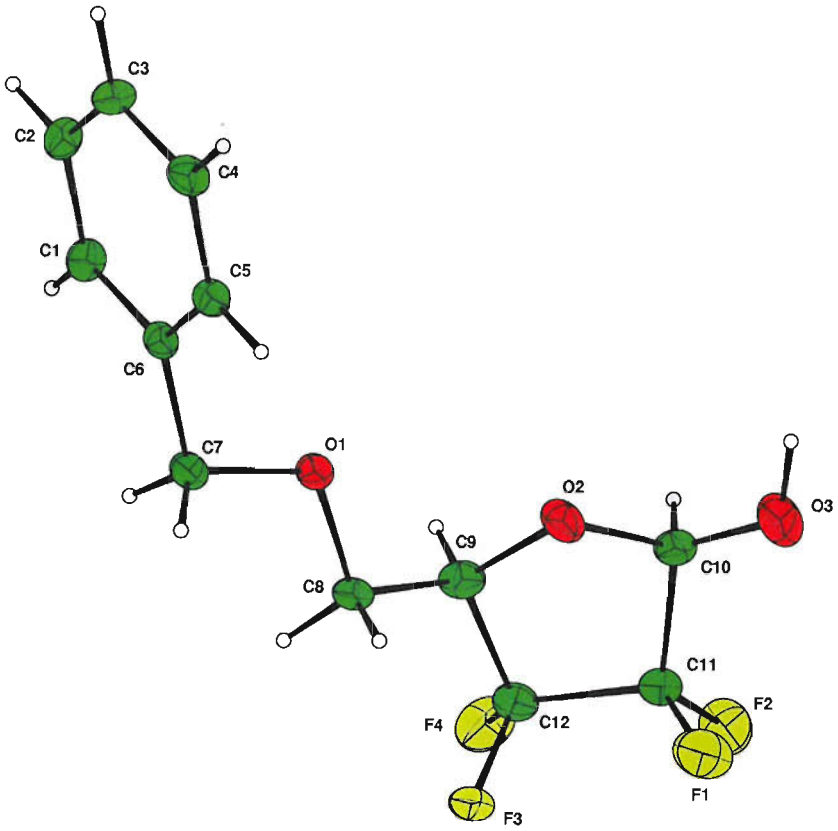
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	−5361	58	4893	39	1
H2	−6345	−595	6068	43	1
H3	−3973	−1817	6746	45	1
H4	−592	−2401	6263	43	1
H5	402	−1778	5081	37	1
H7A	−1027	−1053	3849	40	1
H7B	−2973	−61	3849	40	1
H8A	−389	1003	3148	41	1
H8B	1929	405	3368	41	1
H9	545	2799	3832	43	1
H10	3848	3999	4229	56	1
H3A	6482	3283	4831	111	1

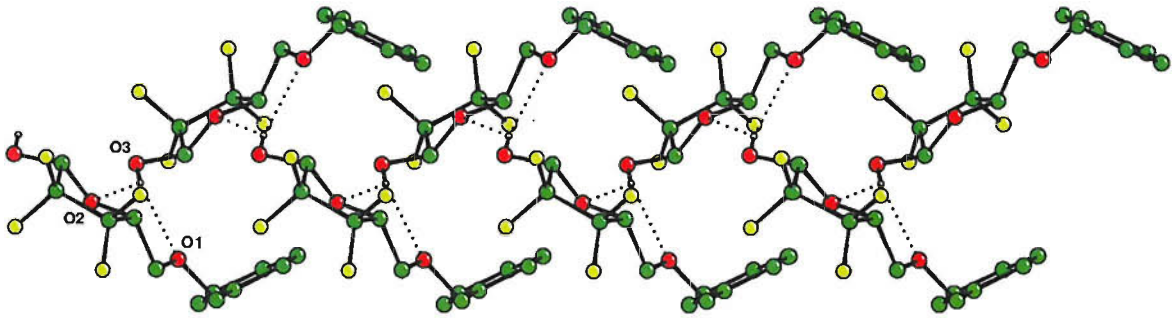
Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*DHA*)
O3–H3A···O2^{i}	0.84	2.28	2.941(6)	136.2
O3–H3A···O1^{i}	0.84	2.34	3.084(7)	147.4

Symmetry transformations used to generate equivalent atoms:
(i) x+1/2,−y+1/2,−z+1



Thermal ellipsoids drawn at the 35% probability level



Hydrogen bonded chains extend along *a*