University of Southampton

Faculty of Engineering, Science and Mathematics

School of Chemistry

Synthesis of Gemcitabine and It's Tetrafluorinated Analogues

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ABSTRACT

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS
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Doctor of Philosophy

Synthesis of Gemcitabine and It's Tetrafluorinated Analogues

by Kylie Jennifer Brown

A novel synthesis of the 2-deoxy-2,2-difluorocytidine nucleoside analogue gemcitabine has been achieved. Starting from the known 3,5-O-dibenzoyl-2-deoxy-2,2-difluororibose, the nucleobase moiety is constructed in a linear fashion, using amino- or urea glycosylation methodology. This methodology has also been employed to synthesise nucleosides containing a tetrafluorinated ribose sugar and has been compared to conventional convergent nucleobase introduction methods. In this respect, a high-yielding Mitsunobu-based protocol has also been developed. Both purine and pyrimidine analogues have been synthesised.

The aminoglycosylation methodology has been investigated with a range of amines. The methodology proves high-yielding for primary amines and less-hindered secondary amines. In contrast to expectations, their stability in acidic media was not very high. Anomerisation and ring isomerisation studies have been conducted.

Contents

Preface

The research described in this thesis was carried out under the supervision of Dr Bruno Linclau at the University of Southampton between October 2007 and March 2011. No part of this thesis has been previously submitted for a degree. All work is my own unless otherwise stated.

Declaration of Authorship

I, Kylie Brown declare that the thesis entitled

Synthesis of Gemcitabine and It's Tetrafluorinated Analogues

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research.
I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- none of this work has been published before submission

Signed: ……..

Date:……

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Firstly, I would like to thank Bruno for all his patience, guidance and encouragement throughout my project.

I would also like to thank my industrial supervisor Alex for all his input. Also to everyone at Dextra, who made me feel very welcome and were the source of many useful suggestions during my time there on placement.

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Thanks must also go to Joan and Neil for keeping the NMR suite in working order and running the multitude of extra spectra that I have required, John and Julie for their efficient management of the mass spec service and Karl, Graham, Tony and Clive in stores for ensuring we always well equipped in the lab.

Lastly, but my no means least, my family, who have been a constant source of support and encouragement throughout my PhD.

Abbreviations

5-FU	5-Fluorouracil
Å	Angstrom
Ac	Acetate
aq	Aqueous
Ar	Aryl
AZT	Azidothymidine
Boc	*tert*-Butyl carbamate
Bn	Benzyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
CSA	Camphor sulfonic acid
d	Doublet
δ	Chemical shift
DAST	Diethylaminosulfur trifluoride
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
de	Diastereomeric excess
DEAD	Diethylazodicarboxylate
dCTP	Deoxycytidine-5′-O-diphosphate
dFdCDP	2′,2′-Difluoro-2′-deoxycytidine-5′-O-diphosphate
dFdCTP	2′,2′-Difluoro-2′-deoxycytidine-5′-O-triphosphate
DHQ	Dihydroquinidine
DIAD	Diisopropylazodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
dNTP	Deoxy-nucleotide-5′-O-triphosphate

dq	Doublet of quartets
dt	Doublet of triplets
dtd	Doublet of triplets of doublets
ee	Enantiomeric excess
EI	Elecrospray ionisation
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
g	Gram
GC	Gas chromatography
HIV	Human immunodeficiency virus
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
IR	Infra Red
IPA	Isopropyl alcohol
J	Coupling constant
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectrometry
m	Multiplet
M	Molar
Me	Methyl
mg	Milligram
MHz	Megahertz
mL	Millilitre
mm	Millimetre
mmHg	Millimetres of mercury
mmol	Millimole
Mp	Melting point
MPC	Medium pressure chromatography
Ms	Mesyl
NFSi	N-Fluorodibenzenesulfonimide
nm	Nanometer

NMR	Nuclear magnetic resonance
petrol	40–60 ℃ petroleum ether
Ph	Phenyl
ppm	Parts per million
PTSA	*para*-Toulene sulfonic acid
py	Pyridine
q	Quartet
RNA	Ribonucleic acid
RP-HPLC	Reverse phase high performance liquid chromatography
RT	Room temperature
s	Singlet
SAD	Sharpless asymmetric dihydroxylation
SAR	Structure activity relationship
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
TIPS	Triisopropylsilyl
TIPDS	1,1,3,3-Tetraisopropyldisiloxanylidene
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Tr	Trityl
Ts	Tosyl

1 Introduction

1.1 Nucleosides

Nucleosides comprise of a ribose or 2-deoxyribose sugar bound to a nucleobase *via* a β-glycosidic bond. Nucleosides are the building blocks of DNA (deoxyribose) and RNA (ribose) and can be sub-divided into two classes, relating to their nucleobase subunit, pyrimidines and purines (Figure 1.1). Uridine is only found within RNA and thymidine only within DNA.

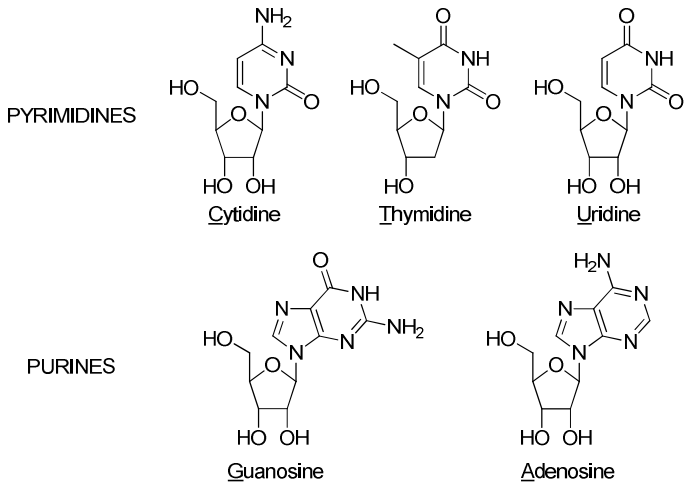


Figure 1.1: Nucleosides.

As with many molecule classes, nucleosides have their own numbering system. The atoms within the nucleobase are numbered first, with the carbons of the sugar denoted by prime numbers (Figure 1.2).

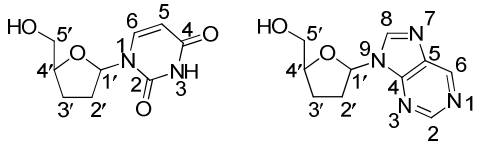


Figure 1.2: Nucleoside numbering.

Nucleoside analogues have been used successfully in the treatment of a wide range of indications. Some notable examples include azidothymidine (AZT) **1.01** and abacavir **1.02**, used in the treatment of HIV and ribavrin **1.03**, used in the

treatment of various viral diseases including hepatitis C (HCV). Other indications for which nucleoside analogues are used in the clinic include cancer, varicella zoster and herpes simplex.

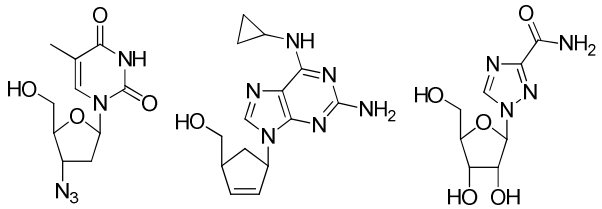


Figure 1.3: Nucleoside analogues.

1.1.1 Nucleoside Analogues

Despite the position of fluorine as the most abundant halogen in the earth's crust, very few fluorine containing natural products have been isolated.[1] Of particular interest is nucleocidin **1.04** (Figure 1.4), a 4′ fluorine substituted adenosine derivative, which has been shown to have broad spectrum antibacterial activity but is too toxic to be of clinical use. First isolated in 1957 from *Streptomyces calvus*, the true structure was not elucidated until 1969.[2]

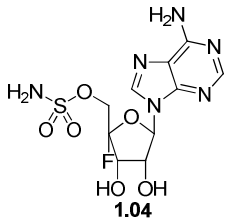


Figure 1.4: Nucleocidin.

Whilst the occurrence of fluorinated compounds in nature is a rarity, they are becoming commonplace in the agrochemical and pharmaceutical industries. An estimated 20% of prescribed or administered pharmaceuticals and 30% of the leading 30 drugs (by sales) contain one or more fluorine atoms.[3]

With its high electronegativity and small size, fluorine is uniquely placed within the periodic table. As such the incorporation of a fluorine containing moiety can

have a dramatic effect upon the physiochemical properties of a molecule, therefore these substitutions are often used within medicinal chemistry.

Table 1.1: Bond lengths.[4]

Bond	Length (Å)	van der Waals Radius (Å)	Total Size (Å)
C–F	1.35	1.47	2.82
C=O	1.23	1.50	2.73
C–OH	1.43	1.52	2.95

The overall size of the C–F bond lies between that of the C=O and C–OH bonds (Table 1.1). However, these substitutions are far from perfect, as the substitution of C–F for C=O involves a change in hybridisation at the carbon centre from sp^2 to sp^3, whilst C–F to C–OH substitution results in the loss of a potential hydrogen bond donor. However this can prove to be a useful tool as a biological function/SAR probe.

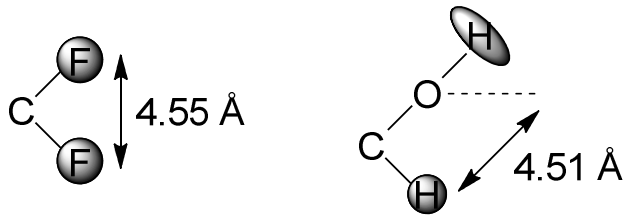


Figure 1.5: Relative sizes of CF_2 *vs* CHOH.[4]

Whilst possessing different electronic properties and hydrogen bonding potential, the CF_2 group is an excellent steric mimic of CHOH (Figure 1.5).

An example of such substitution is that of a CF_2 α to the anomeric centre in nucleoside analogues. This substitution alters the conformation of the sugar, demonstrated by changes in the binding modes within the active sites of enzymes.[5] The acidic and enzymatic stability of the glycosidic bond is also increased, due to the destabilising effect of the electronegative fluorines upon the intermediate oxonium ion.[6]

Several groups have investigated the synthesis of fluorinated nucleoside analogues over the last 50 years, exploring modifications of both the sugar and nucleobase subunits, however few have made it to the clinic.[7]

There are 14 nucleoside antimetabolites approved for use in cancer therapy by the FDA, only five of which were approved prior to 1990.[8] The first nucleoside antimetabolite to be approved was 6-mercaptopurine, in 1953, for the treatment of paediatric leukaemia, for which it is still currently used. Along with other thiopurines it is now used for a number of other indications including inflammatory bowel disease.[9]

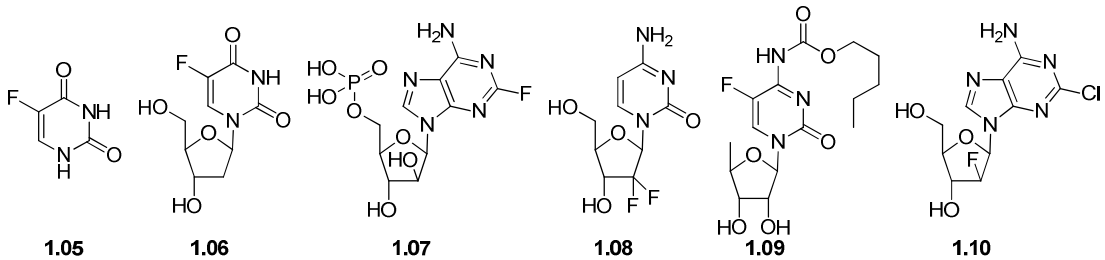
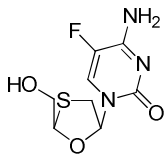


Figure 1.6: Fluorinated nucleoside antimetabolites used in the treatment of cancer.

Of these 14, six are fluorinated (Figure 1.6), however floxuridine **1.06** and capecitabine **1.09** are prodrugs of 5-fluorouracil (5-FU) **1.05**. 5-FU is an analogue of uracil, with C5 fluorine substitution, used in the treatment of cancer and more recently as a topical treatment for the skin condition actinic keratosis.[10]

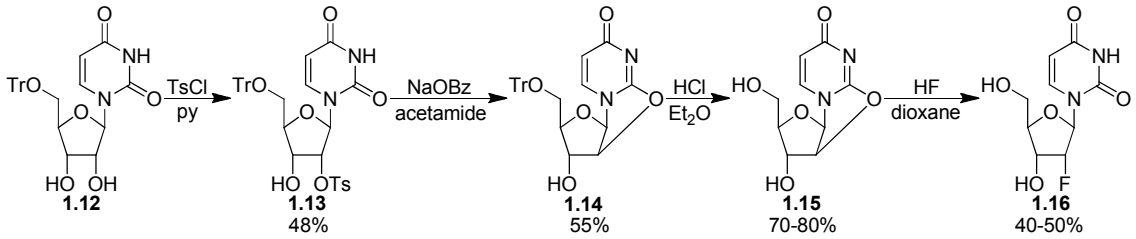
A major class of drugs used in the treatment of HIV are nucleoside reverse transcriptase inhibitor (NRTIs). However within this subclass there has not been such success with fluorinated analogues, with the 5-fluorocytidine analogue emtricitabine **1.11** (Figure 1.7) as the only example.



Emtricitabine
1.11

Figure 1.7: Emtricitabine

The first published nucleoside analogue with a fluorine substitution of the sugar subunit was the 2′ fluoro substituted uridine **1.16** by Codington *et al*[11] in 1961 (Scheme 1.1).



Scheme 1.1: Codington synthesis of 2′-deoxy-2′-fluorouridine **1.16**.

The arabino-nucleoside F-ara-C **1.17** was synthesised by Wright *et al*[12] and found to have potent activity against leukaemia cell lines, prompting the synthesis of a range of other arabino-nucleosides (Figure 1.8). The methyl uridine analogue FMAU **1.18** was synthesised by Watanabe *et al*[13] in 1979 and was shown to have potent activity against a range of viruses and murine leukaemia. However trials as a treatment for leukaemia were terminated in phase I due to exhibition of severe neurological toxicity.[7]

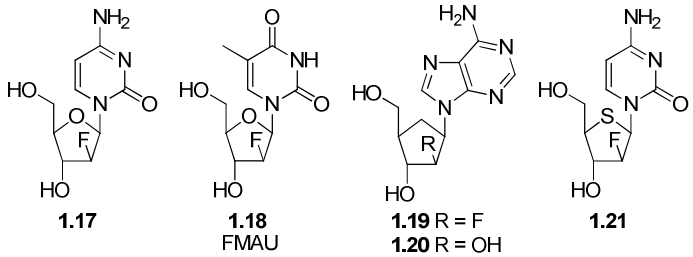
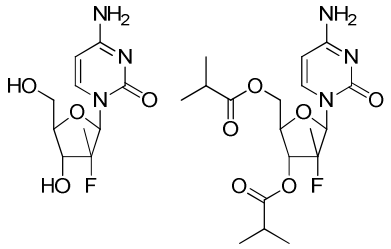


Figure 1.8: Fluorinated arabinose derived nucleoside analogues.

Other modifications were made to the ring such as the carbocyclic fluoroarabino analogue **1.19**, of the natural product aristeromycin, of Biggadike *et al*.[14] Both

1.19 and cyclaridine **1.20**, the non-fluorinated analogue were tested against HSV1 and HSV2 with the fluorinated analogue **1.19** proving to be 10 times more active. Nucleoside analogue **1.19** also proved to be more active than acyclovir against HSV2. Thionucleosides such as **1.21** have also been investigated by Yoshimura *et al*,[15,16] these also proved to have potent antitumour activity *in vitro* against some leukaemias and also solid tumours.

Developed by Pharmasset and Roche for use in the treatment of HCV, PSI-6130 is a 2′ fluorinated analogue of cytidine. PSI-6130 proved to be unsuitable for further development due to its low bioavailability (25%). This problem was overcome by its redevelopment as the diester prodrug R-7128, which has a bioavailability of 75% and is metabolised to the same active agent within the body. R-7128 is currently undergoing phase II clinical trials.[17,18]



PSI-6130 **1.22** R-7128 **1.23**

Figure 1.9: Potential HCV drugs.

Substitutions at other positions have also been undertaken (Figure 1.10). Etzold *et al*[19] synthesised the 3′-deoxy-3′-fluorothymidine analogue FLT **1.24**. It was found to be a potent HIV replication inhibitor, but was also highly cytotoxic, therefore unsuitable for further development.[20] The 4′ substituted analogue of thymidine **1.25** has also been synthesised,[21] whilst the ring oxygen of the sugar ring has also been subject to fluorine substitution such as in the *gem*-difluoromethyl substituted **1.26** of Yang *et al*.[22]

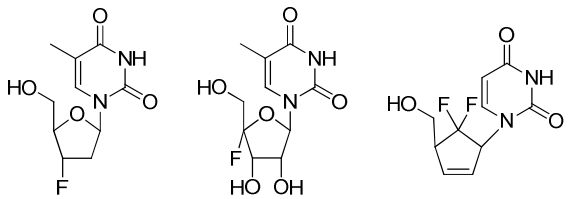


Figure 1.10: Fluorine substitution at the 3′, 4′ and ring oxygen positions.

1.2 Gemcitabine

1.2.1 Background

Gemcitabine **1.08** (Figure 1.11) is a deoxycytidine analogue with *gem*-difluoro substitution at the 2′-position. It is a billion dollar selling anticancer drug marketed as the HCl salt by Lilly, under the trade name of Gemzar. It has been shown to have a broad spectrum of activity against murine leukaemia, murine solid tumours and human tumour xenografts. It is utilised in the treatment of a variety of cancers both as a single agent and in combination therapies.[23] The patent on gemcitabine is due to expire in 2011.

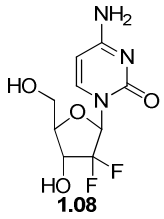


Figure 1.11: Structure of gemcitabine **1.08**.

Gemcitabine is only administered *via* intravenous routes. The dosage of gemcitabine ranges from 1000–1250 mg/m^2, administered as an infusion over 30 min, dependent upon the type of cancer and the dosage schedule undertaken. According to the most recent prescribing information published on the Gemzar website (revised Feb 2011), gemcitabine is administered as the sole agent in pancreatic cancer, but in combination for ovarian (with carboplatin), breast (with paclitaxel) and non-small cell lung cancer (with cisplatin).[24]

1.2.2 Mechanism of Action

Gemcitabine is a nucleoside antimetabolite, exhibiting multiple modes of action. Within the cell, gemcitabine is converted into its active 5′-O-diphosphate (dFdCDP) and triphosphate (dFdCTP) forms by deoxycytidine kinase.[25] dFdCTP inhibits DNA synthesis through its incorporation into the replicating DNA chain, in competition with the endogenous dCTP, causing chain termination and strand breaks. Interestingly it has been shown one further dNTP is added after the incorporation of the dFdCTP, after which further chain elongation is terminated.[26]

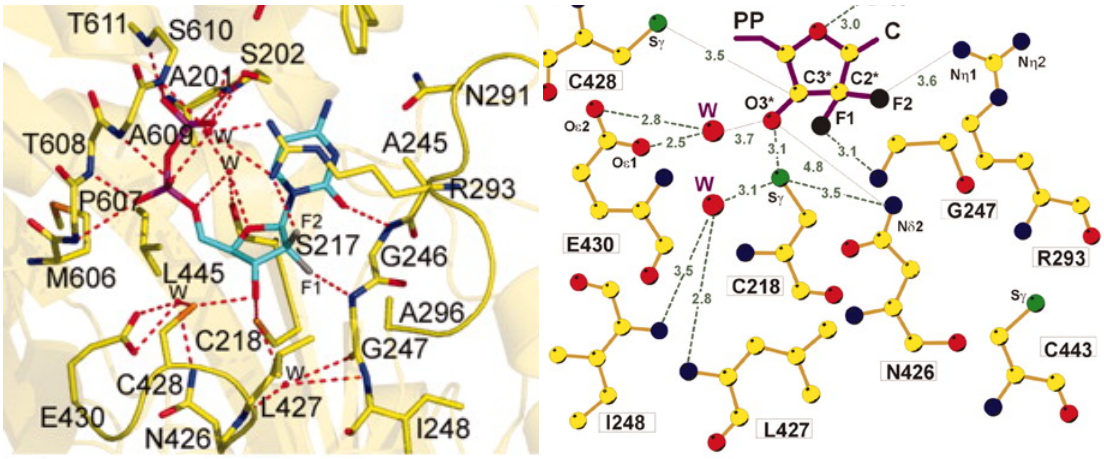


Figure 1.12: dFdCDP binding to ribonucleotide reductase.[5]

dFdCDP causes inhibition of ribonucleotide reductase, which is involved in the generation of the dNTPs required for DNA synthesis and repair. This reduces the intracellular concentration of dNTPs, thus self potentiating both its own phosphorylation and incorporation into the elongating DNA strand.[27,28] It can be seen from the crystallographic analysis (Figure 1.12) that both fluorine atoms interact with aminoacid residues (Gly 247 and Arg 293). The 2′OH of the endogenous substrate, CDP, interacts with S217, G247, L427 and N426, where some of these interactions are mediated *via* a molecule of water (Figure 1.13). This change in binding mode causes dFdCDP to bind higher in the binding pocket with respect to the location of CDP, with the ribose binding position shifted by an average of 2.3 Å and the base by an average of 3.8 Å.

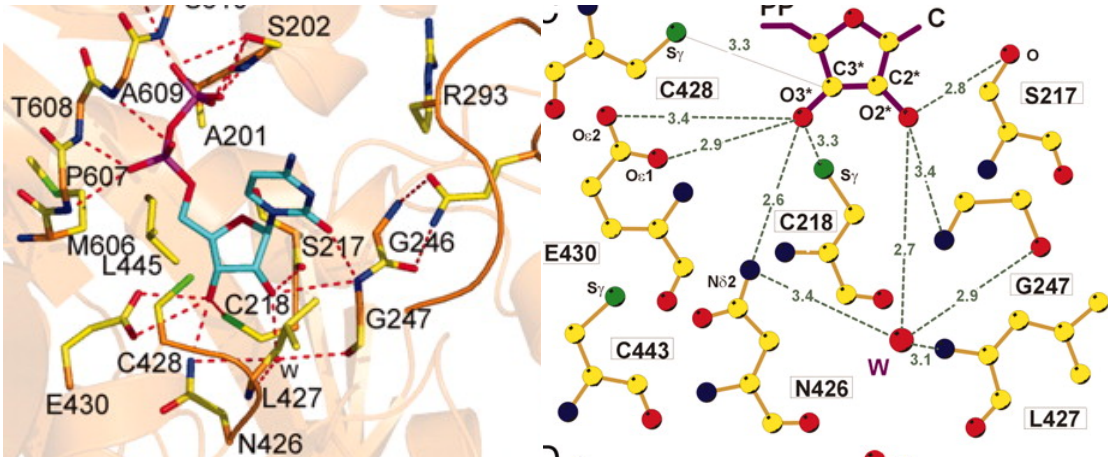
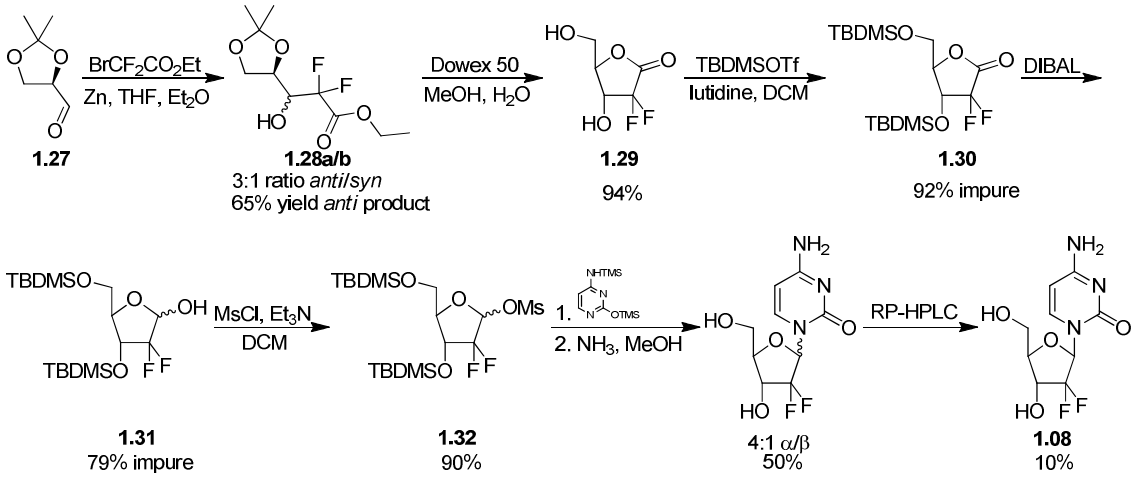


Figure 1.13: CDP binding to ribonucleotide reductase.[5]

Gemcitabine can be inactivated by deamination to its uridine derivative through the action of deoxycytidine deaminase.[29]

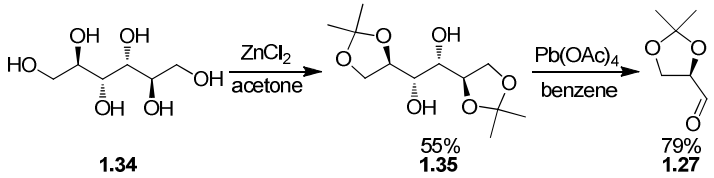
1.3 Gemcitabine Synthesis

The first synthesis of gemcitabine **1.08**, as part of a research program at the Lilly research laboratories, was published by Hertel *et al* in 1988 (Scheme 1.2).[30]



Scheme 1.2: Hertel *et al* synthesis of gemcitabine.

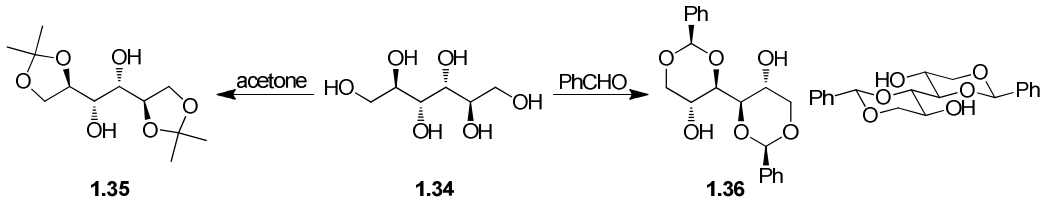
The synthesis starts from the enantiopure glyceraldehyde **1.27** which can be easily obtained by the method of Baer and Fischer[31] from D-mannitol in 2 steps (Scheme 1.3).



1.34 **1.35** **1.27**

Scheme 1.3: Baer and Fischer synthesis of glyceraldehyde **1.27**.

The chiral pool substrate D-mannitol **1.34** is protected as the diacetonide **1.35** before cleavage with lead tetraacetate affording the desired glyceraldehyde **1.27**. Mannitol reacts with acetone to form two 1,3-dioxolane rings **1.35** in contrast to the reaction with benzaldehyde which forms two 1,3-dioxane rings **1.36**. Formation of a 1,3 dioxane acetonide would force one of the methyl groups into an unfavourable axial position, which the formation of the 1,3 dioxolane acetonide **1.35** circumvents.



1.35 **1.34** **1.36**

Scheme 1.4: Mannitol protection selectivity.

The difluoro moiety is inserted *via* Reformatsky reaction of glyceraldehyde **1.27** with ethyl bromodifluoroacetate. A 3:1 *anti*/*syn* diastereomeric mixture is obtained, in favour of the desired *anti* product **1.28a**, this stereoselectivity is achieved under Felkin-Anh control.[32] Separation of the diastereomers was subsequently carried out by HPLC.

Cyclisation to the lactone was effected by the sulfonic acid resin, Dowex 50 to form the γ-lactone **1.29**. This intramolecular cyclisation preferentially furnishes the γ-lactone **1.29** over the δ-lactone **1.37** as the formation is kinetically favourable and γ-lactones have been shown to have less ring strain than δ-lactones with more favourable orbital overlap at the sp^2 C_1 centre.[33,34]

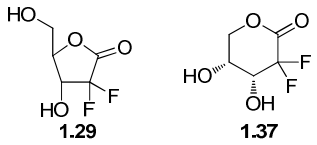


Figure 1.14: Lactone selectivity.

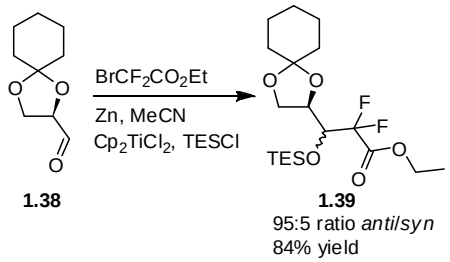
Protection of O_3 and O_5 as TBDMS ethers and subsequent DIBAL reduction furnished the key difluororibose intermediate **1.31** in 68% yield from alcohol **1.28a**. Mesylation provides the requisite leaving group for condensation with the nucleobase. Refluxing mesylate **1.32** in DCE with the silylated nucleobase and TMSOTf followed by deprotection with NH_3/MeOH, gave gemcitabine **1.08** as a 4:1 α/β anomeric mixture in 50% yield. The anomers were then separated by RP-HPLC.

This initial method, whilst suitable on small scale, has many shortcomings which had to be addressed before industrial scale synthesis was possible, for example, the reliance upon HPLC purification methods. There are therefore many revised syntheses of gemcitabine **1.08** in the literature.

1.3.1 Synthesis of Difluororibose - Fluorinated Building Block Approach

1.3.1.1 Lewis Acid Promoted Reformatsky Reaction

Matsumara *et al* investigated the use of catalytic Lewis acid to improve the diastereoselectivity of the Reformatsky reaction *via* activation of the aldehyde.[35]

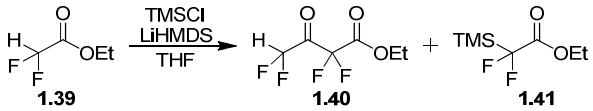


Scheme 1.5: Titanium promoted Reformatsky reaction.

The Cp_2TiCl_2 co-ordinates to the aldehyde, providing further activation allowing attack of the zinc enolate nucleophile, which is also further activated by the addition of TESCl, from the less hindered *si* face. Cyclohexylidene glyceraldehyde **1.38** was found to afford superior diastereoselectivity over the acetonide **1.27** or dibenzyl glyceraldehydes. Thus, a greatly improved 95:5 *anti*/*syn* diastereoselectivity is obtained, in contrast to the 3:1 *anti*/*syn* diastereoselectivity obtained from more traditional Reformatsky conditions.[30]

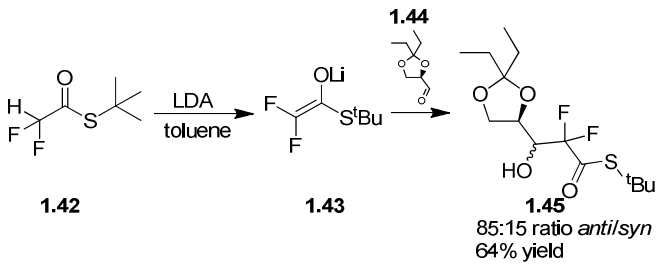
1.3.1.2 Aldol Reaction

One major drawback of the Reformatsky based methodology is the generation of a stoichiometric quantity of zinc waste, to avoid this Weigel investigated the formation of α,α-difluoro-β-hydroxyesters *via* lithium enolate chemistry.[36] The use of ethyldifluoroacetate **1.39** is not possible as the intermediate enolate species is unstable, resulting in the formation of the self condensation product **1.40**. Formation of the silylated product **1.41** was also observed (Scheme 1.6).



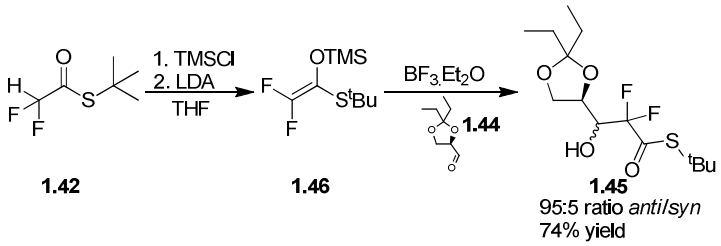
Scheme 1.6: Self-condensation (yields not given).

As a result α,α-thioester substrates were instead investigated, as the differing reactivity of thioesters with respect to esters was expected to lead to a more stable lithium enolate intermediate. Indeed when benzaldehyde was used as a model substrate with thioester **1.42**, the desired alcohol product was isolated in 70% yield and only 10% of the undesired self-condensation product was observed. When the methodology was applied to glyceraldehyde **1.44**, thioester **1.45** was formed in 64% yield with an 85:15 *anti*/*syn* diastereomeric ratio (Scheme 1.7).



Scheme 1.7: Formation of α,α-difluoro-β-hydroxyester intermediate **1.45** from thioester **1.42**.

Kitagawa *et al*[37] showed formation of a silylenolether of bromodifluoroacetate enhanced the diastereoselectivity of the addition to aldehydes, to 1:9 *syn*/*anti*, when the aldehyde used is acetonide glyceraldehyde **1.27**. Weigel found the same to be true in the addition of thiosilylenolether **1.46**, addition of TMSCl was found to increase both the yield and diastereoselectivity in this instance. A yield of 74% was obtained, with a 95:5 *anti*/*syn* diastereoselectivity (Scheme 1.8).



Scheme 1.8: Further improvement of the diastereoselectivity.

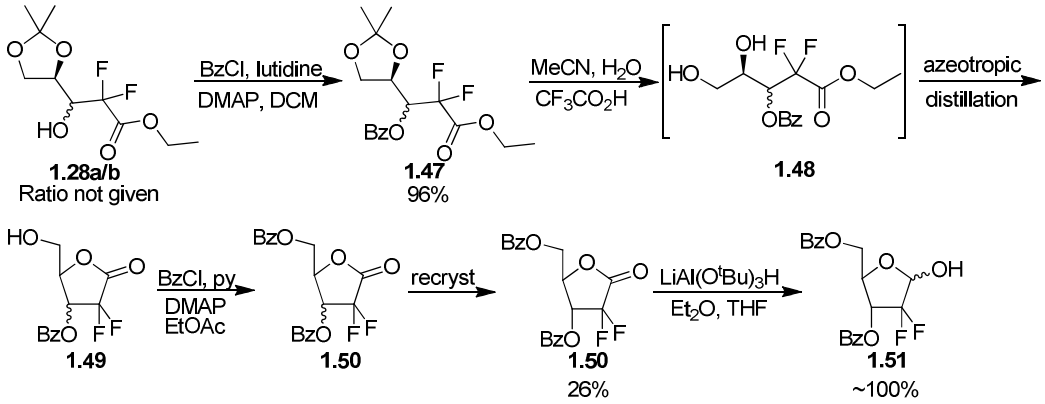
The thioester **1.45** formed would be a suitable substrate for conversion to a protected 2,2-difluororibose through a cyclisation, protection and reduction sequence as typified in other syntheses.[30]

1.3.1.3 Separation of Diastereomers

Separation of the diastereomeric products of the Reformatsky reaction by column chromatography is highly impractical on large scale. There have been several refinements made to the synthesis of gemcitabine **1.08** to allow the separation of the diastereomers by selective recrystallisation, made possible by the use of particular combinations of protecting groups.

One of the most ubiquitous protecting groups utilised in syntheses of gemcitabine **1.08** is benzoate. This method of protection was first disclosed by

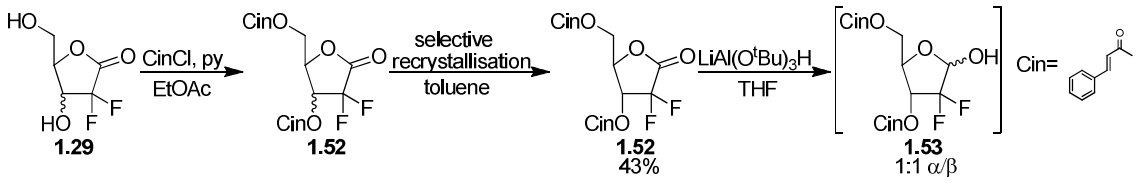
Chou *et al*[38] of Lilly research laboratories in 1992 in their adapted synthesis of that of Hertel *et al*,[30] which allowed for kilo-scale production of gemcitabine **1.08** (Scheme 1.9).



Scheme 1.9: Use of benzoate protection to facilitate diastereomeric resolution.

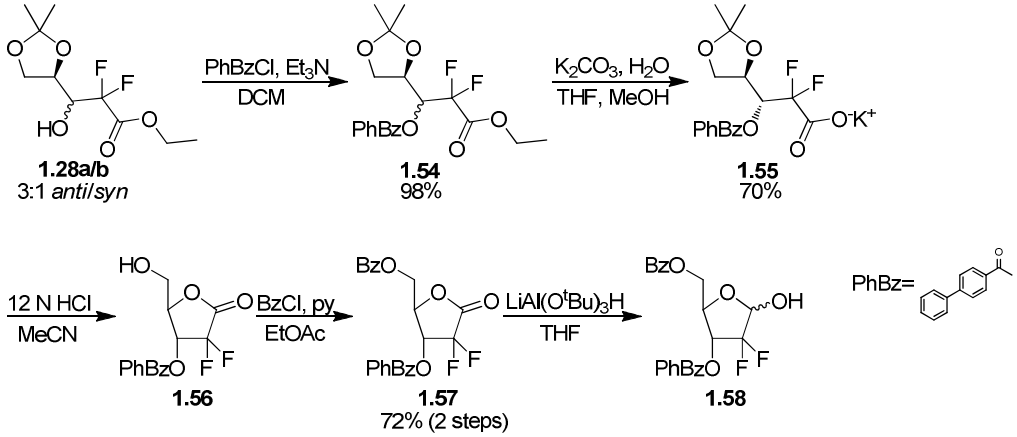
The use of benzoate protection over TBDMS allowed for the selective crystallisation of key intermediates within the synthesis, removing the need for chromatography. After Reformatsky reaction to introduce the difluoro moiety, near quantitative benzoylation of the mixture of diastereomers was undertaken to give ester **1.47**. The acetonide was then hydrolysed with TFA and subjected to azeotropic distillation to effect cyclisation to lactone **1.49**, followed by benzoylation to lactone **1.50**. At this stage a diastereoselective crystallisation from DCM/heptane provided the lactone **1.50** with the desired stereochemistry at C3, which was quantitatively reduced to lactol **1.51** with $LiAl(O^tBu)_3H$. The discovery of this diastereoselective recrystallisation is doubly advantageous due to the difficulty in purification of difluorolactones due to their propensity to undergo ring opening when subjected to column chromatography.

In their 2008 paper Jiang *et al*[39] installed cinnamoyl in preference to benzoate protection to provide a more crystalline lactone intermediate **1.52** (Scheme 1.10). This allowed the selective crystallisation of lactone **1.52** from toluene with the desired C3 stereochemistry in high purity (97.1%) and *ee* (99.3%) in 43% yield. Reduction furnished the lactol **1.53**, which was used directly in the subsequent steps.



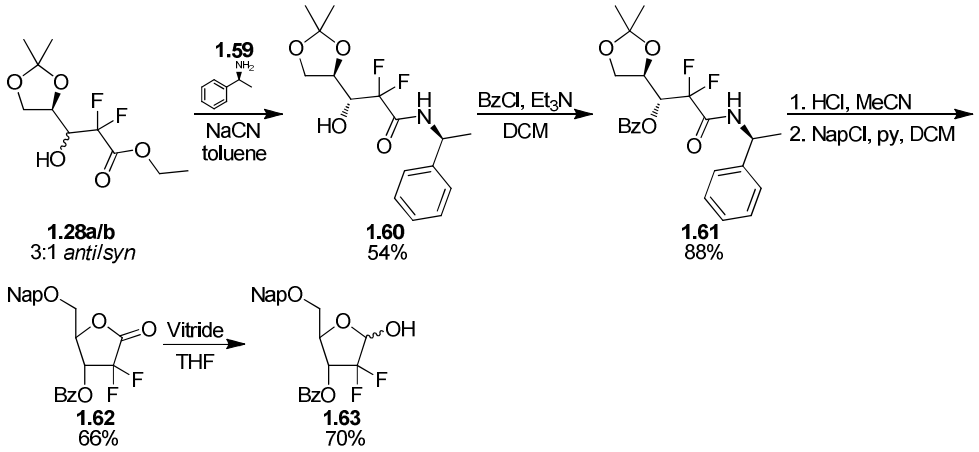
Scheme 1.10: Cinnamoyl mediated diastereomeric resolution.

In a different approach to that of Chou *et al*[38] and Jiang *et al*,[39] Chang *et al*[40] resolved the C3 stereochemistry before cyclisation to the lactone **1.56**. The diastereomeric mixture of **1.28** obtained from the Reformatsky reaction was protected as the *p*-phenzylbenzoate **1.54**, before ester hydrolysis to form the potassium salt. Removal of a third of the solvent volume *in vacuo* resulted in precipitation of the desired *anti* diastereomer **1.55** in 70% yield with an *ee* of 99.8%. Cyclisation and 5-O-benzoylation gave lactone **1.57** with 100% *de* in 72% yield after further recrystallisation.



Scheme 1.11: Diastereomeric resolution as the *p*-phenylbenzoate **1.55**.

Park *et al*[41] also devised a separation method based upon selective recrystallisation. The derivatisation of the ester **1.28** with an optically pure amine such as α-methyl-benzylamine **1.59** produces a mixture from which the desired *anti* diastereomer **1.60** can be recrystallised from hexane or hexane/EtOAc in 54% yield, in its optically pure form.



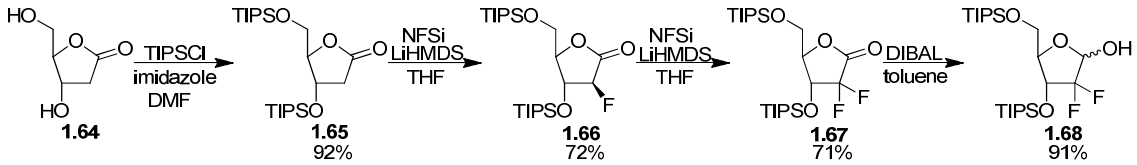
Scheme 1.12: Resolution with α-methyl-benzylamine **1.59**.

The resultant amide **1.60** can be converted to an appropriately protected 2,2-difluororibose of >99.6% *de* such as the 5-O-napthyl-3-O-benzoyl-2,2-difluororibose **1.63** by standard protection, cyclisation and reduction protocols.[38]

1.3.2 Synthesis of Difluororibose - Fluorination of Carbohydrate Derivatives

1.3.2.1 Direct Fluorination of 2-deoxyribonolactone

Cen *et al* developed a method to obtain the protected difluororibose **1.68** from the readily available 2-deoxy-D-ribonolactone **1.64** (Scheme 1.13).[42] This method does not therefore require stereoselective chemistry or laborious separation of diastereomers to obtain the desired stereochemistry at C3 and C4.

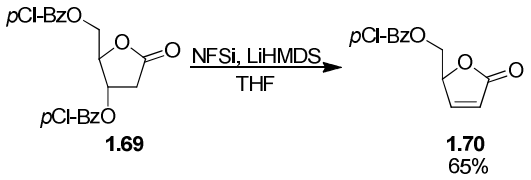


Scheme 1.13: Direct fluorination of 2-deoxyribonolactone **1.68**.

2-Deoxy-D-ribonolactone **1.64** is subjected to protection as TIPS ethers to give **1.65** in 92% yield. Diastereoselective electrophilic fluorination of lactone **1.65** with NFSi yielded the monofluoroarabinolactone **1.66** in 72% yield, the

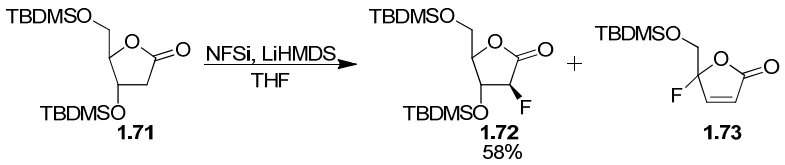
diastereoselectivity of this reaction attributed to the steric bulk of the O3 silyl protection preventing a *syn* attack by the NFSi. A second electrophilic fluorination, again using NFSi, furnished the difluorinated lactone **1.67** in 71% yield. Lactol **1.68** is then obtained *via* DIBAL reduction in 91% yield.

The choice of protecting group is critical in this synthesis. A silyl ether is necessary to suppress the competing elimination obtained when an ester protecting group such as the *p*-chlorobenzoate in **1.69** is utilised (Scheme 1.14).



Scheme 1.14: Elimination product **1.70**.

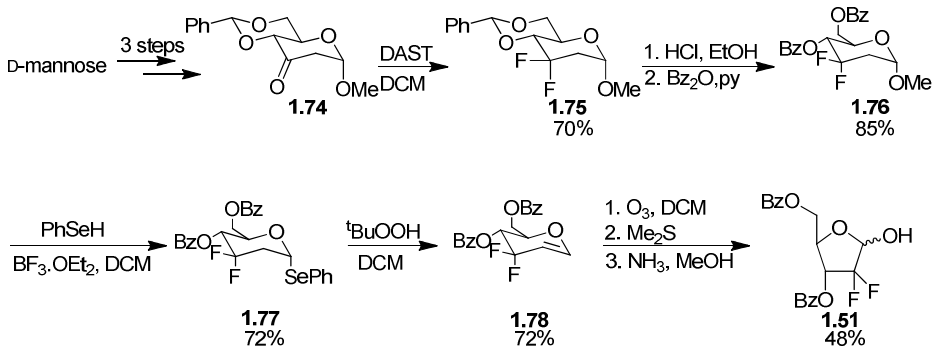
Cen hypothesises an increase in the steric bulk of the protecting group from *p*-chlorobenzoate to TBDMS forces the ring conformation such that O3 is in a pseudoequatorial position, lowering its propensity for elimination compared to the less sterically encumbered *p*-chlorobenzoate. Protection as the TBDMS ether **1.71** did not impart the necessary steric bulk, which was obtained by the use of the TIPS protection, as elimination product **1.73** was still observed (Scheme 1.15).



Scheme 1.15: Fluorination of TBDMS protected lactone **1.71**.

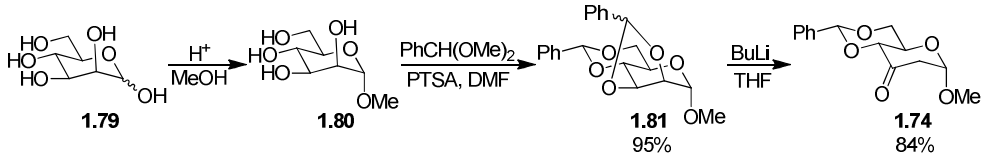
1.3.2.2 Synthesis from D-mannose

Fernandez *et al* synthesised dibenzoyl protected difluororibose **1.51** from D-mannose, as such the stereochemistry at C3 and C4 was set from the outset by their use of a chiral pool substrate (Scheme 1.16).[43]



Scheme 1.16: Synthesis of protected 2,2-difluororibose **1.51** from D-mannose.

Ulose **1.74** was first synthesised by the procedure of Horton *et al*.[44] Starting from D-mannose **1.79**, Fischer glycosylation furnishes the methyl α-mannopyranoside **1.80**, followed by formation of the dibenzylidene acetal **1.81**. Selective cleavage of the five-membered 2,3;4,6-di-O-benzylidene acetal with BuLi yielded the ulose **1.74** in 84% yield.

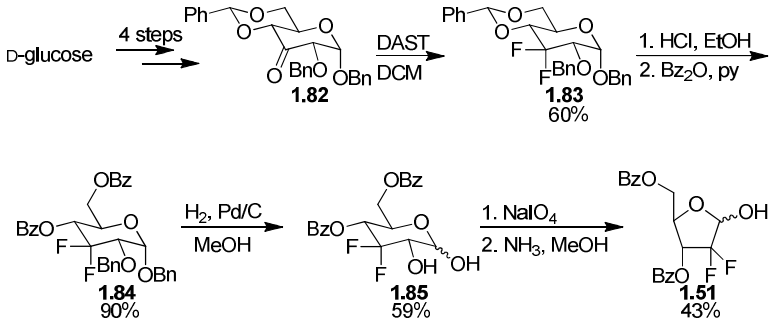


Scheme 1.17: Synthesis of ulose **1.74**.[45]

Reaction of this ulose **1.74** with DAST gave the 2,2-difluorinated **1.75** in 70% yield. The 4,6-O-benzylidene acetal was then hydrolysed to allow installation of the desired benzoates. Conversion of the anomeric methyl ether to the selenium derivative **1.77** in the presence of $BF_3 \cdot OEt_2$ allowed for the oxidative elimination to the glycal **1.78** with *tert*-butyl peroxide in 72% yield. Reductive ozonolysis and subsequent hydrolysis furnished the desired protected difluororibose **1.51** in 48% yield.

1.3.2.3 Synthesis from D-glucose

The protected difluororibose **1.51** can also be synthesised from D-glucose in similar fashion. First ulose **1.82** is synthesised in 4 steps from D-glucose.



Scheme 1.18: Synthesis of protected 2,2-difluororibose **1.51** from D-glucose.

The reaction of ulose **1.82** in DCM in the presence of 5 equiv of DAST provides the difluorosugar **1.83** in 60% yield. This moderate yield was due in part to the formation of the fragmentation product **1.86** (Figure 1.15).[46]

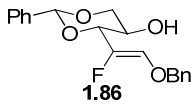
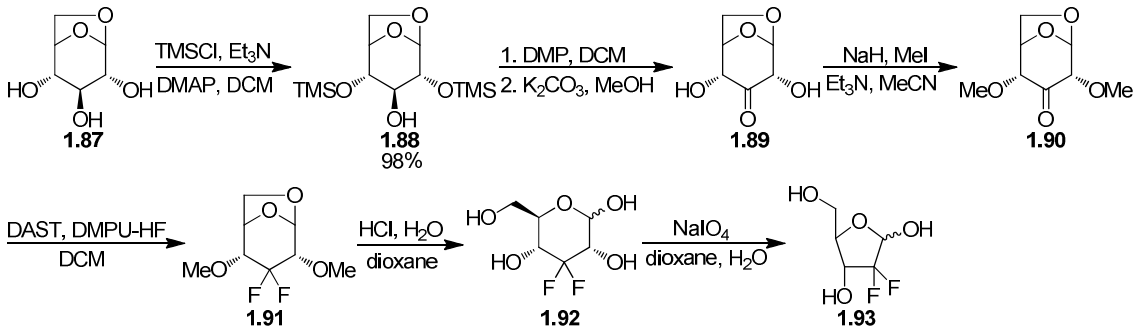


Figure 1.15: Fragmentation product **1.86**.

The benzylidene acetal is hydrolysed to allow for the installation of the desired benzoates, affording difluorosugar **1.84** in 90% yield. Hydrogenation removes the benzyl protecting groups in 59% yield, enabling the sodium periodate cleavage to be undertaken. Subsequent hydrolysis by methanolic NH_3 furnishes the desired protected difluororibose **1.51** in 43% yield.

1.3.2.4 From 1,6-anyhdro-β-D-glucose

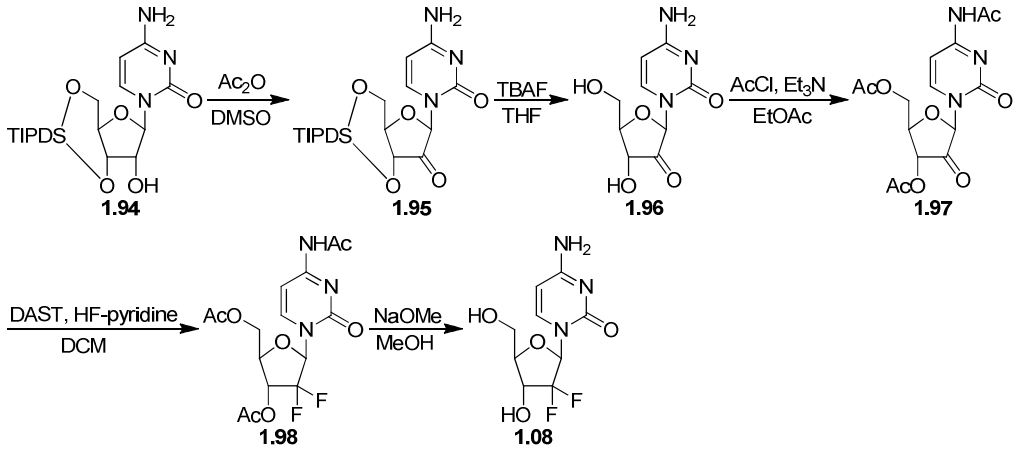
In the synthesis of Chen Gong[47] the protection of O2 and O4 of 1,6-anhydro-β-D-glucose **1.87** as TMS ethers gave a near quantitative yield of alcohol **1.88**, which was oxidised with Dess-Martin periodinane. The TMS ethers were subsequently deprotected to give ulose **1.89**. Reprotection of O2 and O4 as methyl ethers allowed for the fluorination of ulose **1.90** with DAST in the presence of DMPU-HF. The use of both DAST and DMPU-HF not only gave an increased yield of the difluorosugar **1.90**, but also allowed the reaction time to be significantly shortened. Hydrolysis in strongly acidic medium gave difluoro sugar **1.92**, which was treated with sodium periodate furnishing the difluororibose **1.93**.



Scheme 1.19: Synthesis from 1,6-anhydro-β-D-glucose **1.87** (yield and anomeric ratio not supplied for most of the steps).

1.3.2.5 From Protected Cytidine[48]

Cytidine was protected as the 3′,5′-O-TIPDS acetal **1.94**, O2′ was then oxidised by acetic anhydride in DMSO to give ketone **1.95**. Removal of the silyl and reprotection as the triacetate **1.97** was undertaken prior to fluorination with DAST and HF-pyridine. As in the Chen Gong[47] synthesis, DAST alone does not effect the fluorination, in this instance the reaction does not proceed in the absence of HF-pyridine. Finally NaOMe mediated deprotection furnishes gemcitabine **1.08**.



Scheme 1.20: Synthesis of gemcitabine **1.08** *via* fluorination of cytidine (yields not given).

The authors claim this method is not limited by the choice of protecting group or nucleotide.

1.3.3 Nucleobase Introduction - Direct Coupling

Traditional nucleobase addition methods, such as the Hilbert-Johnson and Vorbruggen protocols, are disfavoured in the synthesis of gemcitabine **1.08** due to the highly electron withdrawing nature of the difluoro moiety α to the anomeric centre. Therefore the existing methodologies had to be optimised to circumvent this difficulty.

1.3.3.1 Mesylate Leaving Group

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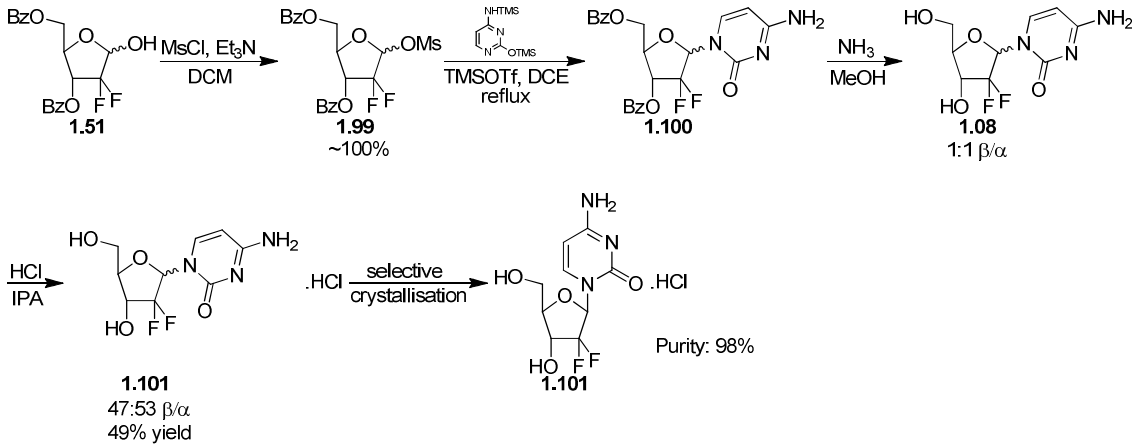


Scheme 1.21: Chou's synthesis of gemcitabine **1.08**.

Mesylation of lactol **1.51** proceeds in near quantitative conversion. Either anomer of the mesylate **1.99** could be selectively purified to a high level of purity. In Chou's 1994 patent[49] the α-enrichment of the mesylate **1.99** is also discussed. If the mesylation is run at low temperature the anomeric ratio is enhanced in favour of the α anomer. At 19 ℃ a 2:1 α/β ratio is obtained in contrast to the 4.4:1 α/β ratio obtained when the reaction is carried out at –83 ℃. No mention is made of the effect the lowere d temperature has upon the yield of the reaction.

Initial investigations into the mesylate displacement gave a 1:1 mixture of protected nucleoside **1.100** regardless of the anomeric ratio of mesylate **1.99**, suggesting a mechanism more S_N1 like in character.[38] However further investigation gave anomerically enriched nucleoside **1.100** starting from α-

enriched mesylate **1.99**.[49] The best reported method was the use of bis-silyl cytosine in anisole at 115 ℃ yielding 79.5% of the protected nucleoside **1.100** as a 1:7.3 α/β mixture. Alternatively nucleoside **1.100** could be synthesised as a 1:14.4 α/β mixture when treated with bis-silylcytosine in MeCN at 75 ℃ in the presence of barium triflate, however a significantly reduced yield of 25% was obtained.

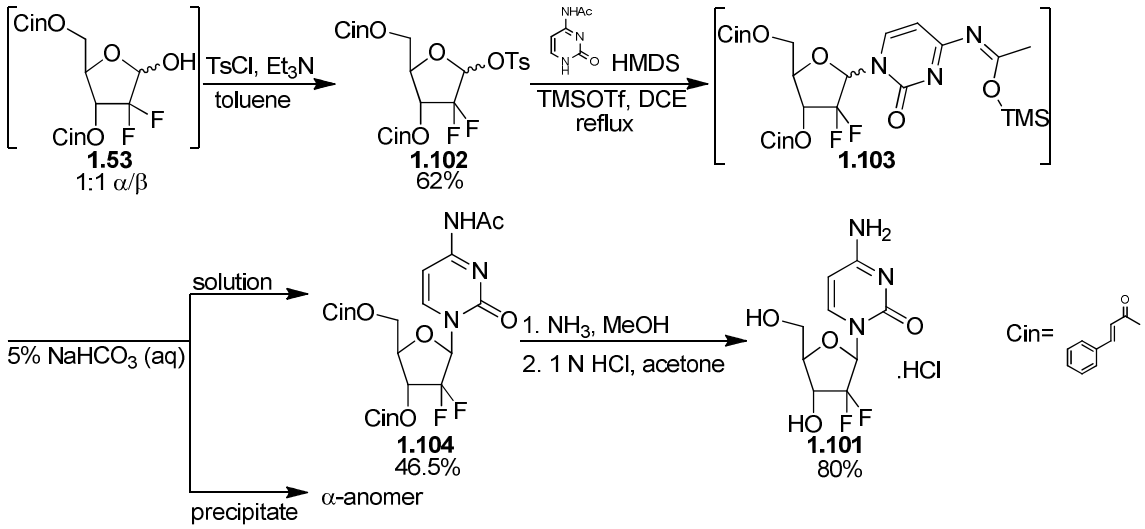
Selective crystallisation of the β anomer of gemcitabine was carried out on the HCl salt **1.101**, from water to give gemcitabine HCl **1.101** in 98% purity. This purity does not comply with USP30 requirements of ≥99.8%.[38]

A later patent from Chou[50] describes the development of a solvent-less protocol for nucleobase addition, once again developed from the α-enriched mesylate **1.99**. The optimal conditions were found to be 10 equiv of bis-silylcytosine at 130 ℃, yielding the protected nucleoside **1.100** in 50% yield as a 1:1.7 α/β mixture. Once again if the yield was sacrificed, the anomeric ratio obtained could be increased to 1:2.3 α/β using 3 equiv of bis-silyl-*N*-acetylcytosine at 110 ℃, but with only a 27% conversion.

A further embodiment from Kjell[51] describes the use of different catalysts, again working from the α-enriched mesylate **1.99** and bis-silylcytosine. The optimal selectivity, of 1:14.9 α/β was obtained with the use of Cs_2SO_4, but with a poor yield of 24%. Use of the caesium salt of triflic acid however, furnished a 1:6.7 α/β mixture of the protected nucleoside **1.100** in 70% yield.

1.3.3.2 Tosylate Leaving Group

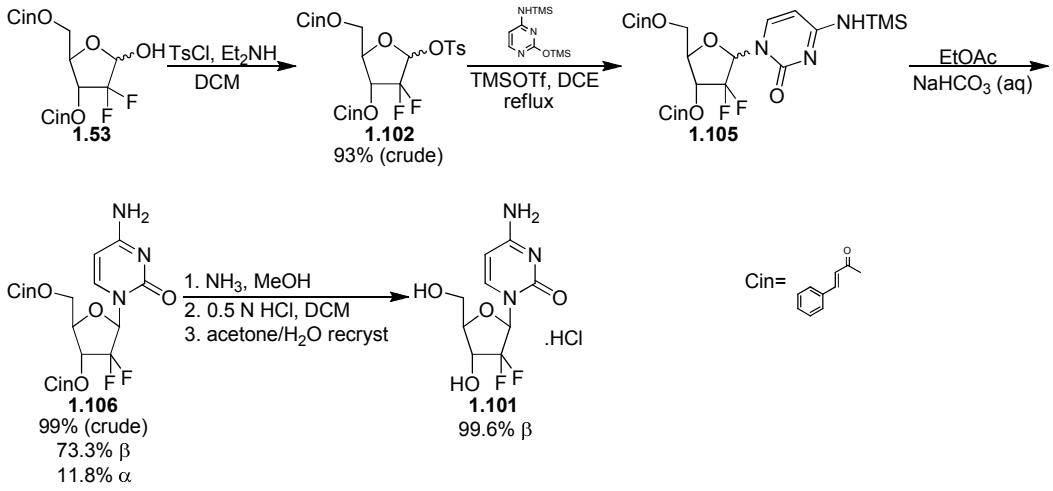
Lactol **1.53** was converted to crystalline tosylate **1.102**. It is reported the base employed in the tosylation has an effect upon the anomeric ratio of the resultant tosylate **1.102**, however no anomeric ratios are reported. When the analogous mesylate compound was synthesised it was found to be an oil, thus showing the tosylate confers a true advantage in this synthesis.



Scheme 1.22: Nucleobase addition by tosylate displacement.

As in the original investigations of Chou *et al*[38], Jiang *et al*[39] found the anomeric ratio of the tosylate **1.102** had no effect upon the ratio of **1.103** formed, a 1:1 anomeric ratio was always obtained. After treatment with 5% $NaHCO_3$ (aq), **1.104α** was found to precipitate from the reaction mixture, allowing its removal by filtration, leaving the desired **1.104β** anomer with a *de* of 90%. This material was subsequently deprotected with NH_3 and converted to the gemcitabine HCl salt **1.101**. Recrystallisation from acetone/water furnished the gemcitabine HCl salt **1.101** with a purity of 99.8%.

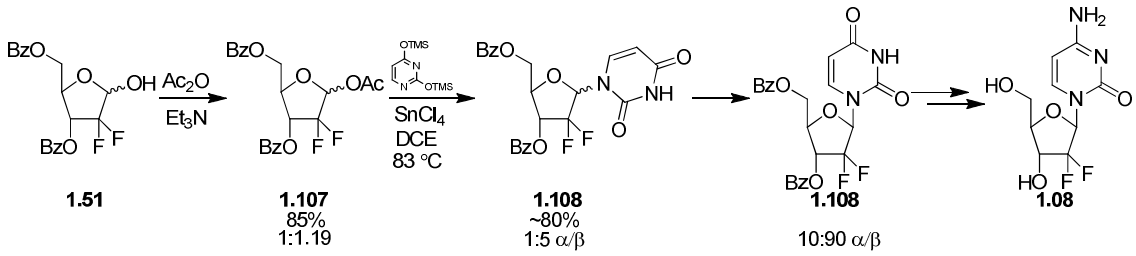
A similar synthesis was published in the patent literature, also in 2008, by Zelikovitch *et al*,[52] employing cinnamoyl protection to facilitate selective crystallisation of an intermediate (Scheme 1.23). They found reduction of the solvent volume, after addition of the nucleobase to form **1.105**, followed by stirring in EtOAc and sat. $NaHCO_3$ (aq) removed the TMS group and allowed for the precipitation of a solid enriched with 73.3% of **1.106β** (1:6.2 α/β mixture). Further enrichment of the β anomer was undertaken after deprotection of the cinnamoyl groups, by recrystallisation of gemcitabine HCl **1.101** from acetone/water, furnishing the β anomer in 99.6% purity.



Scheme 1.23: Zelikovitch synthesis utilising cinnamoyl protection.

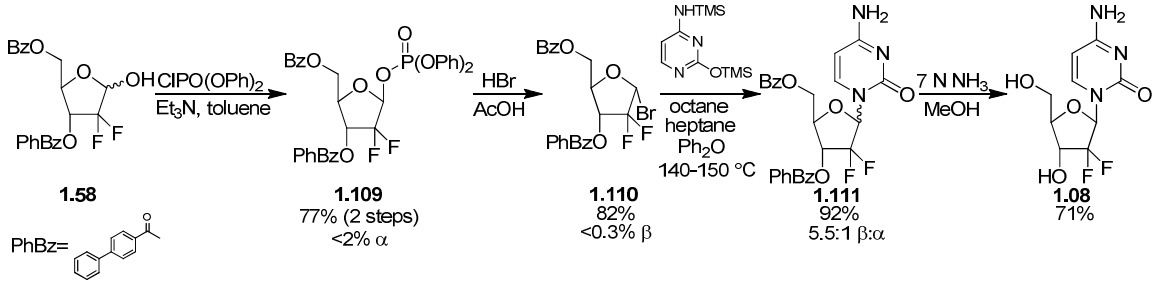
1.3.3.3 Acetate Leaving Group

Born *et al*[53] reported the use of acetate as an alternative leaving group for the addition of uracil (Scheme 1.24). Treatment of acetate **1.107** with bis-silyluracil in the presence of $SnCl_4$ yielded the protected nucleoside **1.108** in approximately 80% yield as a 1:5 α/β anomeric mixture. This anomeric ratio can be further enhanced to 10:90 α/β by trituration in 2:1 heptane/EtOAc. Nucleobase manipulation and deprotection would then yield gemcitabine **1.08**, however this is not explicitly described.



Scheme 1.24: Nucleobase addition - acetate leaving group.

1.3.3.4 Bromide Leaving Group



Scheme 1.25: Nucleobase addition *via* bromide displacement.

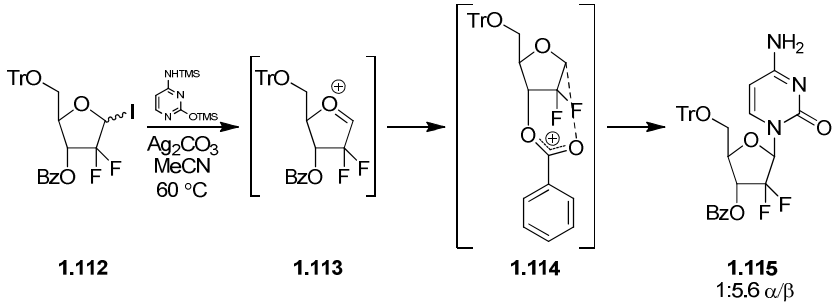
Chang *et al* utilised a bromide leaving group.[40] After reduction, the crude lactol **1.58** was phosphorylated to give the diphenylphosphate **1.109** as a 1:10.8 α/β mixture. Recrystallisation from IPA/water enhanced this mixture to >99:1 α/β. However, this anomeric enhancement was ultimately unnecessary as the anomeric purity of the phosphate **1.109** had no effect upon the outcome of the subsequent bromination step. The bromide **1.110** was obtained as a 10.8:1 α/β mixture, which again could be enhanced by recrystallisation from IPA to give an 82% yield of bromide **1.110** in >99.7:0.3 α/β purity.

Initial studies found protected nucleoside **1.111** to be formed as a 1:1 anomeric mixture, when bromide **1.110** was reacted with disilylcytosine. Chang *et al* hypothesised this total lack of anomeric selectivity was due to anomerisation of the bromide **1.110**, promoted by the TMSBr formed in the reaction mixture. Indeed when the TMSBr was removed from the reaction mixture *via* continuous distillation, using heptane as a co-solvent, the anomeric selectivity increased to 1:5.5 α/β, a significant improvement. This anomeric ratio therefore indicates the reaction mechanism proceeds *via* a mixture of S_N1 and S_N2 type. A non-polar solvent system of 2:1 octane/diphenyl ether was also utilised in an attempt to keep the concentration of the S_N1 oxocarbenium intermediate species as low as possible. The 1:5.5 α/β mixture of **1.111** was deprotected with NH_3 and recrystallised from water as either gemcitabine hemihydrate if the mixture was stirred during the crystallisation, or gemcitabine dihydrate if it was not stirred. Both crystalline forms were found to be of greater than 99.8% β anomer.

In their patent application of the same synthesis[54] it is also disclosed that the addition of a small amount of *N*,*O*-bis(trimethylsilyl)acetamide (1% of the volume of heptane) to the nucleobase addition reaction would further enhance the formation of the β anomer of **1.110** to 1:14 α/β, however a yield was not reported for this method.

1.3.3.5 Iodide Leaving Group

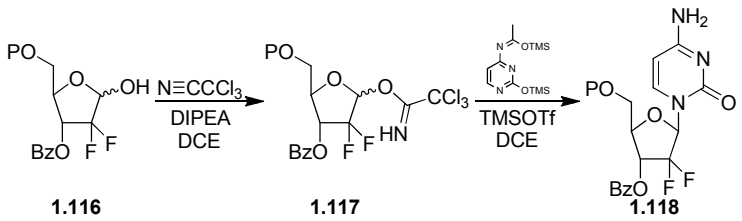
Chu *et al*[55] make use of an iodide leaving group in their synthesis, to provide protected nucleoside **1.115** as a 1:5.6 α/β mixture (Scheme 1.26). They explain the enhanced β-selectivity of the reaction *via* an S_N1 type mechanism whereby the formation of the disfavoured oxonium intermediate **1.113** is facilitated by Ag^+. Also the 3-O-benzoate protection aids *via* stabilisation of the oxonium through formation of a six-membered cyclic oxonium **1.114**. The formation of this cyclic oxonium on the bottom face of the ribose ring causes steric hindrance, blocking that face and favouring attack of the nucleobase nucleophile from the top face, thereby enhancing the formation of the β-anomer.



Scheme 1.26: Nucleobase addition with iodide leaving group.

1.3.3.6 Trichloroacetimidate Leaving Group

Maikap *et al*[56] and Vishnujant *et al*[57] have both reported the use of trichloroacetimidate as a leaving group in the nucleobase addition step however neither patent reports the anomeric selectivity or isolated yields for this method (Scheme 1.27).

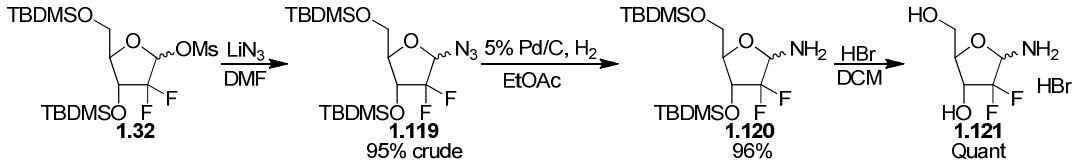


Scheme 1.27: Nucleobase addition - trichloroacetimidate leaving group.

1.3.4 Nucleobase Introduction - Linear Nucleobase Synthesis

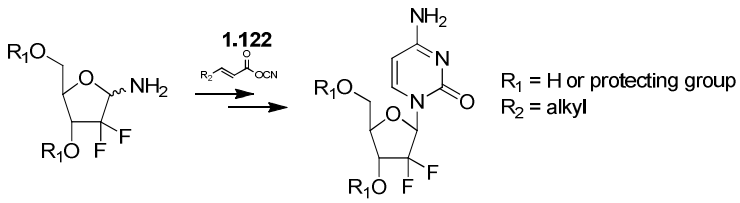
1.3.4.1 Hertel

Hertel *et al*[58] published a patent in 1995 disclosing the synthesis of the primary aminoglycoside as the HBr salt **1.121** (Scheme 1.28). Starting from the known mesylate **1.32**, they installed an anomeric azide in good yield, to form azide **1.119**. Studies were also carried out using the analogous dibenzoylmesylate. If the α-mesylate was used, the β-azide was isolated in 76% yield, however if the β-mesylate was utilised the α-azide was isolated in 73% yield, indicating the displacement with azide may proceed *via* a predominantly S_N2 type mechanism. Reduction to the amine **1.120** and subsequent desilylation to form HBr salt **1.121**, as a foam, proceeded in near quantitative yield.



Scheme 1.28: Synthesis of primary aminoglycoside **1.121**.

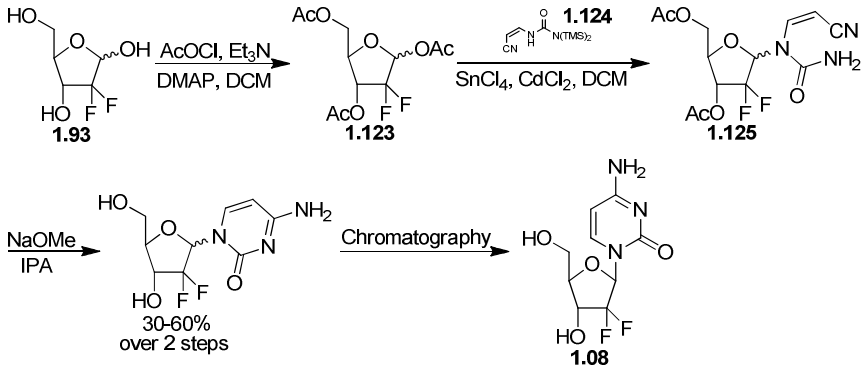
Hertel *et al* outline the utility of primary aminoglycosides of this type in the synthesis of nucleosides (Scheme 1.29) *via* reaction of the amine with an acyl isocyanate such as **1.122**. However, whilst the patent claims the synthesis *via* this method, it is not explicitly described. Subsequent cyclisation and further manipulation of the nucleobase obtained would allow the synthesis of a range of difluorinated nucleosides.



Scheme 1.29: Potential nucleoside synthesis.

1.3.4.2 Chen Gong

In the synthesis of Chen Gong[47] the nucleobase is incorporated *via* the condensation of a straight chain urea **1.124**, followed by cyclisation (Scheme 1.30).



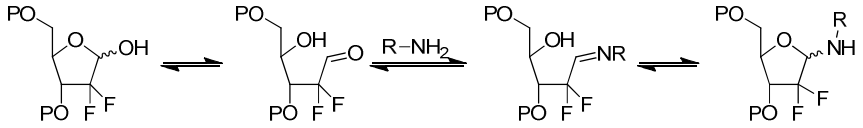
Scheme 1.30: Linear nucleobase synthesis (anomeric ratios not reported).

Triacetylation preceded the reaction with urea **1.124** in the presence of $SnCl_4$ and $CdCl_2$. The resultant urea **1.125** was subjected to a basic cyclisation protocol and concomitant deacetylation to give gemcitabine **1.08** as a mixture of anomers. The only chromatographic purification was undertaken at this point in the synthesis, to yield gemcitabine **1.08** as its β anomer.

1.4 Project Aims

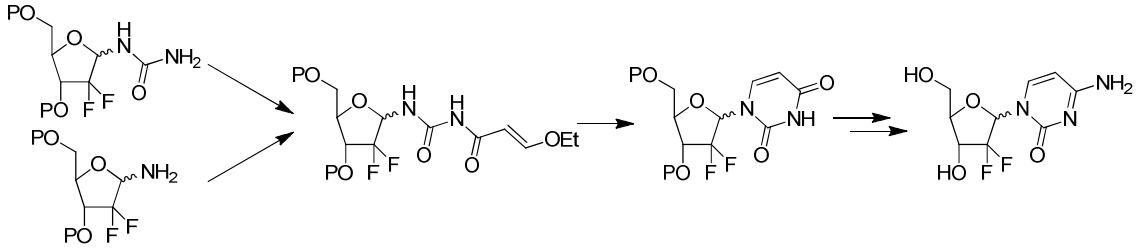
All current syntheses of gemcitabine **1.08** from difluororibose are intrinsically disfavoured at the point of nucleobase incorporation, due to the requisite substitution reaction α to a CF_2 moiety. Our intention was to develop a synthesis that removed the need for this disfavoured reaction, by taking advantage of the

tendency of cyclic hemi-acetals to exist in equilibrium between their open and closed forms (Scheme 1.31).



Scheme 1.31: Mechanism of intended aminoglycosylation.

Ring opening reveals a very electrophilic α-difluoro-substituted aldehyde, which would then react with an available nucleophile, in this instance an amine or urea, to form a similarly reactive imine. This imine would undergo ring closure to form the desired aminoglycoside.



Scheme 1.32: Nucleobase construction.

From the resultant aminoglycoside or glycosylurea, the nucleobase could thus be constructed in an acyclic fashion to form the desired nucleoside analogue, gemcitabine **1.08** (Scheme 1.32). This same methodology could then be applied to the synthesis of other nucleoside analogues, including those comprising of a 2,2,3,3-tetrafluororibose sugar.

2 Synthesis of the Fluorinated Lactols

The initial focus for the project was the synthesis of the required difluorinated and tetrafluorinated lactols (Figure 2.1). Whilst the dibenzoyllactol **1.51** utilised in many of the syntheses of gemcitabine **1.08** was suitable for the planned glycosylurea formation experiments, alternative protection was required for the aminoglycosylation experiments, due to the reactivity of esters with amines. Therefore a novel 5-O-*tert*butyldiphenylsilyl-3-O-benzyllactol **2.01** was also synthesised.

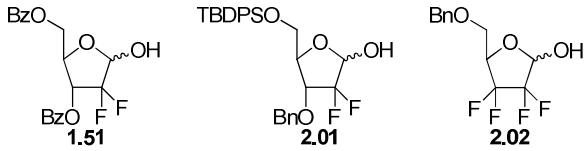
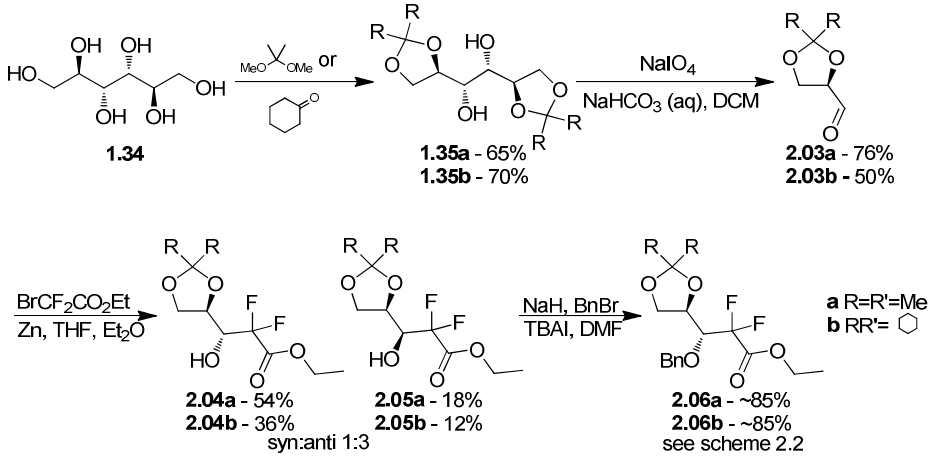


Figure 2.1: Lactol starting materials.

2.1 Synthesis of 5-O-TBDPS difluorolactol

Starting from D-mannitol **1.34** (Scheme 2.1), readily available from the chiral pool, selective 1,2:5,6 protection was carried out with 2,2-dimethoxypropane[59] to give the 1,2:5,6-diacetonide **1.35a** in 65% yield, or with cyclohexanone, to give the 1,2:5,6-dicyclohexylideneacetal **1.35b** in 70% yield.[60] Periodate cleavage then furnished the protected glyceraldehyde **2.03a/b**.[61]



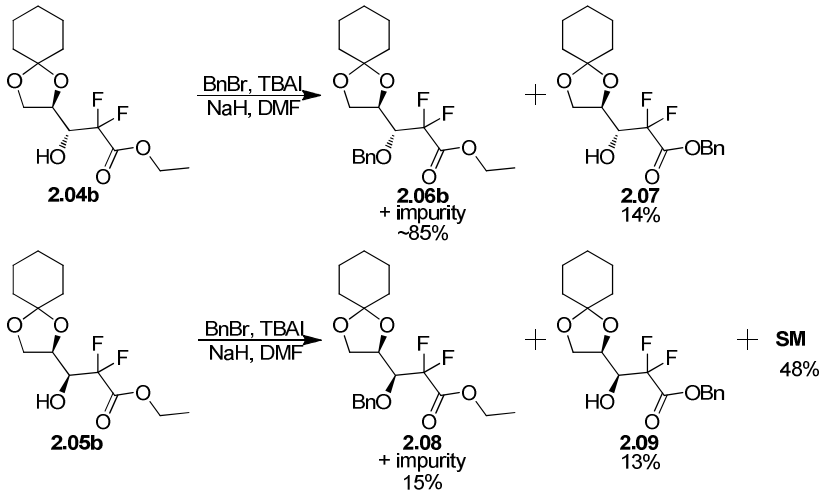
Scheme 2.1: Synthesis of protected difluoroester **2.06**.

The *gem*-difluoro moiety was introduced *via* the Reformatsky reaction, using ethyl bromodifluoroacetate as the fluorinated building block.[62] This gave the desired ester **2.04a/2.05a** in 70% yield as a separable 1:3 diastereomeric mixture in favour of the desired *anti* diastereoisomer.

Both 1,2:5,6-diacetonide **1.35a** and 1,2:5,6-dicyclohexylideneacetal **1.35b** were synthesised, as Matsumara *et al*[35] found the addition of TESCl and Cp_2TiCl_2 increased both the yield and diastereoselectivity of the Reformatsky reaction on these the cyclohexylidene glyceraldehyde substrate **2.03b**.

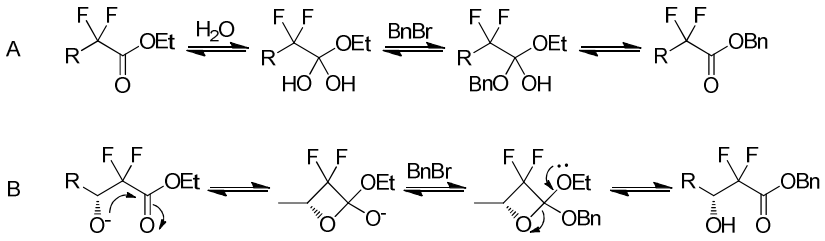
In our hands this method did not offer any major advantage over the more traditional Reformatsky conditions (Scheme 2.1), as whilst the desired increase in diastereoselectivity was seen, the yield obtained was lower. Also practically, the reaction was more difficult to carry out, in part due to the requirement of cannulation of a suspension into the reaction mixture.

Protection of alcohol **2.04a/b** yielded the desired benzyl ether **2.06a/b**, this however contained an unidentified impurity, which was not separable by flash chromatography or HPLC. It was shown this impurity was not due to epimerisation, through comparison with the product of benzylation of the undesired *syn* diastereoisomer **2.05b**, which also contained an analogous inseparable impurity. An unexpected by-product, benzyl ester **2.07/2.09** (Scheme 2.2) was also isolated from these reactions. Surprisingly, despite the use of a slight excess of benzyl bromide, the hydroxyl of benzyl ester **2.07/2.09** remained unprotected.



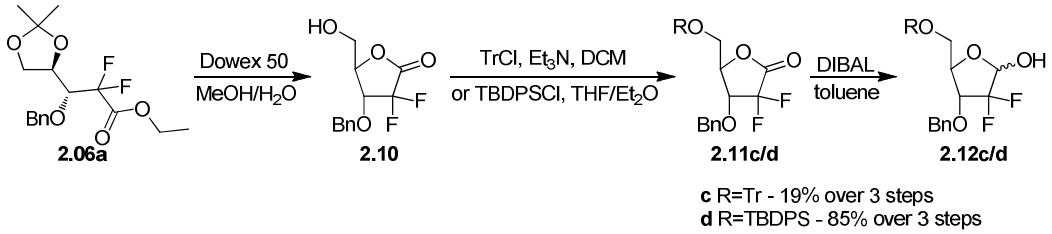
Scheme 2.2: Benzylation by-product.

Possible mechanisms for the formation of benzyl ester by-product **2.07** are outlined in Scheme 2.3. As shown in mechanism A, in the presence of trace amounts of water, hydration of the ester could occur due to the α relationship to the very electron-withdrawing *gem*-difluoromethylene moiety, leading to benzylation and subsequent ethoxy elimination. Alternatively, the deprotonated alcohol could attack the ester intramolecularly to form the oxetane ring after which benzylation and re-opening of the oxetane could occur, as outlined in mechanism B.



Scheme 2.3: Possible mechanism for formation of by-product **2.07**.

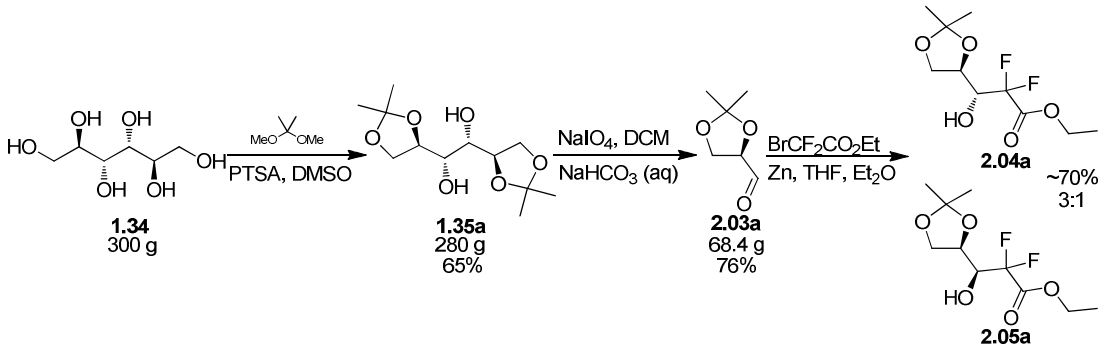
With the ester **2.06** in hand, cyclisation to lactone **2.10** was effected using the sulfonic acid resin, Dowex 50. Due to the relative instability of these lactones to purification, the reaction sequence was telescoped through to lactol **2.12** (Scheme 2.4).



Scheme 2.4: Synthesis of protected lactol **2.12**.

The choice of protecting group for the 5OH of lactone **2.10** was found to be very important, as when protection as the trityl ether was attempted, only 19% of the desired lactol **2.12c** was isolated. In contrast, when protection as the TBDPS ether was undertaken, the corresponding lactol **2.12d** was isolated in a pleasing 85% yield over the 3 steps.

2.2 Scale-up of difluorolactol intermediate 2.04



Scheme 2.5: Scale-up of the difluorolactol intermediate **2.04a**.

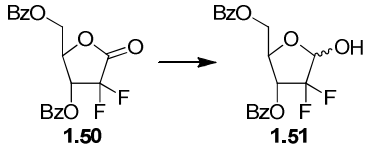
The protection of D-mannitol **1.34** as the diacetonide **1.35a** was conducted on up to 300 g (1.65 mol) scale, with purification by recrystallisation. The acetonide **2.03a** was obtained in 76% on 90 g scale with purification by vacuum distillation (scale was limited here, only by the inability to store the aldehyde **2.03a** for long periods of time due to its propensity to polymerise). The cleavage was run at 0 ℃ and on small scale had to be cooled in an ice bath. Conversely, on large scale the reaction was conducted in an open beaker with vigorous overhead stirring and a warm water bath was required to maintain the reaction temperature at 0 ℃, due to the cooling effect of the evaporation of the DCM.

The scale-up of the Reformatsky reaction was found to be more problematic. The particle size of the zinc dust is extremely important, otherwise the initiation of the reaction is delayed, resulting in a thermal runaway and an uncontrollable reaction. Ultimately the most practical solution, in the time scale available, was to run the reaction in 10–20 g batches and combine the crude products for purification. Anhydrous solvents are required to prevent the formation of an, as yet unidentified by-product, that co-elutes with the desired major *anti* diastereoisomer **2.04a**. Purification was carried out by MPC, however the standard method of dryloading the MPC column was found to be unsuitable, as evaporation onto silica was found to cause the formation of, what appeared by NMR to be, the same by-product as obtained from the utilisation of wet solvents. It was however possible to overcome this problem by wet-loading the MPC column.

2.3 Synthesis of 3,5-O-dibenzoyldifluorolactol

The 3,5-O-dibenzoyl-2-deoxy-2,2-difluoro-D-ribonic acid-1,4-lactone **1.50** is commercially available from Carbosynth at £48/10 g. At this price, it is cheaper to buy the lactone than to synthesise it in house from D-mannitol **1.34**.

There are several examples of the reduction of lactone **1.50** to lactol **1.51** (Scheme 2.6) in the literature, both on small and large scale, with large differences in the yields obtained, from the near quantitative yield of Chou *et al*[38] to the 33% yield obtained by Kotra *et al* for the reduction of the diastereomeric L-ribonolactone,[62] both of which employ $LiAl(O^tBu)_3H$ as the reducing agent. A small screen of reduction conditions was therefore carried out to ascertain which conditions performed best in our hands (Table 2.1).



Scheme 2.6: Dibenzoyllactone reduction.

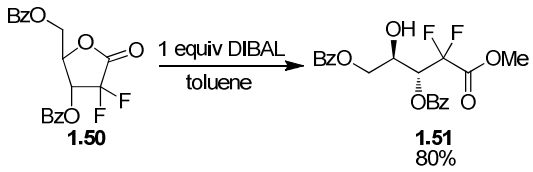
Vitride ($NaAlH_2(OCH_2CH_2OMe)_2$) is the favoured reducing agent of Polturi *et al*,[63] due to ease of handling and cost. Initial trials were carried out using Vitride (entries 1–4) with increasing yield as the temperature was lowered and reaction time lengthened. A by-product was seen in the crude NMR which, from the peak shifts in the ^{19}F NMR, appeared to be acyclic, however this was not isolated. When $LiAl(O^tBu)_3H$ was utilised (entry 5) some lactol **1.51** was obtained however it was found to co-elute with another by-product during column chromatography.

Table 2.1: Lactone reduction optimisation.

Entry	Reagent (equiv)	Temperature (℃)	Time (h)	Quench	Major Product	Yield (%)[a]
1	Vitride (1.1)	–20	1	MeOH	Lactol **1.51**	Low
2	Vitride (1.1)	–30	1.5	MeOH	Lactol **1.51**	27
3	Vitride (1.0)	–20	1.25	MeOH	Lactol **1.51**	42
4	Vitride (1.0)	–30 then –20	1.5	MeOH	Lactol **1.51**	70
5	$LiAl(O^tBu)_3H$	–10–0	1.25	MeOH	Impure lactol **1.51**	N/A
6	DIBAL (1.0)	–78	6	MeOH	Acyclic methyl ester **2.13**	80
7	DIBAL (2.0)	–78	6	MeOH	Unidentified	N/A
8	DIBAL (1.1)	–78	6	Na_2SO_4 $10H_2O$	Unidentified	N/A

a: isolated yield

After treatment with 1 equiv of DIBAL (entry 6), the acyclic methyl ester **2.13** was isolated in 80% yield, presumably due to attack of the MeOH used to quench the reaction. However the benzoate protecting groups remained intact, which had been a source of concern as the literature does show precedent for benzoate lability when treated with DIBAL (Scheme 2.7).[64] The methyl ester **2.13** slowly epimerised in $CDCl_3$ over time to give a 1:6.9 diastereomeric mixture.



Scheme 2.7: Formation of the acyclic by-product **2.13**.

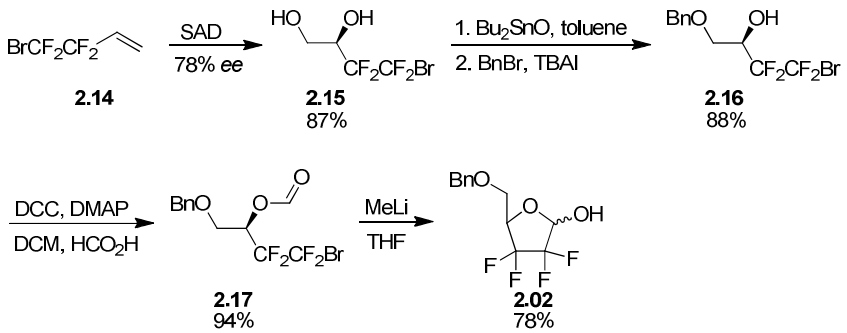
However, when 2 equiv of DIBAL was used (entry 7) a different, unknown but also apparently acyclic, by-product was seen to form. The reaction was therefore repeated using $Na_2SO_4 \cdot 10H_2O$ to quench (entry 8), however the desired lactol was not isolated.

Ultimately addition of 1 equiv of Vitride at –30 ℃ then stirring for 1.5 h at –20 ℃ (entry 4) furnished the best yield of 70%, for the reduction to furnish lactol **1.51**.

2.4 Synthesis of Tetrafluorolactol 2.02

2.4.1 Synthesis

Following methodology previously developed in the group, tetrafluororibose **2.02** was synthesised from 4-bromo-3,3,4,4-tetrafluoroalkene **2.14** (Scheme 2.8).[65] The alkene **2.14** was subjected to Sharpless asymmetric dihydroxylation conditions, utilising an in-house prepared AD-mix, containing $(DHQ)_2PYR$ as the ligand, to furnish the desired diol **2.15** in 87% with 78% *ee*. This yield and enantioselectivity is excellent for a terminal deactivated alkene of this type.



Scheme 2.8: Synthesis of tetrafluorolactol **2.02**.

Whilst the primary alcohol of diol **2.15** is less sterically encumbered, the secondary alcohol is more basic, though less nucleophilic, due to the α tetrafluoroethylene, therefore the secondary alcohol is benzylated preferentially under basic conditions. Selective benzylation of the primary alcohol is instead effected *via* a stannylene acetal.[66] The origin of the regioselectivity in this reaction is due to the steric bulk of the dibutyltin acetal intermediate formed. Stannylene acetals have been shown to exist as dimeric structures in which the apical oxygen then reacts preferentially (Figure 2.2),[67] although the more electronegative oxygen would typically occupy the apical position, which would give the opposite regioselectivity to that which we obtained.

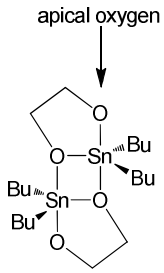
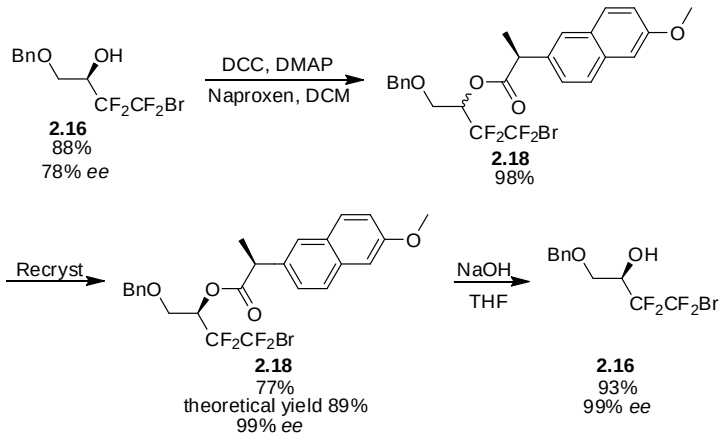


Figure 2.2: Dimeric stannylene acetal.

This is then succeeded by a DCC mediated formylation, before the key bromine-lithium exchange anionic cyclisation to give the lactol **2.02**.

2.4.2 Enantiomeric Resolution

In order to obtain lactol **2.02** as an enantiopure mixture of anomers, resolution of the enantiomers was required (Scheme 2.9).[66] Derivatisation of alcohol **2.16** with (*S*)-naproxen, was quantitative, flash chromatography removed the major by-products of the reaction, allowing the selective recrystallisation of the desired major diastereomer from hexane. The recovery of the naproxen ester **2.18** was 77%, a very pleasing 89% of the theoretical maximum yield of diastereomerically pure material. Saponification then furnished the further enantioenriched benzyl alcohol **2.16**.



Scheme 2.9: Naproxen resolution.

X-ray crystallographic analysis proved the relative stereochemistry of the major diastereomer of the naproxen ester **2.18** (Figure 2.3).

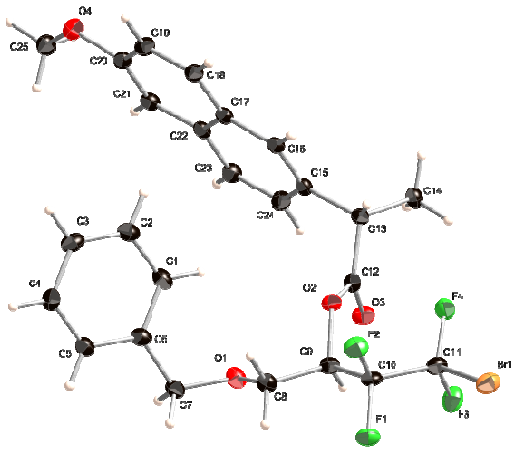
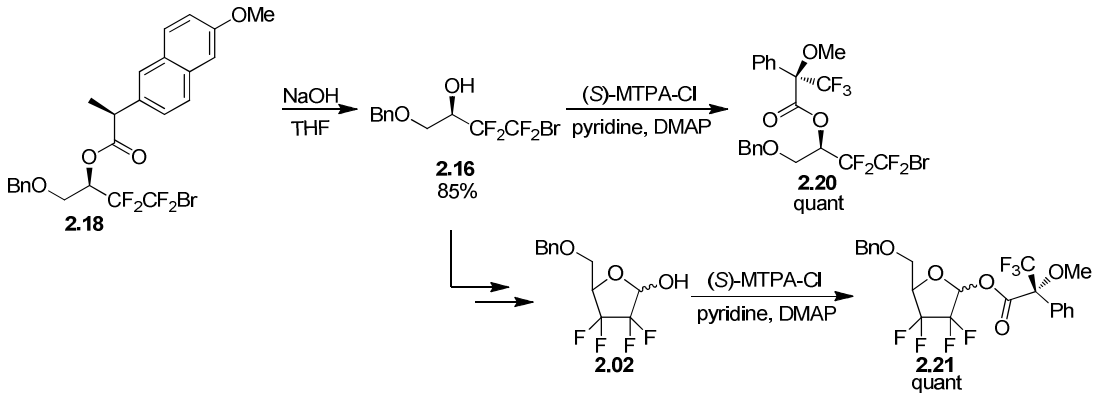


Figure 2.3: Crystal structure of naproxen ester **2.18**.

It has been reported in the literature that fluorinated compounds can be liable to epimerise α to the fluorination under basic conditions.[68,69] Gouverneur *et al* saw a 4% erosion in *ee* after esterification of alcohol **2.16** (Scheme 2.10).

Scheme 2.10: Epimerisation in Gouverneur system.

In order to confirm epimerisation does not occur during the saponification of naproxen ester **2.18**, the presumed enantiopure alcohol **2.16** was derivatised to the Mosher ester **2.20** (Scheme 2.11).



Scheme 2.11: *ee* Confirmation *via* Mosher esters.

Examination of the NMR data showed our resolved benzyl alcohol **2.16** had an *ee* of 99% (Figure 2.4). Two distinct peaks, relating to the CF_3, were readily apparent in the ^{19}F NMR spectrum of the Mosher ester of the racemic material; whilst the ^{19}F NMR spectrum of the enantioenriched material showed 2 peaks with a ratio of 99.3:0.7, giving an *ee* of 99%.

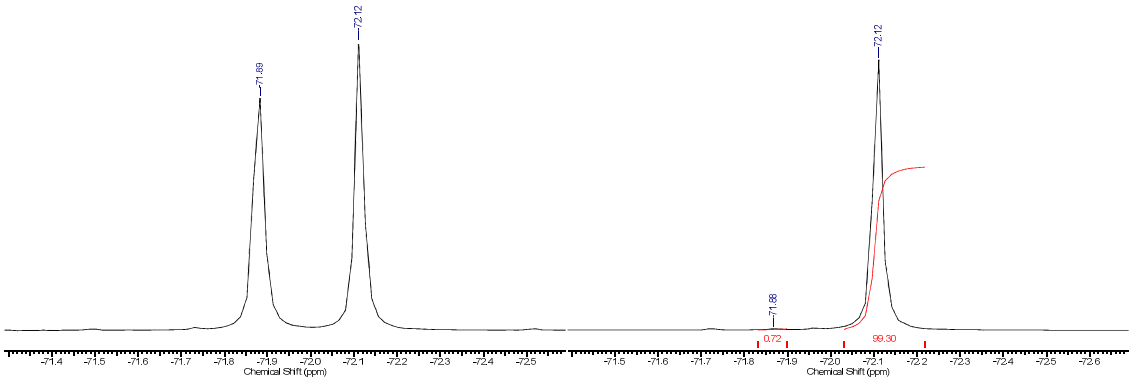


Figure 2.4: Mosher ester **2.20** ^{19}F NMR, racemate and 99% *ee* material, CF_3 peak.

The enantiopurity of the lactol **2.02** was also reconfirmed *via* the Mosher ester **2.21** to ensure no further epimerisation had occurred during the formylation and cyclisation. The ^{19}F NMR spectrum for the racemate can be seen to contain the expected four peaks relating to the CF_3 peak of the four possible diastereomers, in comparison with the spectrum for the enantiopure material, which displays

only two readily discernable CF_3 peaks, one for each of the two anomers (Figure 2.5). This therefore proves the stereochemical integrity at C4 is conserved through the steps following the stereoselective resolution.

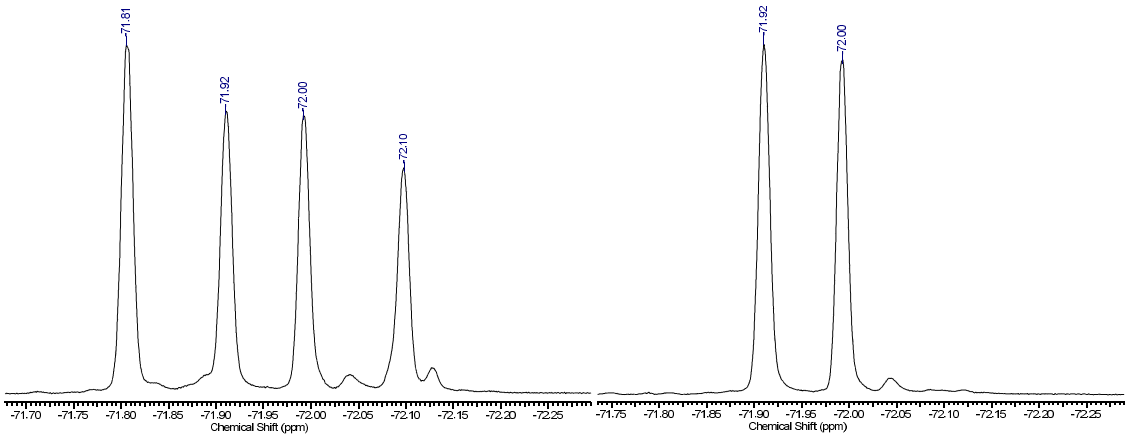
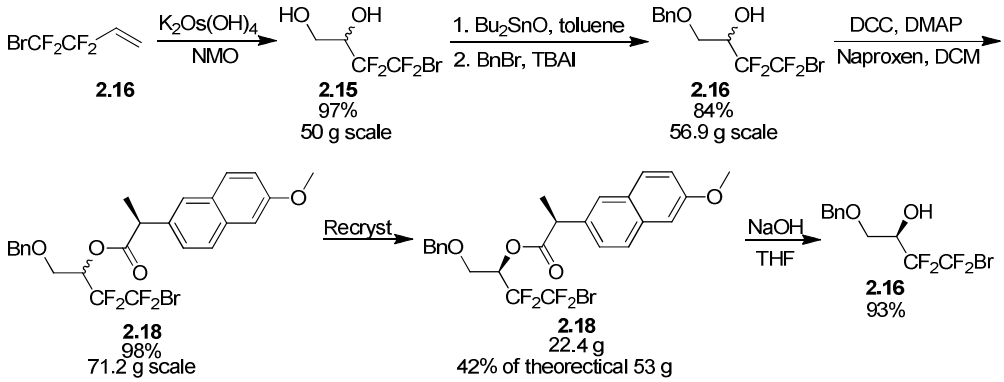


Figure 2.5: Mosher ester **2.21** ^{19}F NMR, racemate and enantiopure material, CF_3 peak.

*2.4.3 Upscaling of the Tetrafluororibose Intermediate **2.16***

Due to the prohibitive cost of the reagents for the Sharpless asymmetric dihydroxylation on large scale, in particular the $(DHQ)_2PYR$ ligand, the initial dihydroxylation of alkene **2.14** was carried out racemically on 50 g (0.24 mol) scale *via* standard Upjohn conditions. The resultant diol **2.15** was sufficiently pure to be carried through without further purification.



Scheme 2.12: Scale-up of tetrafluoroalcohol **2.16**.

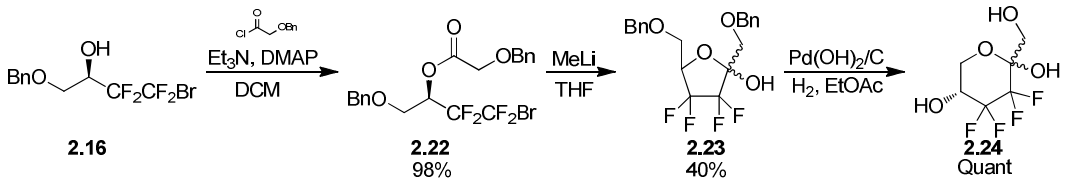
The subsequent benzylation and naproxen ester formation, both purified by MPC, went smoothly. The selective recrystallisation of the desired naproxen ester diastereomer **2.18** from the racemic mixture furnished a yield of 42% of the available diastereomerically pure material. Unfortunately this low recovery negated the saving made from performing the dihydroxylation racemically.

The use of the cheaper $(DHQ)_2PHAL$ ligand only affords diol **2.15** with an *ee* of 54%,[65] representing a significant drop in comparison to the 78% *ee* obtained when $(DHQ)_2PYR$ is used. However, as $(DHQ)_2PHAL$ is approximately half the price of $(DHQ)_2PYR$ this could potentially be more cost effective.

Deprotection of the remaining unresolved naproxen ester **2.18**, now enriched with the undesired enantiomer, followed by resolution with the enantiomeric (*R*)-naproxen would have potential as another solution. However (*R*)-naproxen is not as readily available and is significantly more expensive than (*S*)-naproxen.

2.5 Synthesis of Enantiopure 2,2,3,3-Tetrafluorofructose 2.24

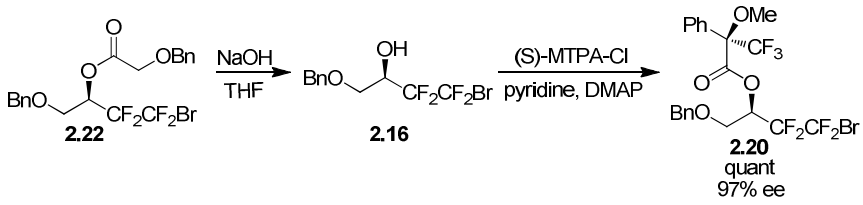
With the 99% *ee* tetrafluorobenzyl alcohol **2.16** in hand, enantioselective synthesis of tetrafluorofructose **2.24** was undertaken, which had previously been carried out within the group in an enantioenriched fashion.[66]



Scheme 2.13: Synthesis of 2,2,3,3-tetrafluorofructose **2.24**

Esterification of alcohol **2.16** proceeds smoothly with benzyloxyacetyl chloride in 98% yield. Ester **2.22** is then cyclised *via* anionic bromine-lithium exchange to afford the protected furanose **2.23**. Debenzylation then furnishes the tetrafluorofructose **2.24** quantitatively, which has undergone isomerisation to the more thermodynamically stable pyranose form.

The enantiopurity of ester **2.22** was verified by saponification of the ester back to alcohol **2.16** using NaOH/THF, conditions known from the saponification of naproxen ester **2.18** not to induce epimerisation. Derivitisation to the Mosher ester was then undertaken.



Scheme 2.14: Determination of *ee* of ester **2.22**.

Analysis of the ^{19}F NMR of the enantioenriched Mosher ester **2.20** derived from ester **2.22**, showed the *ee* of the benzyl alcohol **2.16** was 97% (Figure 2.6).

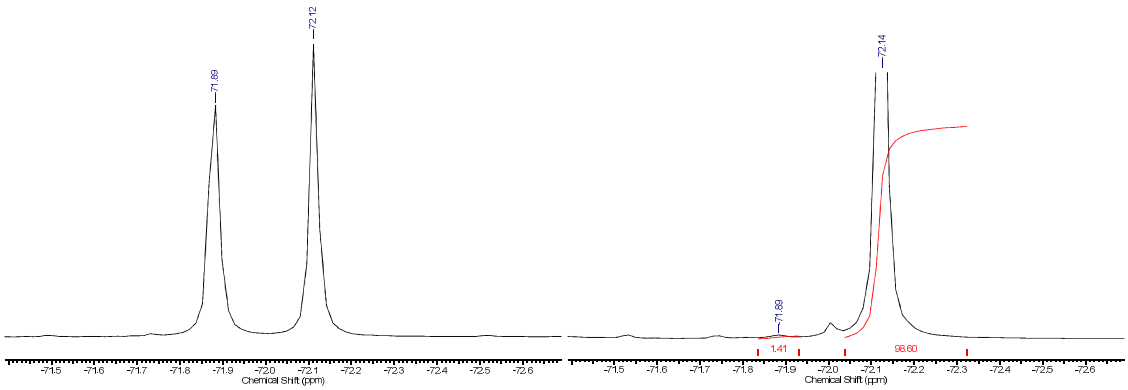


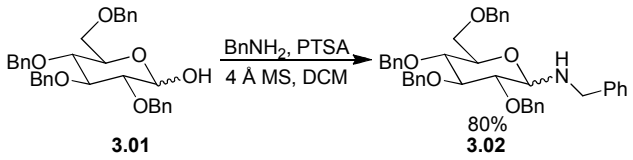
Figure 2.6: Mosher ester **2.20** ^{19}F NMR, racemate and enantiopure material, CF_3 peak.

3 Fluoronucleoside Formation From Aminoglycosides

3.1 Aminoglycosylations

3.1.1 Aminoglycosides

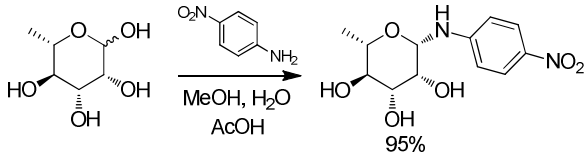
Aminoglycosylations are well known in the literature. Examples of aminoglycosylations in acidic media include that of Cipolla *et al*[70,71] where the reaction of tetrabenzylglucose **3.01** and benzylamine in anhydrous acidic conditions yielded the aminoglycoside **3.02** in 80% yield as a mixture of anomers (Scheme 3.1).



3.01 **3.02**

Scheme 3.1: Aminoglycosylation of tetrabenzylglucose **3.01**.

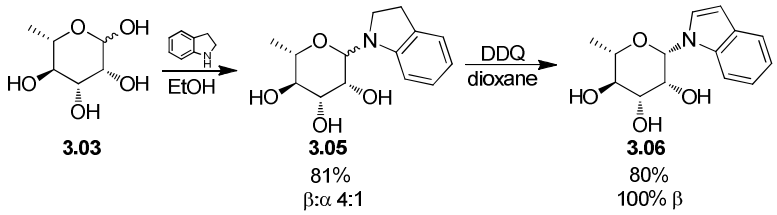
Another example is that of Mons and Fleet[72] in which unprotected L-rhamnose **3.03** is reacted with *p*-nitroaniline under aqueous acidic conditions to form the more thermodynamically stable β-aminoglycoside **3.04** in 95% yield after refluxing for just 3 min (Scheme 3.2).



3.03 **3.04**

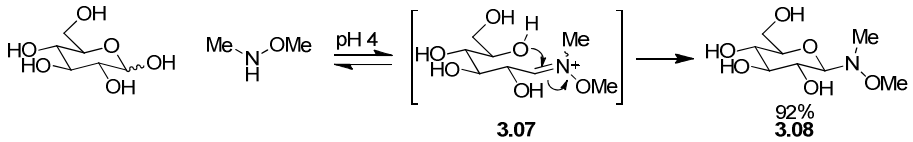
Scheme 3.2: Aminoglycosylation of L-rhamnose **3.03** with *p*-nitroaniline.

Libnow *et al*[73] undertook a similar aminoglycosylation of L-rhamnose **3.03** with indoline but under neutral conditions, to afford the aminoglycoside **3.05** in 81% yield as a 1:4 α/β anomeric mixture (Scheme 3.3). The subsequent dehydrogenation to the indole derivative did however furnish the pure β aminoglycoside **3.06** in 80% conversion.



Scheme 3.3: Aminoglycosylation of L-rhamnose **3.03** with indoline.

The reaction of glucose with *N*,*O*-dimethylhydroxylamine selectively yields the β-glucosylamine **3.08** with >96% *de* in 92% (Scheme 3.4).[74] The same reaction with galactose yields the corresponding β-galactosylamine in 80% yield, but in contrast the reaction with mannose yields the α-mannosylamine in 60% yield. The lower yields for the galactose and mannose derivatives are due to the formation of, 20% and 13% respectively of the furanose derivatives.



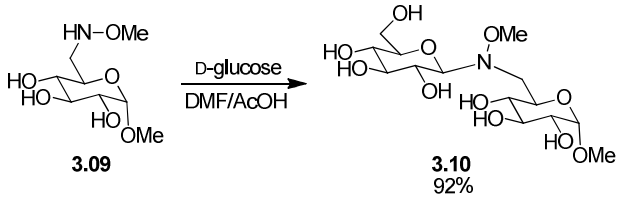
Scheme 3.4: Formation of hydroxylamine **3.08**.

The anomeric substituent almost exclusively occupies the more stable equatorial position, resulting in formation of the β anomer in high selectivity, due to the limited influence of the anomeric effect. The reaction proceeds under thermodynamic control, *via* an acyclic imine intermediate **3.07**. The existence of the acyclic intermediate was further supported by the *in situ* quenching of the reaction with $NaBH_3CN$ and subsequent isolation of the acyclic hydroxylamine.

The reaction of glucose with a secondary hydroxylamine leads to the corresponding cyclic glycosylamine **3.08**. In contrast, studies have shown that reaction with a primary hydroxylamine can give rise to a product existing as a mixture of the open-chain oxime and the closed-ring glycosylamine products. The ratio of open to closed forms does rely, in part, upon the sugar used. In solution, the oxime of arabinose exists solely in the acyclic form, in contrast to the oxime of glucose, which only comprises 47% of the open form in solution.[75,76] This further supports the existence of the acyclic iminium intermediate in the formation of these glycosylamines.

The stability of methoxyamine linked glycosylamines such as **3.08** has been investigated, with the glycosylamines found to hydrolyse under acidic conditions. Glycosylamines with an electron-rich monosaccharide were found to hydrolyse more quickly.[77,78]

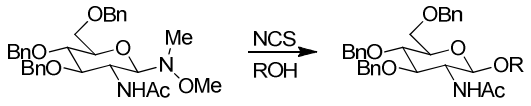
Peri *et al* further extended this aminoglycosylation methodology to include the formation of di- and tri-saccharides with methoxyamine linkages (Scheme 3.5).[79,80]



3.09 **3.10** 92%

Scheme 3.5: Formation of disaccharide **3.10**.

N,*O*-Dimethylhydroxylamine has also been evaluated as an anomeric protecting group, due to the ease of installation and it's compatibility with other functionalities. If arming protecting groups, such as benzyl, are used, this renders the hydroxylamine suitably activated for limited use as a leaving group in glycosylation reactions (Scheme 3.6), however further investigation is required to increase their reactivity to further the scope of this application.[81]



3.11

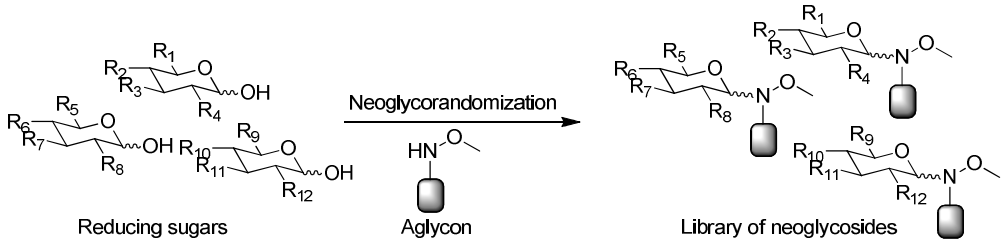
3.12 R = Me (62%)
3.13 R = Bu (54%)

Scheme 3.6: Glycosylation from hydroxylamine **3.11**.

3.1.2 Neoglycorandomization

Neoglycorandomization allows the formation of glycoside libraries *via* the chemoselective ligation of glycosidic bonds between unprotected reducing sugars and secondary alkoxyamine containing aglycons (Scheme 3.7).[82]

Thorson *et al* have synthesised a range of neoglycoside libraries of a range of natural products, with methoxyamine glycosidic linkages.



Scheme 3.7: Neoglycorandomization.

Many pharmaceutically relevant compounds are glycosylated, across a wide range of therapeutic areas (Figure 3.1) including the antibiotic erythromycin **3.14**, the anti-tumour agent staurosporine **3.15** and the cardiac glycoside digitoxin **3.16**.[83]

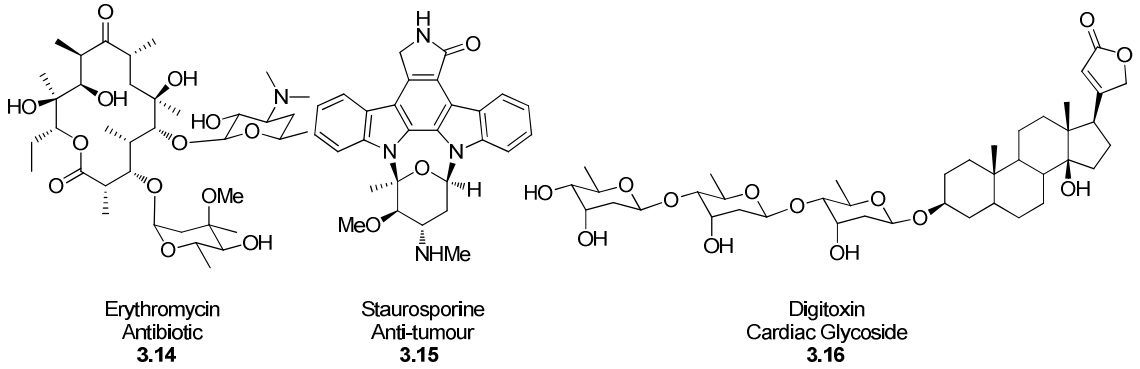
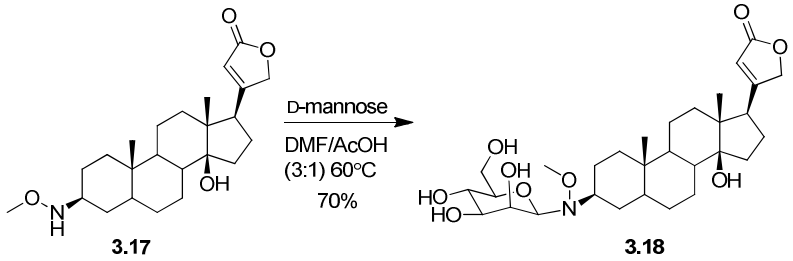


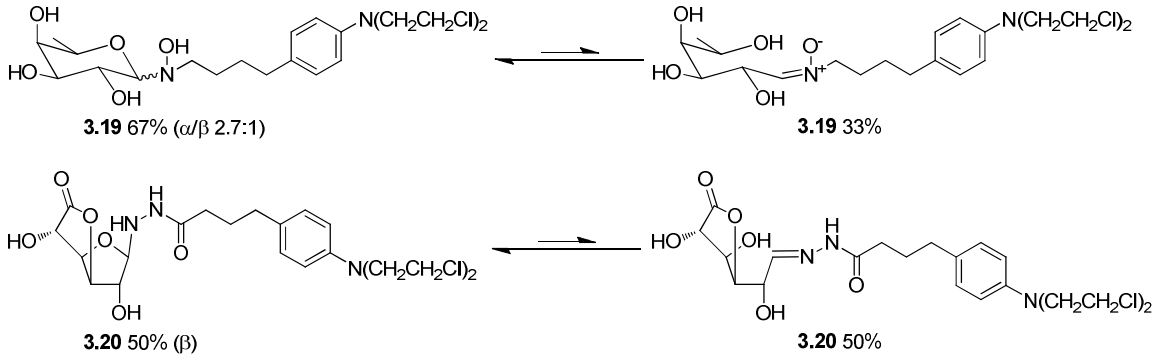
Figure 3.1: Glycosylated natural products.

An interesting case is that of digitoxin, a cardiac glycoside, which has also shown anti-tumour properties in *in vitro* studies. Digitoxin derivative **3.17**, was linked *via* a methoxyamine glycosidic linkage to D-mannose, the resultant glycoside **3.18** displayed an increased anti-tumour effect, but decreased cardiac glycoside function. Formed under thermodynamic control, the more stable pyranose sugar **3.18** is formed (Scheme 3.8).



Scheme 3.8: Glycosylation of digitoxin derivative **3.17**.

These cardiac glycosides exhibit a low chemical and enzymatic stability.[82] A range of neoglycosides were also synthesised based upon the antineoplastic compound chlorambucil and their stability investigated (Scheme 3.9).[84]



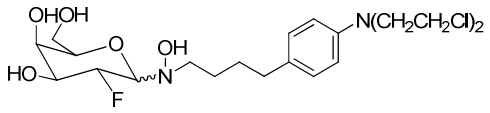
Scheme 3.9: Equilibrium of open and closed ring neoglycosides.

These were found to exist in equilibrium between their open and closed forms, where the equilibrium position was dependent upon the type of sugar and the nature of the glycosidic linkage. The open forms were evident from the low field signals indicative of the imine double bond. For example the D-fucose derived hydroxylamine **3.19** exists predominantly in the closed form, with just 33% existing in the open nitrone form. In contrast the equivalent D-threose derived analogue exists exclusively in the open nitrone form.

Similarly when a hydrazide aglycon was utilised, the resultant glycosides also adopted mixtures of the open and closed ring forms. For example the D-glucoronolactone derived **3.20** exists as a 50:50 mixture of the open and closed forms (Scheme 3.9). However in contrast the D-fucoside analogue exists

exclusively in the closed form and the D-threose derived analogue exclusively in the open imino form.

To our knowledge the only example of the direct aminoglycosylation of a 2-deoxy-2-fluorosugar is the synthesis of the 2-deoxy-2-fluoro-D-glucose chlorambucil glycoside **3.21** (Figure 3.2).[84]



3.21

Figure 3.2: 2-deoxy-2-fluoro-D-glucose chlorambucil derivative **3.21**.

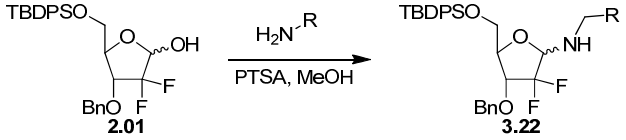
3.2 Aminoglycosylations with Primary and Secondary Amines

3.2.1 Optimisation of the Reaction of 2-Deoxy-2,2-difluororibose

Initial efforts in the synthesis of difluorinated aminoglycosides from difluororibose **2.01** were hampered by problems in product isolation. Despite evidence of product formation by crude NMR, recovered starting material was the major product of isolation after chromatography (entries 1–4). Use of basic alumina as the chromatographic agent afforded a slightly increased yield of 16% of aminoglycoside **3.22b** (entry 5). However, after increase of napthylamine to 3 equiv and the use of stoichiometric PTSA, near complete conversion to the desired glycosylamine **3.22a** was observed by crude NMR. It was evident, from the problems encountered in the isolation of the aminoglycosides that they did not display the chemical stability that it was hoped the 2,2-difluorination would impart. Doping of the column eluent with 0.5% Et_3N was found to be sufficient to suppress the decomposition of the product glycosylamines on silica, allowing the isolation of napthylglycosylamine **3.22a** in 85% yield (entry 6). The PMB-glycosylamine **3.22b** (entry 8) and phenylglycosylamine **3.22c** (entry 7) were subsequently isolated in 98% and 95% yield respectively using the same method. In an attempt to reduce the quantity of amine used, PTSA was substituted for PPTS and the amount of

amine reduced to 2 equiv. Whilst a decrease to 75% yield was observed, it was not so significant to suggest further optimisation utilising a reduced quantity of amine would not be possible.

Table 3.1: Difluorinated aminoglycosylations - optimisation.



Entry	Amine	Product	Equiv Amine	Acid	Temp (℃)	Time (h)	Column	Yield[d]
1	napthyl	N/A	1	none	RT	22	silica	0%
2	PMB	N/A	1	none	RT	22	silica	0%
3	napthyl	**3.22a**	2	none	RT	20	silica	11%
4	napthyl	N/A	1	PTSA[a]	reflux	4	silica	0%
5	PMB	**3.22b**	1	none	RT	30	alumina	16%
6	napthyl	**3.22a**	3	PTSA[b]	reflux	4	basified silica[c]	85%
7	aniline	**3.22c**	3	PTSA[b]	reflux	4.5	basified silica[c]	95%
8	PMB	**3.22b**	3	PTSA[b]	reflux	5	basified silica[c]	98%
9	aniline	**3.22c**	2	PPTS[b]	reflux	6	basified silica[c]	75%

a: catalytic; b: 1 equiv; c: 0.5% Et_3N added to column eluent; d: isolated yield.

The aminoglycosides were found to largely exist in the expected ring-closed form, however NMR analysis also indicated the presence of trace amounts of the open form.

3.2.2 Investigation of the Scope of the Reaction

A wider range of amines were subsequently trialled to investigate the scope of the method and the tolerance to different functionalities (Table 3.2). Reaction

with simple unhindered primary amines proceeded smoothly in high yields of 85–98%, affording 1:1 mixtures of anomers (entries 1–5).

2,2,2-Trifluoroethylamine is deactivated due to the presence of the electon-withdrawing trifluoromethyl moiety β to the NH_2, rendering it significantly less nucleophilic. This is demonstrated by the difference in pK_a values for ethyl amine (10.6)[85] and 2,2,2-trifluoroethylamine (5.7).[86] However despite this, a pleasing 75% yield of aminoglycoside **3.22f** was obtained when 2,2,2-trifluoroethylamine was utilised (entry 6).

The aminoglycosylation with 4,6-diamino-2-(thiomethyl)pyrimidine (entry 7) proceeded in a satisfying 70% yield, although slightly more forcing conditions were required. This result was especially pleasing as substituted pyrimidines such as that in **3.22g** can be used as a starting point for the construction of purine nucleobases.

An increase in steric bulk of the amine had a marked effect upon the outcome of the reaction, as demonstrated by the use of an α-branched methylamine (entry 8). Here the aminoglycoside **3.22h** yield dropped to a disappointing 46%.

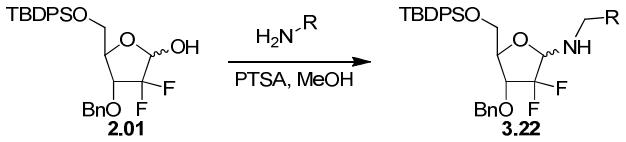
With this result regarding increased steric bulk in mind, the possibility of reaction with secondary amines was explored. From those secondary amines trialled, piperidine proved to be the best (entry 10), most likely as the substituents are tethered in the ring, reducing the steric hindrance. As the hindrance was increased with the use of *N*-methyl allyl amine (entry 11) the yield decreased. When the very hindered diisopropylamine was utilised (entry 12), none of the desired product was isolated.

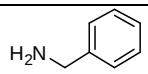
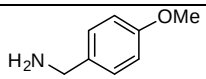
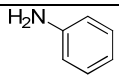
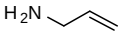
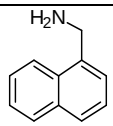
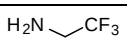
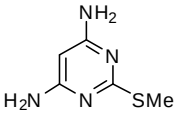
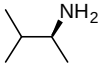
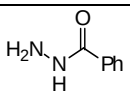
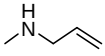
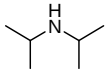
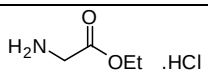
Also notable was the increase in the anomeric ratio obtained as the steric bulk of the amine was increased, from 1:1 for **3.22a**-**e** to 1:1.5 for **3.22h** and 1:3 for the glycosylamines derived from secondary amines, **3.22j** and **3.22k**.

The desired aminoglycoside product was not isolated from the reaction with glycine methyl ester (entry 13). This is believed to be due to deprotection of the

5-O-TBDPS ether, most likely due to the increased acidity of the reaction mixture, as the amine was in the HCl form.

Table 3.2: Difluorinated aminoglycosylations - scope of the reaction.



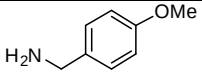
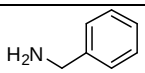
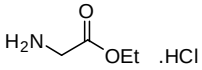
Entry	Amine	Product	Equiv Amine	Time	Yield[a]	Anomeric Ratio
1		**3.22d**	3	5 h	98%	1:1
2		**3.22b**	3	5 h	98%	1:1
3		**3.22c**	3	5 h	95%	1:1
4		**3.22e**	3	5 h	88%	1:1
5		**3.22a**	3	4 h	85%	1:1
6		**3.22f**	3	18 h	75%	1:1.3
7		**3.22g**	5	3 d	70%	1:1.2
8		**3.22h**	3	22 h	46%	1:1.5
9		**3.22i**	3	4 h	90%	1:2
10		**3.22j**	3	22 h	73%	1:3
11		**3.22k**	3	22 h	60%	1:2.9
12		N/A	3	22 h	0%	N/A
13		N/A	3	29 h	0%	N/A

a: Isolated yield.

3.2.3 Reaction with Tetrafluororibose

The optimal conditions developed for the condensation of difluororibose **2.01** and amines were applied to the tetrafluororibose **2.02**, with a smaller range of amine substrates (Table 3.3). Reaction with PMB-amine (entry 1) and benzylamine (entry 2) proceeded as expected in 93% and 79% yield respectively. However, no desired product was isolated from the reaction with glycine methyl ester (entry 3), despite apparent complete conversion by crude NMR. This result served to reconfirm the instability of the glycosylamines to silica, as due to insolubility, the crude product from this reaction was evaporated onto silica before chromatography and most likely decomposed at this point.

Table 3.3: Tetrafluorinated aminoglycosylations.

Entry	Amine	Product	Equiv Amine	Time	Yield[a]	Anomeric Ratio
1		**3.23a**	3	5	93%	1:1
2		**3.23b**	3	5	79%	1:1.5
3		N/A	3	96	0%	N/A

a: isolated yield.

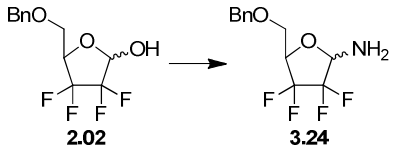
3.3 Investigations into the Synthesis of Primary Aminoglycosides

3.3.1 Synthesis of Primary Tetrafluoroaminoglycoside

It was discovered that it was also possible to synthesise the primary aminoglycoside **3.24** from tetrafluororibose **2.02** (Table 3.4). Stirring in NH_3 (aq) with or without EtOH only furnished low yields of the desired aminoglycoside **3.24** (entry 1–2). When tetrafluororibose **2.02** was stirred in a saturated solution of NH_4HCO_3 for 7 days, with MeOH as solvent, only a very small amount of

aminoglycoside **3.24** formed (entry 3). However, when water was added to the solvent, near quantitative conversion was obtained (entry 4–5).

Table 3.4: Primary tetrafluoroaminoglycoside **3.24** synthesis.



Entry	Reagent	Solvent	Time	Yield[a]
1	NH_3 (aq)	EtOH	6 h	29%
2	NH_3 (aq)	None	3 d	35%
3	NH_4HCO_3	MeOH	7 d	Negligible
4	NH_4HCO_3	1:1 H_2O/MeOH	7 d	98%
5	NH_4HCO_3	H_2O	7 d	Quantitative

a: isolated yield.

Glycosylamine **3.24** was found to be crystalline and X-ray crystallographic analysis revealed the crystalline material to be composed exclusively of the β anomer (Figure 3.3). As glycosylamine **3.24** exists as an anomeric mixture in solution, a dynamic crystallisation must occur.

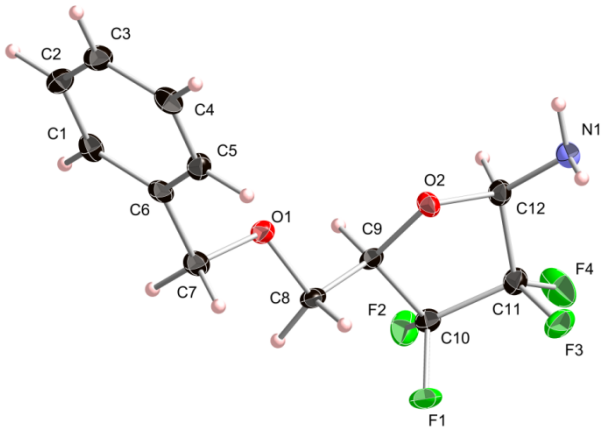
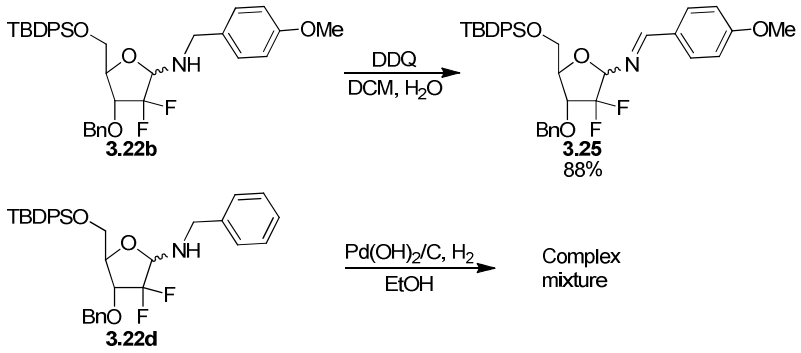


Figure 3.3: Primary tetrafluoroaminoglycoside **3.24β**.

3.3.2 Synthesis of Primary Difluoroaminoglycoside

Despite success in the synthesis of the primary tetrafluoroaminoglycoside **3.24**, attempts to synthesise the analogous primary difluoroaminoglycoside *via* the same methods, with NH_3 (aq) or NH_4HCO_3, were unsuccessful.



Scheme 3.10: Attempted methods to synthesise the primary difluoroaminoglycoside.

Attempts were therefore made to synthesise the primary aminoglycoside *via* deprotection of an appropriate aminoglycoside (Scheme 3.10). Deprotection of the PMB glycosylamine **3.22b** resulted in isolation of the imine oxidation product **3.25**. Similarly, attempted hydrogenation of the benzyl glycosylamine **3.22d** only yielded a complex mixture.

3.4 NMR Assignment of the Difluoroglycosylamines

In the ^{19}F NMR spectra of the difluoroaminoglycosides **3.22**, there are four sets of multiplets, two for each anomer, one corresponding to each of the ^{19}F atoms. As can be clearly seen from the ^{19}F-^{19}F COSY spectra of **3.22b** and **3.22d**, the lowest and highest field multiplets correspond to one anomer, whilst the two central multiplets correspond to the other anomer (Figure 3.4). Unfortunately it has not been possible to assign each to a specific anomer as yet. The H–F coupling constants do not provide conclusive evidence for anomeric assignment and use of GOESY NMR was not possible due to overlap of the relevant peaks in the ^{1}H NMR.

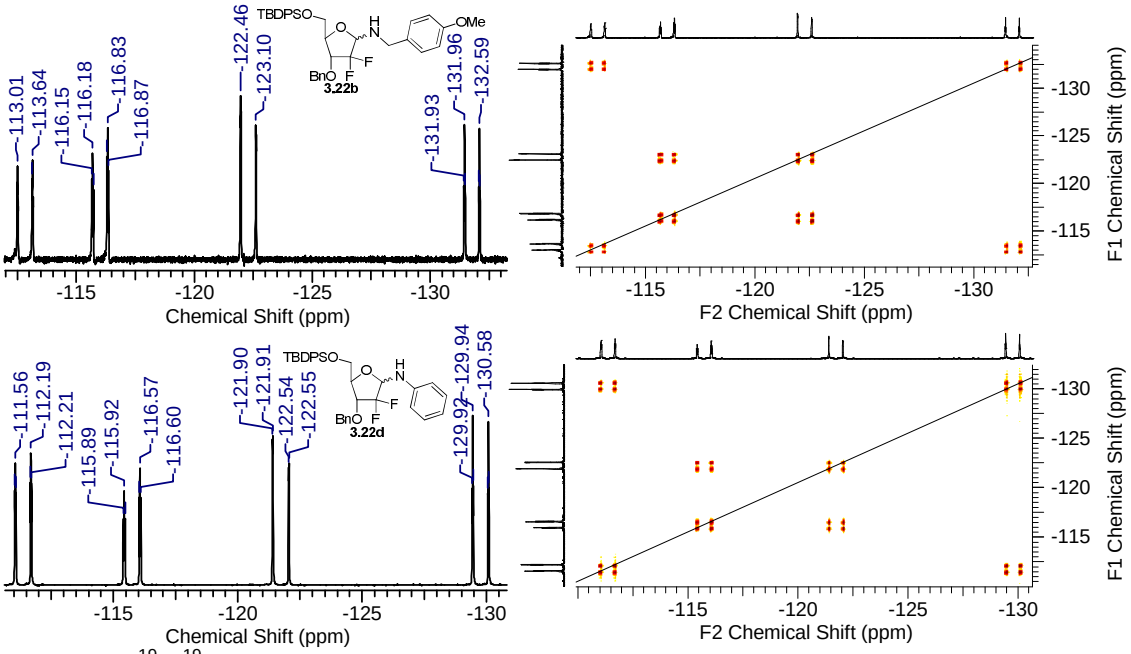


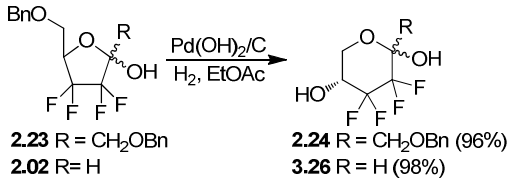
Figure 3.4: ^{19}F-^{19}F COSY of difluoroaminoglycosylamines **3.22b** and **3.22d**.

3.5 Stability of the Difluoroaminoglycosides

3.5.1 Furanose to Pyranose Isomerisation

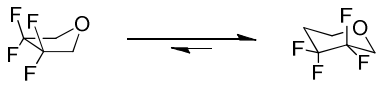
We investigated the robustness of the aminoglycosides with respect to anomeric equilibration and hydrolysis of the anomeric substituent. It was anticipated that the fluorination at C2 would exert a stabilising influence, as any protonation/carbenium ion formation would be hampered by the strong electron withdrawing effect.

However, research in the group had already found that furanose to pyranose isomerisation of tetrafluorinated ribose **2.02** is very fast (Scheme 3.11), indicating ring opening readily occurs.[65,66]



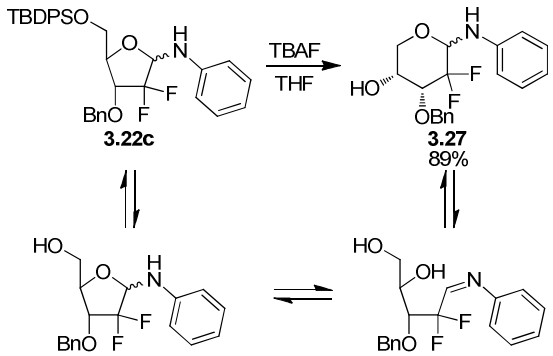
Scheme 3.11: Furanose to pyranose isomerisation.

This was explained by the near-eclipsed C–F bonds at the furanose ring, leading to unfavourable stereoelectronic repulsion between the electron dense fluorines. In the pyranose C–F bonds are staggered, reducing the stereoelectronic repulsion (Scheme 3.12). The decreased stereoelectronic repulsion encountered in the pyranose helps drive the ring opening of the furanose and subsequent isomerisation to the pyranose.



Scheme 3.12: Comparison of stereoelectronic repulsion between fluorines in furanose to pyranose isomerisation (other substituents omitted for clarity).

The corresponding process for the aminoglycosides could be studied by deprotection of the 5-O-TBDPS ether in **3.22c** (Scheme 3.13). Indeed treatment of **3.22c** resulted in rearrangement to the pyranose, affording aminoglycoside **3.27** as a 1:16 anomeric ratio.



Scheme 3.13: 5-OH deprotection.

As the equilibrium is under thermodynamic control, the anomeric substituent will occupy the equatorial position, as the anomeric affect is diminished within aminoglycosides,[87] resulting in the formation of a pentapyranose. Due to the absence of a conformationally locking group such as a CH_2OH and the *cis* substitution of the remaining substituents, there are 2 potential chair conformations in which pyranose **3.27** could exist, either the $^4C_1$ or $^1C_4$ form (Figure 3.5). Analysis of NMR coupling constants enables the elucidation of the conformation present in this instance.

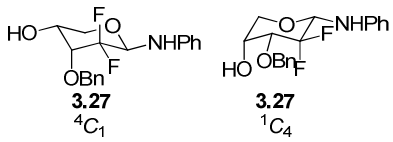


Figure 3.5: Possible conformations of pyranose **3.27**.

The H5 protons appear as a triplet (J = 10.9 Hz) and a dddd (J = 11.3, 5.3, 2.1, 1.0 Hz) respectively. The largest J value in each instance corresponds to the geminal H–H coupling, whilst the 2nd coupling of 10.9 Hz for the lower field H5 corresponds to a $^{3}J_{H5ax\text{-}H4ax}$ coupling. The coupling of 5.3 Hz for the higher field H5 corresponds to a $^{3}J_{H5eq\text{-}H4ax}$, hence, H4 must exist in the axial position. This indicates the existence of a $^{4}C_{1}$ conformation. The remaining J values of 2.1 and 1.0 Hz are long range couplings from $^{5}J_{H5eq\text{-}F2}$ and $^{4}J_{H3\text{-}H5}$ respectively, shown by the disappearance of the 2.1 Hz but not the 1.0 Hz in the $^{1}H\{^{19}F\}$ NMR spectrum.

The Linclau group has an interest in diagnostic NMR data relating to fluorine atoms in relation to conformational analysis.[88] Indeed the conformational assignment above was confirmed by a similar analysis of the $J_{C\text{-}F}$ values. It is known that the orientation of the substituents on a carbon has a marked effect upon the $^{2}J_{C\text{-}F}$ values. Typical $^{2}J_{C3\text{-}F}$ values of 2-deoxy-2-fluoro substituted carbohydrates are shown in Figure 3.6Figure 3.6.[89]

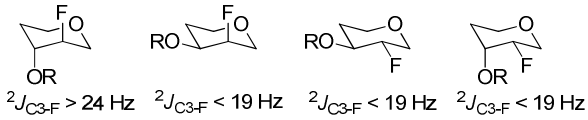


Figure 3.6: Typical $^{2}J_{C3\text{-}F}$ coupling constants.[89]

If $^{2}J_{C3\text{-}F}$ > 24 Hz this is known to correspond to a *trans*-diaxial orientation of substituents and if $^{2}J_{C3\text{-}F}$ < 19 Hz this is known to correspond to a *trans*-diequatorial or *cis* orientation of substituents.[89] For pyranose **3.27** the $^{2}J_{C3\text{-}F}$ are 32.1 and 19.4 Hz, indicative of a *trans*-diaxial and a *cis* configuration, therefore the C3 substituent would be axial, providing further evidence for the $^{4}C_{1}$ conformation.

There are few examples of 2-deoxy-2-fluoro-aminosugars in the literature, therefore there is insufficient data available for unequivocal conclusions to be drawn.

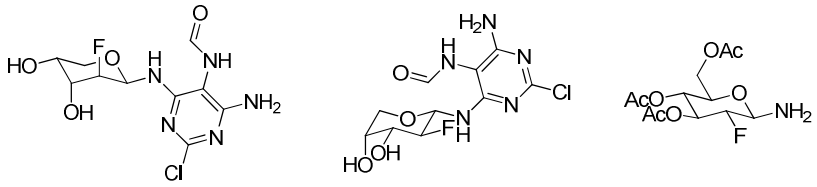


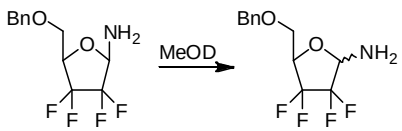
Figure 3.7: $^{2}J_{C1\text{-}F}$ coupling constants in 2-deoxy-2-fluoro-aminosugars.[90,91]

In the examples found (Figure 3.7), a *cis* orientation with F2 in the axial position, gives a $^{2}J_{C1\text{-}F}$ coupling of 15.8 Hz. By comparison substituents with a *trans*-diequatorial relationship lead to a $^{2}J_{C1\text{-}F}$ coupling in the region of 20–24 Hz. No example of a fluorinated aminoglycoside with an axial anomeric substituent was available. For pyranose **3.27**, $^{2}J_{C1\text{-}F}$ are 26.2 and 19.4 Hz, 26.2 Hz falls close to the expected range for *trans*-diequatorial substituents, whilst 19.4 Hz is only ~3 Hz larger than the values seen for a *cis* orientation where F2 is axial. Hence, analysis of the $^{2}J_{C1\text{-}F}$ values indicates that the anomeric substituent is in the equatorial position, further supporting the proposed $^{4}C_{1}$ conformation.

H1 is observed as a dd (J = 17.8, 10.2 Hz). The coupling of 10.2 Hz is the ^{3}J coupling to the exocyclic NH. The remaining 17.8 Hz coupling corresponds to the $^{3}J_{H1\text{-}F2ax}$. Analysis of the $^{1}H\{^{19}F\}$ spectrum confirmed this assignment, showing the disappearance of the coupling of 17.2 Hz.

3.5.2 Anomerisation

Primary aminoglycoside **3.24β** cleanly interconverts slowly between the α and β anomers in solution.



Scheme 3.14: Anomerisation of aminoglycoside **3.24β**.

The rate of this anomerisation was studied in MeOD at RT (Scheme 3.14). The initial sample, containing a 10:90 ratio of α:β anomers, was prepared in MeOD and ^{1}H and ^{19}F NMR spectra were taken at increasing intervals.

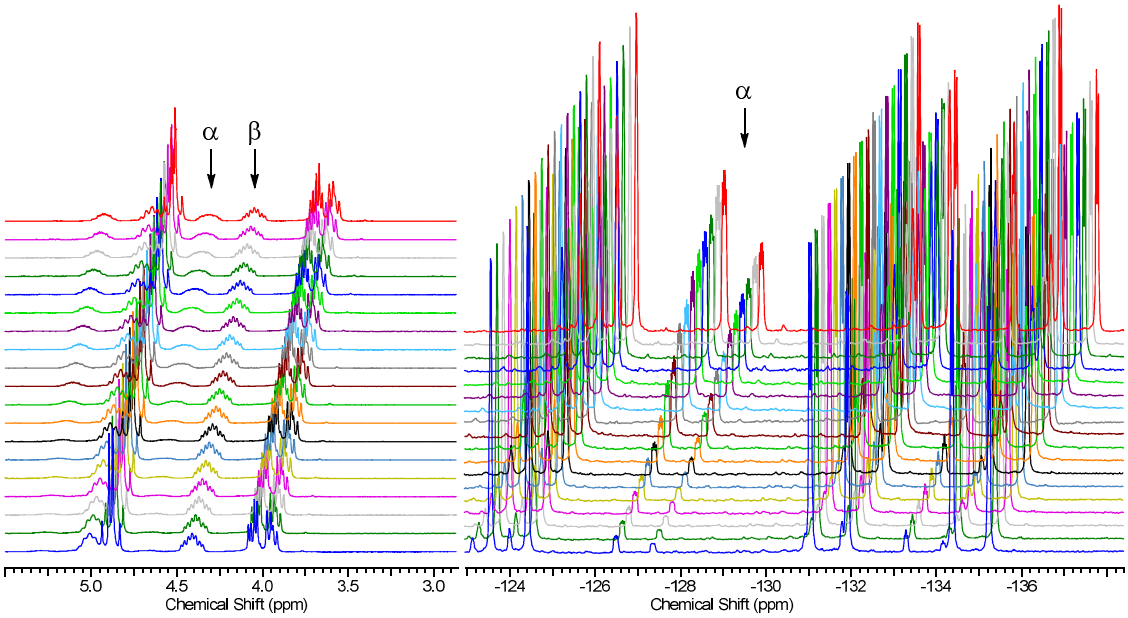
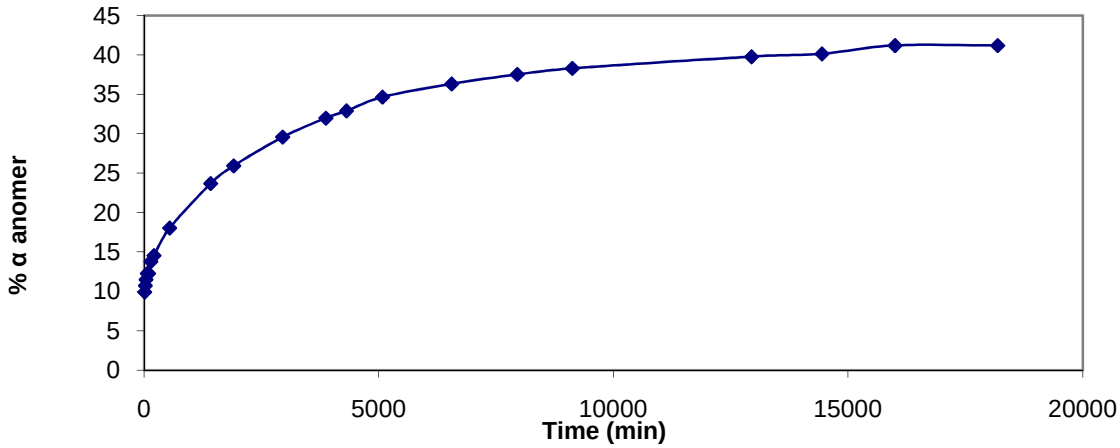


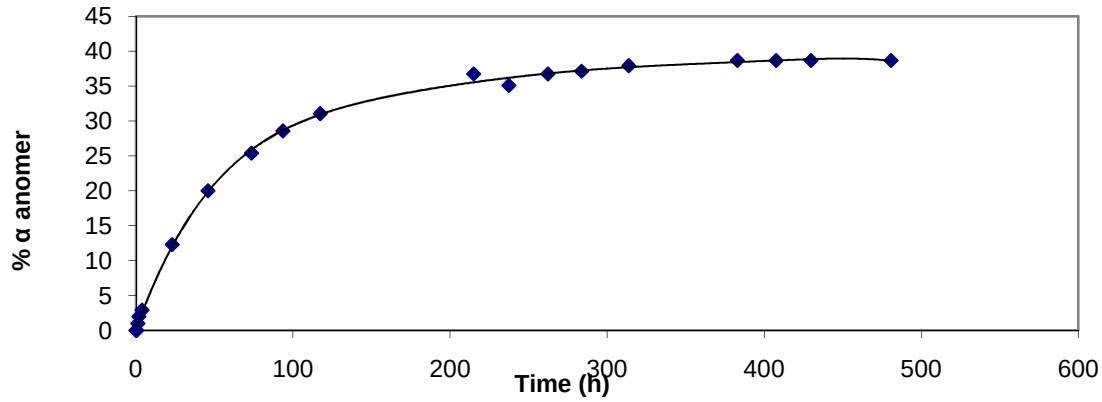
Figure 3.8: Overlays of ^{1}H and ^{19}F NMR as anomerisation of **3.24** progresses.

The increase of **3.24α** can be easily seen in the NMR overlays shown in Figure 3.8. The equilibrium point was found to be 41:59 α:β and this was attained after 11 days. The integrals from H4 were used to calculate the ratio of anomers present at each time point (Graph 3.1).

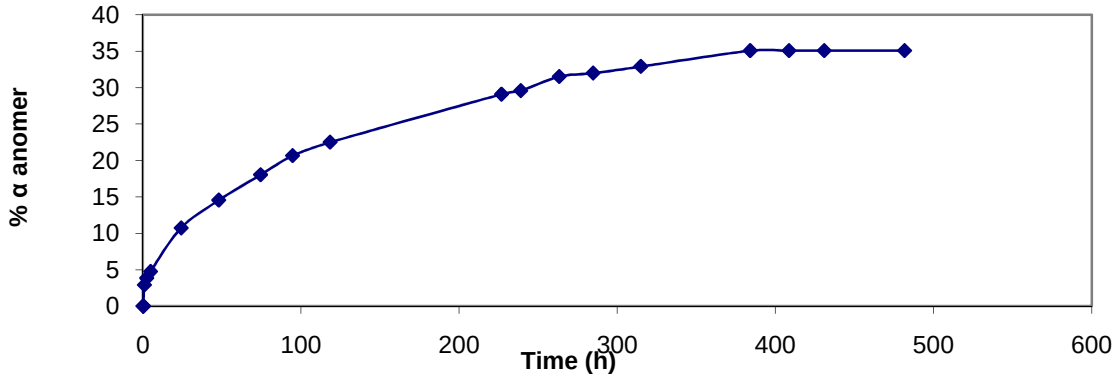


Graph 3.1: Rate of anomerisation of aminoglycoside **3.21β** in MeOD (% α/time).

The rate of anomerisation was also investigated in toluene-d_8 (Graph 3.2), CD_2Cl_2 (Graph 3.3), and CD_3CN. All exhibited different rates of anomerisation and different equilibrium points.



Graph 3.2: Anomerisation in toluene-d_8 (equilibrium after 16 days at 39:61 α:β).



Graph 3.3: Anomerisation in CD_2Cl_2 (equilibrium after 16 days at 35:65 α:β)

Most notable was the anomerisation in CD_3CN, in which after 12 days very little anomerisation had occurred, with an anomeric ratio of 4:96 α:β. Even after heating for 1.5 h at 60 ℃ the anomerisation rate o nly slightly increased to give an anomeric ratio of 7:93 α:β.

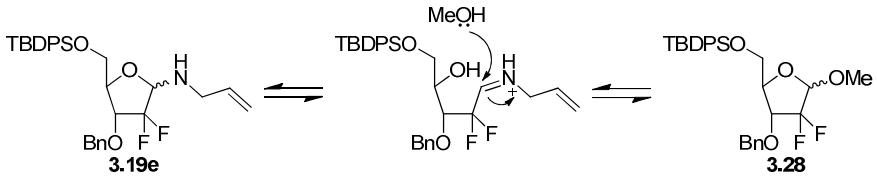
3.5.3 Stability of Difluoroaminoglycosides Under Acidic Conditions

Investigation of the stability of the difluoroaminoglycosides was required, especially due to the apparent instability to silica gel, rendering the need for

Et_3N to be added to chromatography solvents. The exemplar compound studied was the allylaminoglycoside **3.22e**.

3.5.3.1 Stability to CSA

Addition of 1 equiv of CSA to 50 mg of aminoglycoside **3.22e** in MeOH-d_4 at RT rapidly caused complete degradation to what is assumed to be the methanolysis **3.28** product (Figure 3.9). The degradation occurred in the time taken to mix the reagents and submit the resultant sample for the required NMR experiment (<10 min).



Scheme 3.15: Mechanism of decomposition to give methanolysis product.

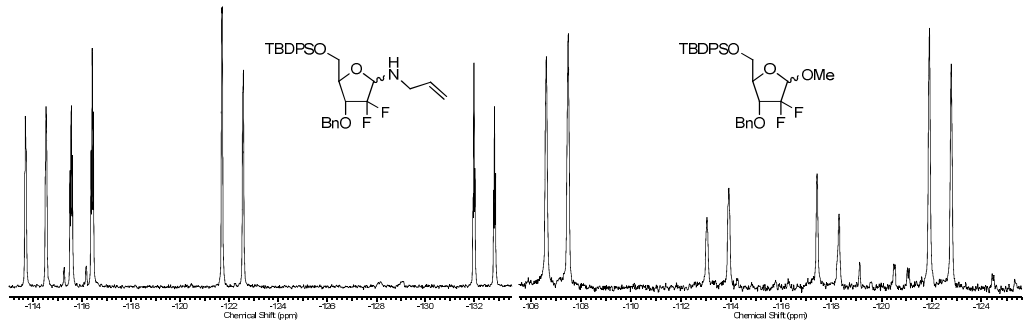


Figure 3.9: Addition of 1 equiv of CSA.

It is thought this decomposition is in equilibrium as outlined above (Scheme 3.15). Indeed after the sample was reduced *in vacuo* and subjected to column chromatography in an attempt to isolate the supposed methanolysis product **3.28**, a large proportion of the starting aminoglycoside **3.22e** was instead recovered. This indicates the reversal of the equilibrium as the MeOH was removed.

3.5.3.2 Stability to PTSA

Similar rapid decomposition was seen when CSA was substituted for PTSA. However, as PTSA has a molecule of water associated with it, this resulted in a change in the product of decomposition. The starting material used for the experiments with PTSA was the same allylglycosylamine **3.22e**, but as a 94:6 mixture with the lactol precursor **2.01** (Figure 3.10).

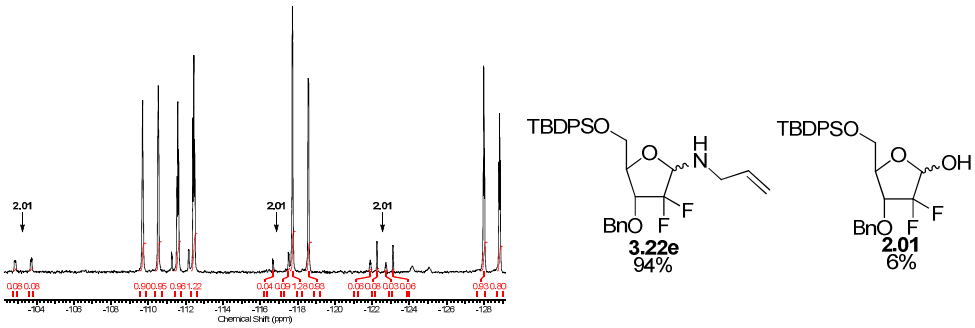


Figure 3.10: Before addition of PTSA.

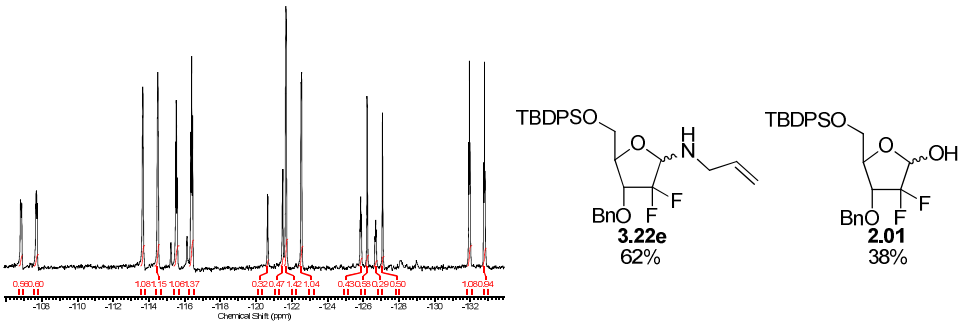


Figure 3.11: After addition of 0.28 equiv PTSA.

After the addition of 0.28 equiv of PTSA, the amount of lactol **2.01** present increased by 32%, a near stoichiometric increase, with respect to PTSA (Figure 3.11).

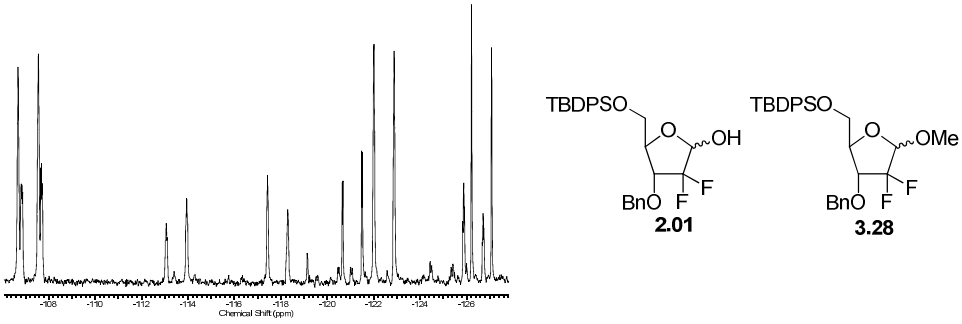


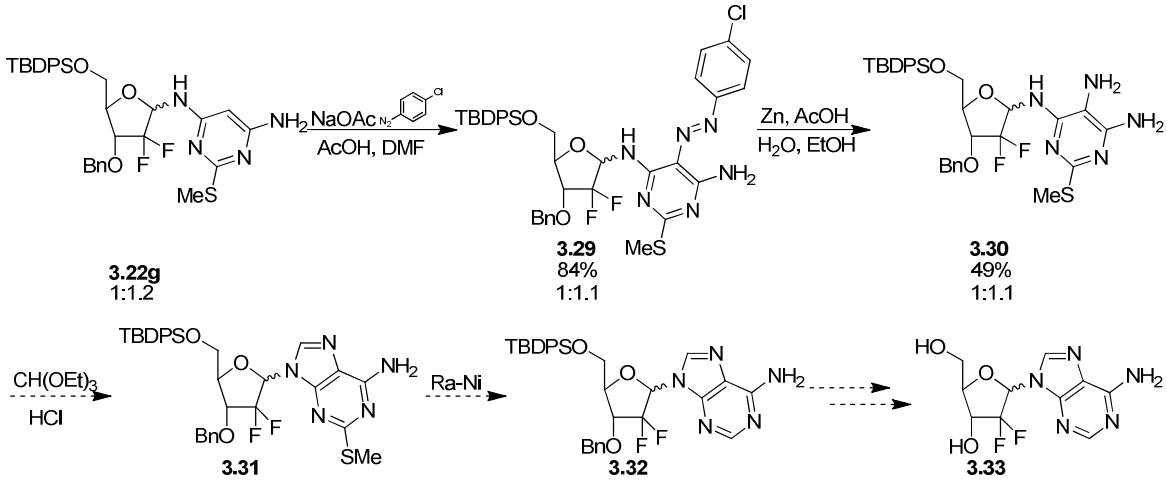
Figure 3.12: After addition of 1 equiv PTSA.

After addition of a further 0.62 equiv of PTSA, complete degradation of the starting allylglycosylamine was seen, giving rise to a mixture of lactol **2.01** and the proposed methanolysis product **3.28** (Figure 3.12).

3.6 Synthesis of 2′,2′-Difluoroadenosine 3.33

The aminopyrimidine **3.22g** is a suitable precursor for purines. Conversion of aminopyrimidine **3.22g** to the corresponding 2,2-difluoroadenosine **3.33** was investigated (Scheme 3.16).

Diazotisation at the unsubstituted 5 position of the pyrimidine proceeded smoothly to furnish **3.29** in 84% yield, with negligible anomerisation observed. Subsequent reduction with zinc in acidic medium afforded the amine **3.30**.

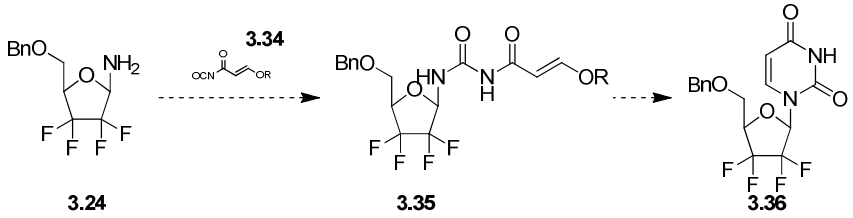


Scheme 3.16: Difluoroadenosine **3.33** synthesis.

From amine **3.30**, ring closure to the purine **3.31**, subsequent cleavage of the C2 thiomethyl and a global deprotection would yield 2′,2′-difluoroadenosine **3.33** as a mixture of anomers.

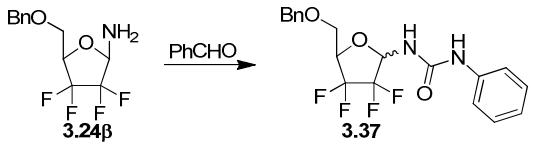
3.7 Initial Investigations into Nucleoside Synthesis From Primary Aminoglycoside 3.24

With the selectively crystallised tetrafluoroamine **3.24β** in hand, a stereoselective pyrimidine nucleoside synthesis *via* derivatisation with isocyanate **3.34** was investigated (Scheme 3.17). As NMR studies had shown a slow rate of anomerisation in MeOD, it was hoped the rate of reaction may prove to be significantly faster than that of anomerisation.



Scheme 3.17: Potential route to tetrafluorinated pyrimidines.

Initial studies were carried out with the simple commercially available phenylisocyanate in DCM (Scheme 3.18). Conversion to glycosylurea **3.37** was observed, however significant anomerisation was also observed during the reaction (Table 3.5, entry 1). Reducing the reaction time to 2 h from 22 h only decreased the conversion considerably and had little effect upon the anomerisation observed.



Scheme 3.18: Reaction with phenylisocyanate

Anomerisation studies with aminoglycoside **3.24β** were performed in a range of solvents (see section 3.5.2). Anomerisation was found to be slowest in CD_3CN,

therefore MeCN was used in subsequent reactions of glycosylamine **3.24β** and phenylisocyanate.

Despite the slow rate of anomerisation of glycosylamine **3.24β** in CD_3CN, when MeCN was utilised as the solvent in the reaction with phenylisocyanate, significant anomerisation was still observed (entries 2–3).

Table 3.5: Optimisation of reaction with phenylisocyanate.

Entry	Equiv PhNCO	Solvent	Temp (℃)	Time (h)	Yield[a]	Anomeric Ratio[b]
1	1.1	DCM	RT	22	50%	1:2
2	10	MeCN	RT	3	44%	1:2.4
3	10	MeCN	60	1	71%	1:2.5

a: isolated yield; b: calculated after column chromatography due to peak overlap in crude NMR.

An NMR in $CDCl_3$ was taken of the glycosylurea product **3.37** (anomeric ratio of 1:2.4). After 36 h in solution at RT, further NMR experiments showed no anomerisation had occurred. The $CDCl_3$ was removed *in vacuo* and replaced with CD_3CN, NMR showed the anomeric ratio remained at 1:2.4 after 3 d in solution at RT. These results show the glycosylurea **3.37** formed does not appear to undergo anomerisation in the reaction solvent, equally the anomerisation rate of the starting glycosylamine **3.24β** in CD_3CN is very slow, suggesting the anomerisation is therefore occurring during the reaction itself.

3.8 Conclusions

The desired aminoglycosylations have been developed in high yield. However the fluorinated aminoglycosides formed have proven to be significantly less stable to anomerisation and hydrolysis than expected, especially when the enhanced stability expected to be imparted by the 2,2-difluorination is considered.

The pyrimidyl aminoglycoside **3.22g** has been successfully utilised in the initial steps towards the construction of a difluorinated adenosine **3.33**.

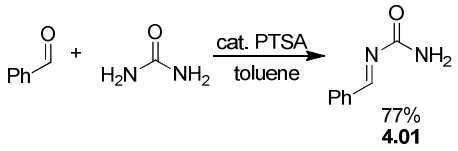
Initial studies into the anomerically selective construction of pyrimidine nucleobases from the primary tetrafluoroaminoglycoside **3.24β** showed little success, due to the significant anomerisation observed during reaction with model isocyanates.

4 Fluoronucleoside Formation From Glycosylureas

4.1 Glycosylureas

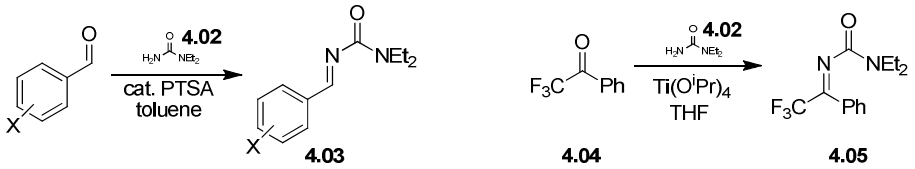
The condensation of aldehydes and ureas is not a commonly reported transformation. In particular there are few examples of this reaction incorporating α,α-fluorinated aldehydes.

Muñoz-Muñiz and Juaristi[92] undertook the condensation of benzaldehyde and urea with PTSA, to form benzylidene urea **4.01** in 77% yield (Scheme 4.1).



Scheme 4.1: Formation of benzylidene **4.01**.

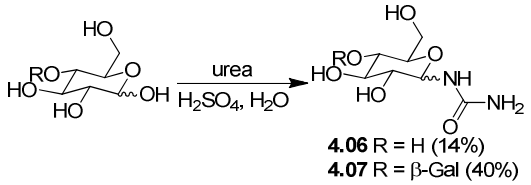
Armstrong *et al*[93] also used similar chemistry in their syntheses of oxaziridines. Substituted benzaldehydes reacted with *N*,*N*-diethylurea **4.02** in the presence of PTSA to give arylimines **4.03** with good conversion (isolated yields not available as crude compounds taken on). The trifluoroacetophenone **4.04** did not undergo the condensation reaction to form imine **4.05** under these conditions, however milder Lewis acid mediated conditions with $Ti(O^iPr)_4$ were found to be successful (Scheme 4.2).



Scheme 4.2: Armstrong syntheses of arylimines.

In more complex substrates such as carbohydrates, one of the earliest examples of glycosylurea formation is that of Schoorl from 1903.[94] He observed the reaction of glucose and urea in acidic aqueous medium yielded the glucosylurea **4.06** as a crystalline solid (Scheme 4.3). This reaction has been

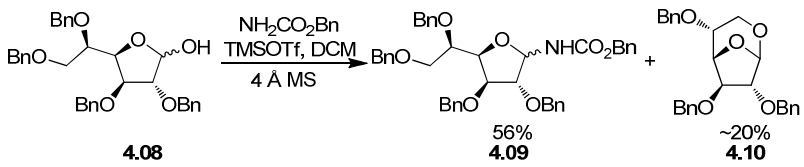
revisited with disagreement over the acid stability of the urea linkage formed. Benn and Jones[95] obtained a 14% yield of glucosylurea **4.06**, but include the *caveat* that this product was slowly hydrolysed by dil. H_2SO_4 at 0 ℃ and more readily so by dil. HNO_3 at 0 ℃. In contrast, Helm and Karchesy [96] report these same glycosylureas to be acid stable.



Scheme 4.3: Synthesis of simple glycosylureas.

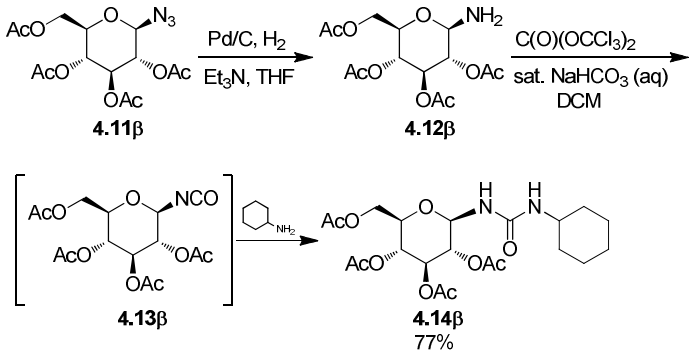
Cerbulis *et al*[97] studied this reaction further with lactose as the substrate and found the best yield of the desired lactosylurea **4.07** obtained was 40% (Scheme 4.3), when the reaction was performed at pH 2, with the majority of the remaining mass found to be unreacted lactose (50%).

Liautard *et al*[98,99] investigated the formation of glycosyl carbamates in the presence of Lewis acid, based upon the work of Sugiura *et al*.[100] Whilst Sugiura used the anomeric acetate as the reaction substrate, Liautard found this extra acetylation step to be unnecessary as using the free sugar **4.08** also afforded good conversion (Scheme 4.4). The desired glycosylamine **4.09** was isolated in 56% with 20% of the anhydride by-product **4.10** also obtained. Indeed, the authors reported reduced yields due to degradation of the products on silica gel, during purification.



Scheme 4.4: Synthesis of glycosyl carbamate **4.09**.

Many methods of glycosylurea formation are undertaken *via* an intermediary anomeric substituent. An example of this is the synthesis by Ichikawa *et al* of glucopyranosyl ureas *via* isocyanates (Scheme 4.5).[101]

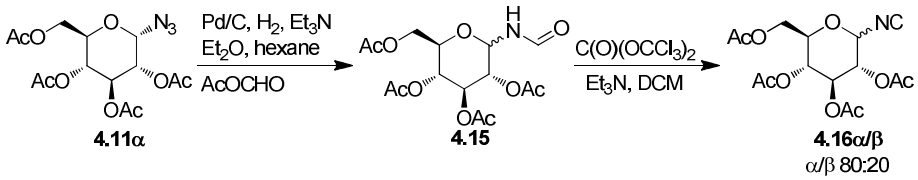


Scheme 4.5: Synthesis of β-D-glucopyranosyl urea **4.14β**.

From the β-azide **4.11β**, hydrogenation and treatment with triphosgene affords the reactive intermediate isocyanate **4.13β**. Reaction of the isocyanate **4.13β** with cyclohexylamine furnishes the β-glucopyranosyl urea **4.14β** in 77% yield.

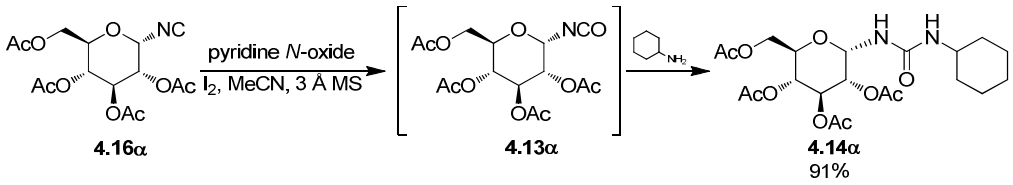
This method is unsuitable for the selective synthesis of the α-glucopyranosyl urea **4.14α** starting from the α-azide **4.11α**, as the intermediate glucosylamine **4.12α** readily anomerises to the more thermodynamically favourable β-amine.

The α-glucopyranosyl urea can instead be synthesised *via* the isocyanide **4.16**. α-Azide **4.11α** is hydrogenated, with minimal anomerisation due to the *in situ* trapping as formamide **4.15α/β**. Subsequent dehydration with triphosgene furnishes the isocyanide **4.16** as a separable 80:20 α/β mixture (Scheme 4.6).



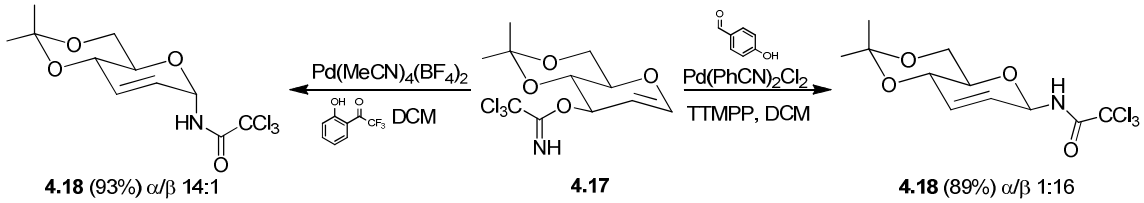
Scheme 4.6: Formation of isocyanide **4.16**.

Pyridine *N*-oxide oxidation afforded the desired isocyanate intermediate **4.13α**, which was reacted with cyclohexylamine, to form the α-glucopyranosyl urea **4.14α** with complete retention of configuration at the anomeric centre (Scheme 4.7).



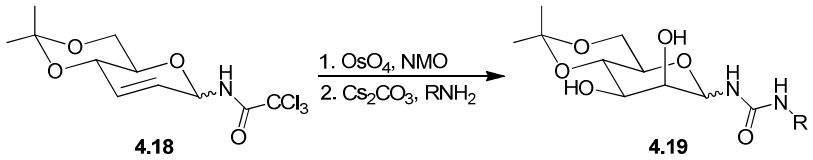
Scheme 4.7: Synthesis of α-D-glucopyranosyl urea **4.14α**.

Nguyen *et al* effected the stereoselective synthesis of α-glycosylureas *via* the palladium catalysed rearrangement of glycal imidates to trichloroacetimidates and their subsequent conversion to glycosylureas.[102]



Scheme 4.8: Stereoselective trichloroacetimidate rearrangement.

Glycal imidate **4.17** selectively rearranges to the β trichloroacetimidate **4.18β** under neutral palladium catalysed conditions, but to the α trichloroacetimidate **4.18α** under cationic conditions.

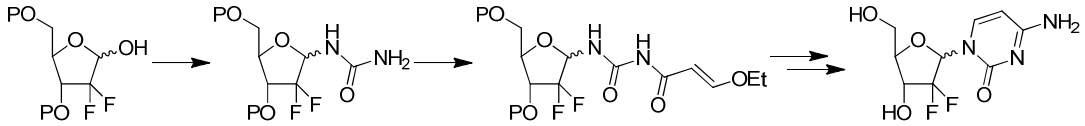


Scheme 4.9: Conversion of trichloroacetimidate **4.18** to glycosylureas.

Dihydroxylation, treatment with base furnishing an intermediate isocyanate, then treatment with a nitrogen nucleophile affords the desired glycosylureas **4.19**. Use of the soft Cs_2CO_3 as base allows the conversion to the glycosylurea with retention of the stereochemical integrity at the anomeric centre and without extensive hydrolysis of the trichloroacetimidate to the free amine.

4.2 Synthesis of Fluorinated Glycosylureas

Fluorinated glycosylureas could be utilised as a scaffold for the construction of nucleosides in an acyclic fashion to form fluorinated nucleoside analogues, such as the 2-deoxy-2,2-difluorocytidine analogue gemcitabine **1.08** (Scheme 4.10). It was anticipated the glycosylureas may prove to be superior intermediates in comparison to the glycosylamines, as they would be more likely to crystallise, providing the opportunity for selective crystallisation to achieve anomeric separation.

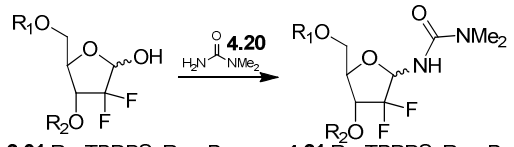


Scheme 4.10: Acyclic nucleoside synthesis.

4.2.1 Initial Investigation Towards Difluoroglycosylurea Formation

Initial studies into the condensation of difluororibose **2.01** with urea were carried out using *N*,*N*-dimethylurea **4.20**, to ensure dimerization could not occur. A range of solvents and acids, both protic and Lewis acids, were utilised (Table 4.1) with little success (entries 1–9). Only those reactions utilising PTSA (entries 10–13), provided any basis for optimisation studies, with yields of 17–38% obtained dependent upon the exact reaction conditions. Increasing the quantity of urea and PTSA (entry 14), resulted in a decrease in the yield of glycosylurea **4.21**. This is most likely due to deprotection of the 5-O-TBDPS ether, by the combination of high temperature and stoichiometric PTSA. This assumption was supported when the less acid labile 3,5-O-dibenzoyldifluororibose **1.51** was instead submitted to the same reaction conditions (entry 15) and a more promising 65% of glycosylurea **4.22** was obtained.

Table 4.1: Difluoroglycosylurea synthesis - initial optimisation.



2.01 R_1=TBDPS, R_2 = Bz
1.51 R_1=R_2=Bz

4.21 R_1=TBDPS, R_2 = Bz
4.22 R_1=R_2=Bz

Entry	Catalyst	Mol. Sieves	Solvent	Equiv urea	Temp (℃)	Time	Yield[a]
1	$Ti(O^iPr)_4$	N	THF	1	RT	18 h	0%
2	TMSOTf	Y	DCM	1	RT	2 h	0%
3	PTSA	Y	DCM	1	Reflux	22 h	0%
4	PTSA	Y	CF_3CF_2OH	1	Reflux	5 h	0%
5	PTSA	Y	$(CF_3)_2CHOH$	1	Reflux	18 h	0%
6	CSA	N	Toluene	1	Reflux	5 h	negligible
7	4 M HCl	Y	Toluene	1	Reflux	18 h	negligible
8	AcOH	N	DMF	2	RT–110	2 d	negligible
9	TFA	Y	Toluene	1	80	18 h	negligible
10	PTSA	Y	Toluene	2	Reflux	18 h	17%
11	PTSA	N	Toluene	2	Reflux	5.5 h	22%
12	PTSA	N	Toluene	1	Reflux	5 h	29%
13	PTSA	Y	Toluene	1	Reflux	5.5 h	38%
14	PTSA[b]	Y	Toluene	3	Reflux	24 h	19%
15[c]	PTSA[b]	Y	Toluene	3	Reflux	20 h	65%[d]

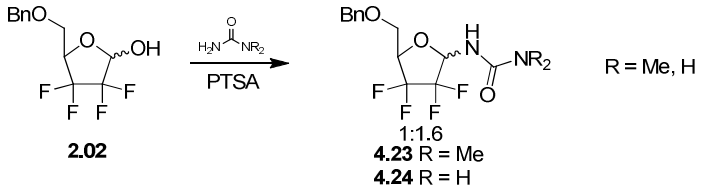
a: isolated yield; b: 1 equiv PTSA; c: 3,5-dibenzoyldifluororibose **1.51** used; d: 1:2.7 anomeric ratio.

4.2.2 Investigations Towards Tetrafluoroglycosylurea Formation

At this stage further optimisation of the glycosylurea formation was undertaken with the racemic tetrafluororibose **2.02** (Table 4.2). Protecting group lability under acidic conditions was not a factor with the 5-O-benzyl protection. Also until the 3,5-O-dibenzoylribonolactone **1.50** became commercially available, the synthesis of 3,5-O-dibenzoyldifluororibose **1.51** was more laborious than that of the racemic tetrafluororibose **2.02**.

A solvent screen was undertaken for the reaction with *N*,*N*-dimethylurea **4.20**, which showed alcoholic solvents to be ineffective (entries 1–3), whilst DMF furnished an improved 25% yield of glycosylurea **4.23**. Toluene showed initial promise (entry 6), with a reduction in *N*,*N*-dimethylurea and PTSA still furnishing a 54% yield of glycosylurea **4.23** (entry 5). However when urea was instead used, the yield of glycosylurea **4.24** dropped to a disappointing 17% (entry 7). In contrast use of dioxane furnished a vastly improved 90% of glycosylurea **4.24** (entry 8), although this was found to fall to 73%, upon scale-up (entry 9).

Table 4.2: Optimisation of tetrafluoroglycosylurea synthesis.



Entry	Equiv urea	R	Equiv PTSA	Solvent	Mol. sieves	Temp (°C)	Time (h)	Yield[a]
1	3	Me	1	MeOH	No	Reflux	5	Negligible
2	3	Me	1	MeOH	Yes	Reflux	20	Negligible
3	3	Me	1	*n*BuOH	Yes	Reflux	22	Negligible
4	3	Me	1	DMF	Yes	125	22	25%
5	1.2	Me	0.1	Toluene	Yes	Reflux	20	54%
6	3	Me	1	Toluene	Yes	Reflux	24	60%
7	3	H	1	Toluene	Yes	Reflux	18	17%
8[b]	3	H	1	Dioxane	Yes	Reflux	22	90%
9[b]	3	H	1	Dioxane	Na_2SO_4	Reflux	22	73%

a: isolated yield; b: entry 8 carried out on 87 mg scale, entry 9 carried out on 1.2 g scale.

We were able to achieve crystallisation of the racemic glycosylurea **4.24** to give crystals of sufficient quality for X-ray crystallographic analysis (Figure 4.1). Unfortunately it has proved impossible to obtain suitable crystals of the enantiopure glycosylurea **4.24**.

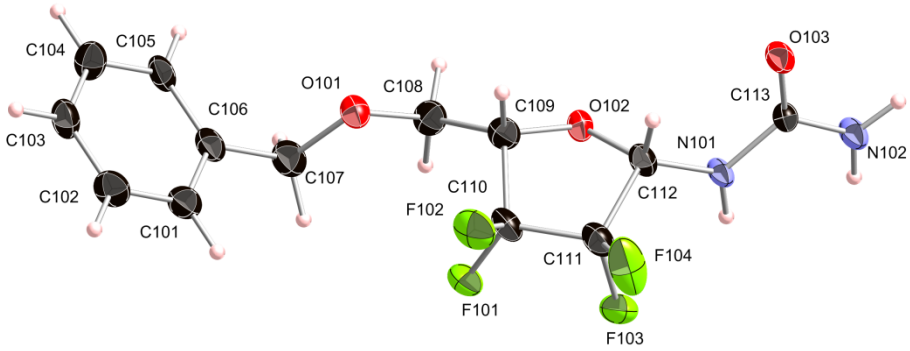


Figure 4.1: X-ray structure of tetrafluorourea **4.24** (single diastereomer from racemic mixture).

Unfortunately the crystal packing within the asymmetric unit is heavily disordered, therefore difficult to model well (Figure 4.2). However, both enantiomers of each anomer can be seen. Within the asymmetric unit the central molecules are more orderly and of β configuration. In contrast the outer two molecules exhibit substantial disorder and can be of either α or β configuration.

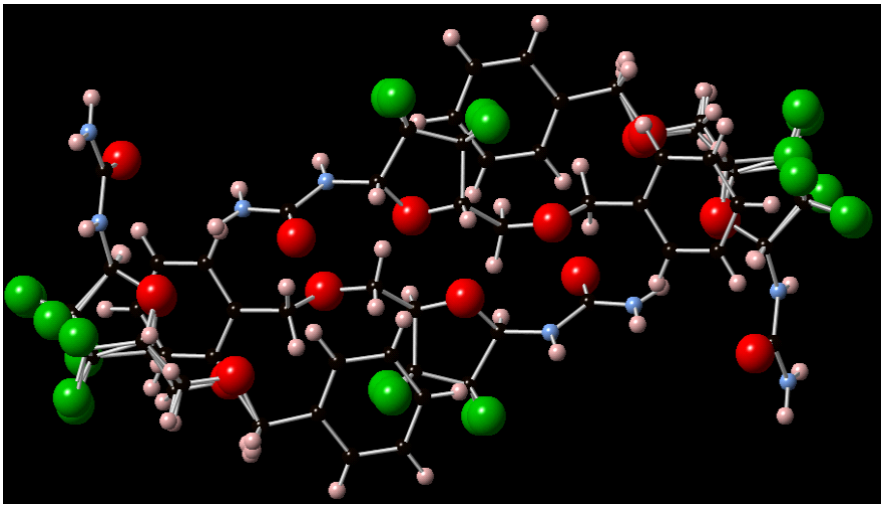


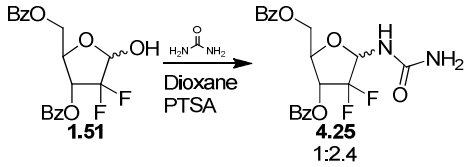
Figure 4.2: Crystal packing of racemic tetrafluorourea **4.24**.

4.2.3 Further Investigations Towards Difluoroglycosylurea Formation

Due to the lability of the TBDPS ether, further optimisation experiments were carried out exclusively with the 3,5-O-dibenzoyldifluororibose **1.51** (Table 4.3). The reaction solvent was changed to dioxane, the optimal solvent in the synthesis of the tetrafluoroglycosylurea **4.24**, however a disappointing 40%

yield was obtained (entry 1). An increase in the quantity of urea only increased the yield to 59% (entry 2). As good conversion was seen by crude NMR, it was proposed the low yields may be due to losses during the workup. As the molecular sieves became crushed from the stirring action during the course of the reaction, they tended to form a sticky layer, blocking the filter agent. However, a change of drying agent to Na_2SO_4 (entries 3–6), whilst facilitating the work-up, did not have a significant effect upon the yield, regardless of urea stoichiometry. Replacement of the aqueous work-up with a filtration through celite (entry 8) was found to be beneficial, with 79% of the desired glycosylurea **4.25** obtained on small scale. This was further improved to 88% upon scale-up (entry 9).

Table 4.3: Optimisation of dibenzoylglycosylurea **4.25** synthesis.



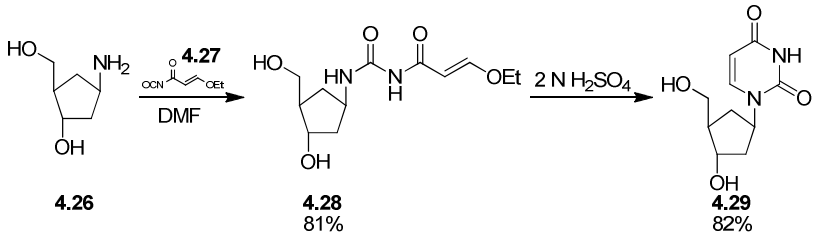
Entry	Drying Agent	Et_3N Column?	Equiv Urea	Work-up	Time (h)	Yield[a]
1	Mol Sieves	Y	3	Aqueous	18	40%
2	Mol Sieves	Y	5	Aqueous	44	59%
3	Na_2SO_4	Y	3	Aqueous	18	61%
4	Na_2SO_4	Y	3	Straight to column	36	62%
5	Na_2SO_4	Y	5	Aqueous	72	64%
6	Na_2SO_4	Y	3	Silica filtration	66	65%
7	None	N	3	Celite filtration	36	76%
8	Na_2SO_4	N	5	Celite filtration	36	79%
9[b]	Na_2SO_4	N	3	Celite filtration	36	88%

a: isolated yield; b: carried out on 870 mg scale.

4.3 Linear Pyrimidine Synthesis

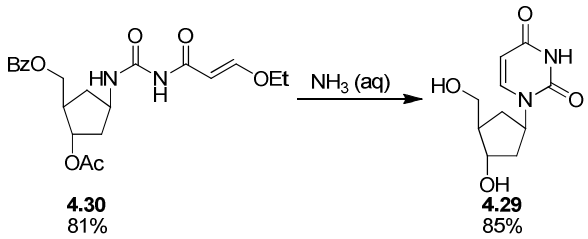
Aside from convergent nucleoside syntheses, methodology for the linear synthesis of nucleosides, where the nucleobase is constructed from a sugar

precursor is also available. Shaw and Warrener developed acyclic methods for the syntheses of pyrimidine nucleobases from acyl carbamates.[103,104] This methodology has since been applied, not only to the synthesis of nucleosides, but also to carbanucleosides. For example, Shealy *et al* have synthesised the carbocyclic deoxyuridine analogue **4.29** from amine **4.26** and isocyanate **4.27**. Acidic conditions are used in the cyclisation of **4.28** to **4.29** (Scheme 4.11).[105]



Scheme 4.11: Acyclic synthesis of uridine analogue **4.29** with acidic cyclisation conditions.

Balzarini *et al* also effected the same cyclisation, with concomitant deprotection under basic conditions.[106] Treatment of acyl carbamate **4.30** with NH_3 (aq) furnished the carbocyclic uridine analogue **4.29** efficiently in 85% yield.

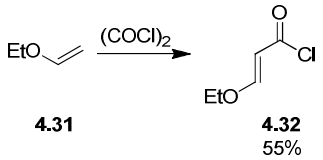


Scheme 4.12: Acyclic synthesis of uridine analogue **4.29** with basic cyclisation conditions.

With regard to the synthesis of gemcitabine **1.08**, as discussed in Chapter 1, most syntheses utilise the convergent method of nucleobase introduction. To our knowledge the only acyclic synthesis of gemcitabine **1.08** is that of Cheng Gong.[47] Hertel also outlines the potential utility of primary difluoroaminoglycosides, with regard to the acyclic synthesis of the nucleobase,[58] however he does not explicitly describe their use in syntheses of this nature.

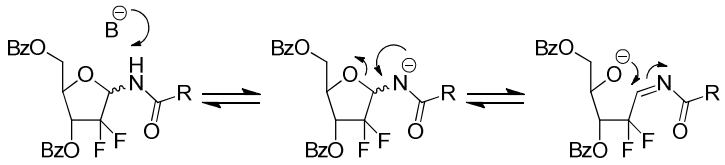
*4.3.1 Synthesis of Gemcitabine **1.08***

Before cyclisation to the nucleobase could be undertaken, the requisite acyl carbamate **4.33** had to be synthesised. This was accomplished through the reaction of urea **4.25** with acyl chloride **4.32**, synthesised *via* the method of Tietze *et al* from ethyl vinyl ether **4.31** and oxalyl chloride (Scheme 4.13).[107]



Scheme 4.13: Synthesis of acyl chloride **4.32**.

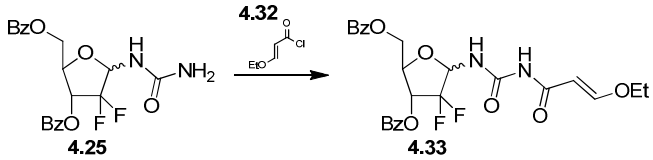
Treatment of glycosylurea **4.25** with 1 equiv of acyl chloride **4.32** in pyridine with DMAP (Table 4.4, entry 2), only afforded 30% of the desired product **4.33**, with significant anomerisation seen to occur (1:2.4 to 1:1). This anomerisation may be due to NH deprotonation by pyridine, leading to ring opening. Subsequent non-selective ring closure results in anomerisation (Scheme 4.14).



Scheme 4.14: Possible mechanism of anomerisation.

Replacement of pyridine by DCM yielded none of the desired product after 3.5 d (entry 1). Refluxing in MeCN with 2 equiv of acyl chloride **4.32** (entry 3) increased the yield to 45% with a further increase to 71% seen when the amount of acyl chloride **4.32** was increased to 4 equiv (entry 6). These conditions also resulted in less anomerisation (1:2.4 to 1:1.5). The least anomerisation was seen when $ZnCl_2$ was employed, with a 1:1.9 anomeric ratio seen in the isolated product. However, the highest yields were obtained when no additional reagents were utilised. MeCN was found to be the solvent of choice, furnishing acyl carbamate **4.33** in a 71% yield (entry 7).

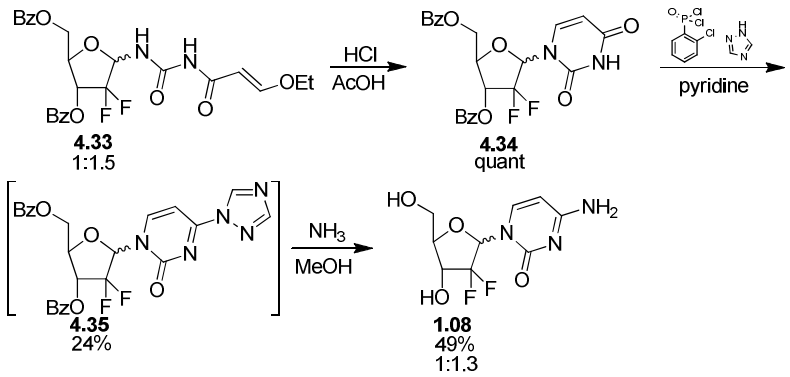
Table 4.4: Optimisation of reaction with acyl chloride **4.32**.



Entry	Equiv **4.32**	Reagents	Solvent	Temp (℃)	Time	Yield[a]	Anomeric Ratio
1	1	1 equiv DMAP	DCM	RT	3.5 d	0%	N/A
2	1.5	0.25 equiv DMAP	Pyridine	Reflux	40 h	30%	1:1
3	2	None	MeCN	Reflux	18 h	45%	1:1.5
4	3	0.25 equiv $ZnCl_2$	$CHCl_3$	Reflux	24 h	45%	1:1.9
5	5	None	Dioxane	Reflux	22 h	47%	1:1.1
6	4	None	Dioxane	Reflux	18 h	61%	1:1.15
7	4	None	MeCN	Reflux	18 h	71%	1:1.5

a: isolated yield

With the acyl carbamate **4.33** in hand, cyclisation to the protected difluorouridine **4.34** was studied. Various acidic protocols were trialled, with HCl/AcOH emerging as the most efficient, effecting quantitative conversion to protected difluorouridine **4.34**.



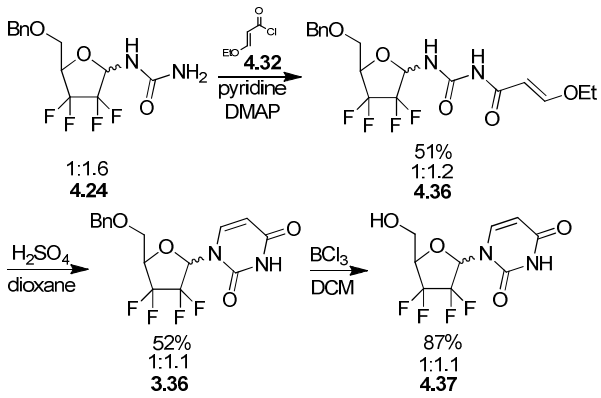
Scheme 4.15: Conversion of acyl carbamate **4.33** to gemcitabine **1.08**.

Conversion of uridine to cytidine is known in the literature. Sung effected this transformation *via* a triazole intermediate, followed by amination.[108] Triazole

intermediate **4.35** was formed from uridine **4.34**, by treatment with 2-chlorophenyl phosphorodichloridate and 1,2,4-triazole in pyridine. Subsequent triazole/ammonia exchange with concomitant benzoate deprotection furnished gemcitabine **1.08** (Scheme 4.15).

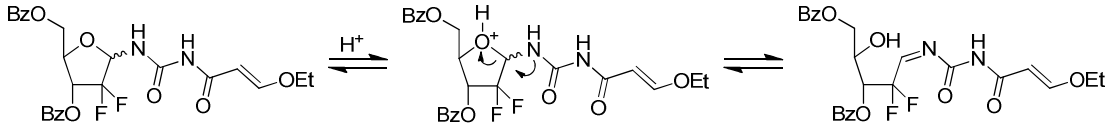
*4.3.2 Synthesis of Tetrafluorouridine **4.37***

The pyrimidine base for the tetrafluorinated nucleosides was constructed in the same manner as for the difluorinated nucleosides discussed above (section 4.3.1). Glycosylurea **4.24** was reacted with acyl chloride **4.32** to afford acyl carbamate **4.36** in 51% yield as a 1:1.2 anomeric ratio. Anomerisation was not as marked in this instance as in the difluorinated system. However the initial anomeric ratio of the tetrafluoroglycosylurea **4.24**, at 1:1.6, is not as high as that of 1:2.4 for the difluoroglycosylurea **4.25**.



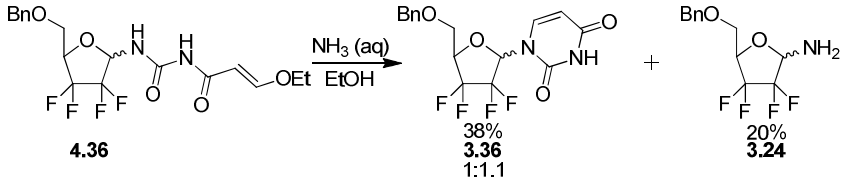
Scheme 4.16: Tetrafluorouracil **4.37** synthesis.

Acid mediated cyclisation was performed to yield the protected tetrafluorouridine **4.36** as a 1:1.1 anomeric ratio. To our surprise, even in acidic medium, anomerisation was again observed. A possible mechanism for this anomerisation is shown in Scheme 4.17, however this mechanism would be highly surprising as it would be expected an intermediate oxonium anion of the type shown would be highly unfavourable, due to the destabilising effect of the highly electron withdrawing tetrafluoroethylene moiety.



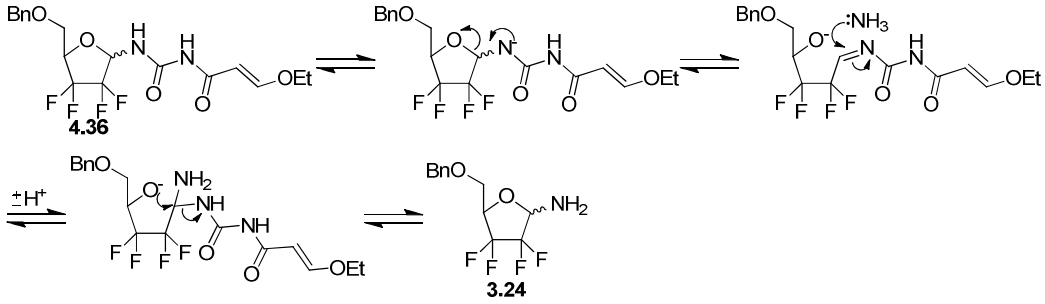
Scheme 4.17: Possible mechanism of anomerisation.

Cyclisation to **3.36** was also investigated under basic conditions with NH_3/EtOH. However the yield of the desired tetrafluorouridine **3.36** is significantly reduced due to the unexpected formation of the primary aminoglycoside **3.24**.



Scheme 4.18: Formation of primary aminoglycoside by-product **3.24**.

It is proposed the mechanism of formation of aminoglycoside **3.24** proceeds *via* an open chain imine intermediate as shown in Scheme 4.19, leading to the displacement of the acyl carbamate side chain by ammonia and ring closure, affording aminoglycoside **3.24**.



Scheme 4.19: Proposed mechanism of formation of aminoglycoside **3.24**.

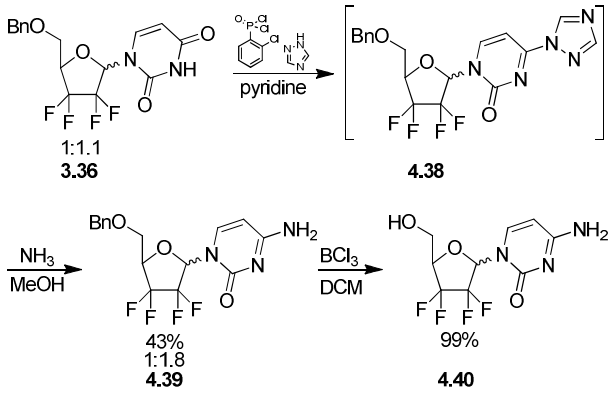
This mechanism *via* an open chain intermediate also explains the propensity for anomerisation during cyclisation, as unselective ring closure will lead to a 1:1 anomeric ratio.

The benzyl ether is an unusual protecting group within nucleoside chemistry. Traditional hydrogenation methods of debenzylation cannot be utilised due to

the unsaturated nucleobase. Deprotection is therefore smoothly undertaken using boron trichloride to afford tetrafluorouridine **4.37**.

*4.3.3 Synthesis of Tetrafluorocytidine **4.40***

The protected tetrafluorocytidine **4.40** is formed from uridine **3.36**, *via* triazole intermediate **4.38**, in the same manner as the nucleobase interconversion in the synthesis of gemcitabine **1.08**. Again significant anomerisation is seen during this nucleobase conversion, from 1:1 to 1:1.8. Based on the chemical shifts in the ^{19}F NMR (see chapter 6), it is proposed that the direction of this anomerisation is in favour of the desired β-tetrafluorocytidine **4.39**. From here near quantitative debenzylation affords tetrafluorocytidine **4.40**.



Scheme 4.20: Tetrafluorocytosine **4.40** synthesis.

4.4 Conclusions

Further development of the aminoglycosylation chemistry described in chapter 3 has lead to the formation of the di- and tetrafluoroglycosylureas. However, anomeric separation of these was not possible and in any case significant anomerisation was observed in the nucleobase forming transformations.

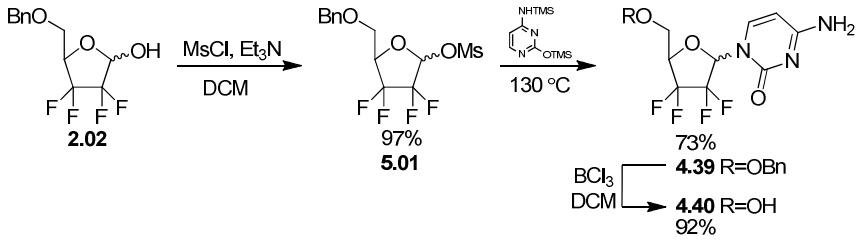
These glycosylureas have been utilised as the scaffold in the successful construction of gemcitabine **1.08**, tetrafluorouridine **4.37** and tetrafluorocytidine **4.40** described herein.

5 Nucleoside Synthesis - Other Methods

5.1 Tetrafluoropyrimidines

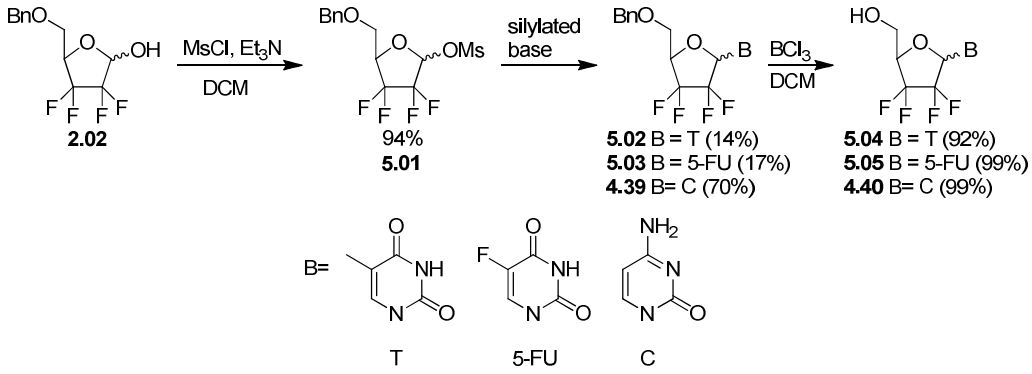
The direct comparison of our newly developed acyclic synthesis of pyrimidine analogues, described in chapter 4, with more traditional displacement methods of pyrimidine base incorporation was desirable. Therefore the synthesis of a small number of tetrafluoropyrimidines, *via* mesylate displacement, was undertaken.

Previous investigations within the group[109] found the solventless fusion procedure of Chou *et al*[50], where the reaction medium is the molten silylated nucleobase, furnished optimal yields when tetrafluororibose **2.02** was employed (Scheme 5.1). Working from the 78% *ee* tetrafluororibose **2.02**, mesylation to **5.01** allowed the nucleobase displacement reaction to afford protected tetrafluorocytidine **4.39**. Subsequent debenzylation with BCl_3 furnishes tetrafluorocytidine **4.40**.



Scheme 5.1: Boydell synthesis of the enantioenriched tetrafluorocytosine **4.40**.[109]

With the successful resolution of the precursor for tetrafluororibose **2.02**, synthesis of enantiopure tetrafluorinated nucleosides could now be undertaken. The bis-TMS-cytosine is the most nucleophilic of the three nucleobases utilised, demonstrated by the significantly higher yield of 70% for the formation of protected tetrafluorocytosine **4.39**. This is in contrast to yields of <20% for the introduction of thymine and 5-FU, due to the significant deactivation of mesylate **5.01** by the presence of the tetrafluoroethylene moiety (Scheme 5.2).



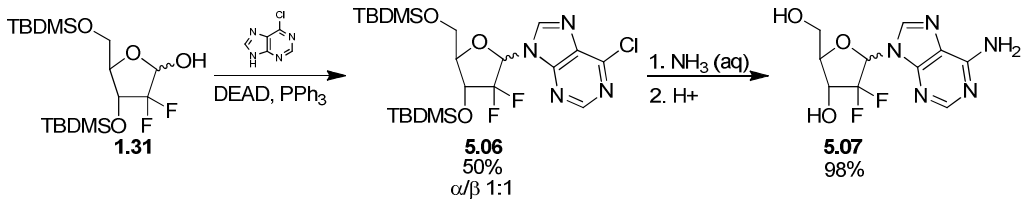
Scheme 5.2: Enantiopure tetrafluoropyrimidine synthesis *via* mesylate displacement.

Near quantitative debenzylation with boron trichloride efficiently yielded the tetrafluorinated nucleosides.

With regard to anomeric selectivity, neither traditional displacement mediated nucleobase introduction nor our acyclic method of nucleobase introduction confers any true advantage. However mesylate displacement as a means of cytosine introduction is significantly more efficient with regard to yield and number of steps, 3 steps from tetrafluororibose **2.02**, in contrast to 5 steps for the acyclic method. The advantage of the mesylate displacement is less marked with regard to the introduction of other, less nucleophilic, pyrimidine nucleobases. The mesylate displacement method consists of 3 synthetic steps from tetrafluororibose **2.02** in contrast to 4 steps in the acyclic method.

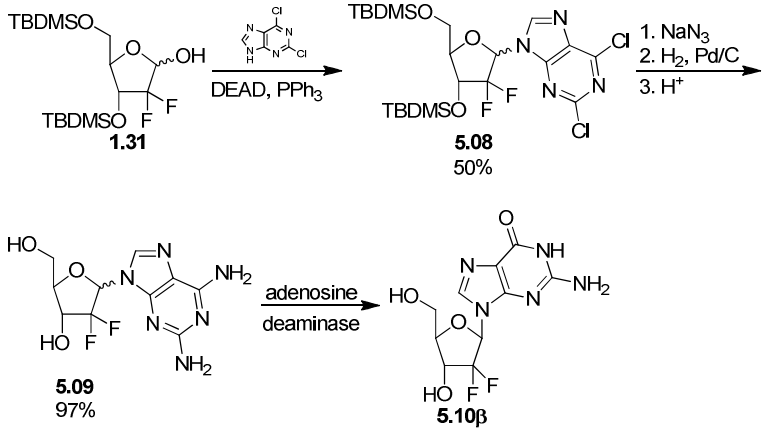
5.2 Tetrafluoropurines

There are few examples of 2′,2′-difluorinated purine nucleosides in the literature. Hertel *et al* synthesised 2′,2′-difluoroadenosine **5.07** (Scheme 5.3) and 2′,2′-difluoroguanosine **5.10** (Scheme 5.4) *via* Mitsunobu chemistry.[110,111]



Scheme 5.3: Hertel *et al* synthesis of difluoroadenosine **5.07**.

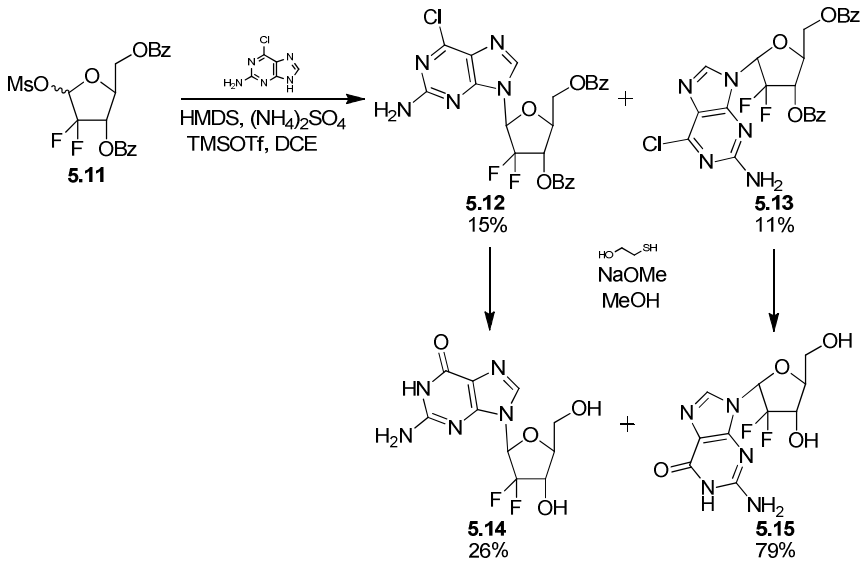
Mitsunobu reaction of protected difluororibose **1.31**, with 6-chloropurine, to afford difluoropurine **5.06** in 50% yield was followed by amination and silyl ether hydrolysis to afford 2′,2′-difluoroadenosine **5.07**. Anomeric separation was then effected by RP-HPLC (Scheme 5.3).



Scheme 5.4: Hertel *et al* synthesis of difluoroguanidine **5.10β**.

For the synthesis of 2′,2′-difluoroguanidine the same Mitsunobu reaction was utilised, but with 2,6-dichloropurine. Reaction of **5.08** with sodium azide, hydrogenation and silyl ether hydrolysis yielded diaminopurine **5.09** (Scheme 5.4). Enzymatic hydrolysis with adenosine deaminase selectively acted upon the β-anomer to yield β-2′,2′-difluoroguanidine **5.10β**.

Kotra *et al* synthesised a series of 2′,2′-difluorinated L-nucleosides, including purine analogues.[62,112] A mesylate displacement reaction was utilised for the synthesis of 2′,2′-difluoroguanidine (Scheme 5.5). The anomers of the chloropurine derivative from the displacement reaction were found to be separable. Subsequent dechlorination and debenzoylation furnished the two anomers of 2′,2′-difluoroguanidine.



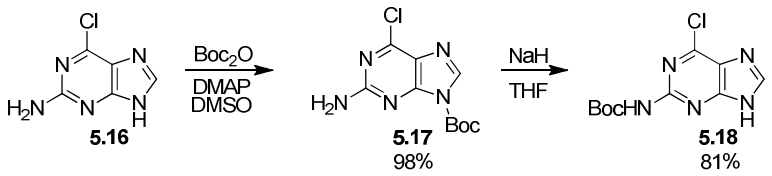
Scheme 5.5: Kotra *et al* synthesis of L-difluoroguanidine.

*5.2.1 Tetrafluoroguanidine **5.21***

Initial attempts at the synthesis of the tetrafluoroguanidine analogue **5.21**, *via* the mesylate or Mitsunobu chemistry utilised by Kotra *et al* in their syntheses of L-difluoropurines,[62] met with little success.

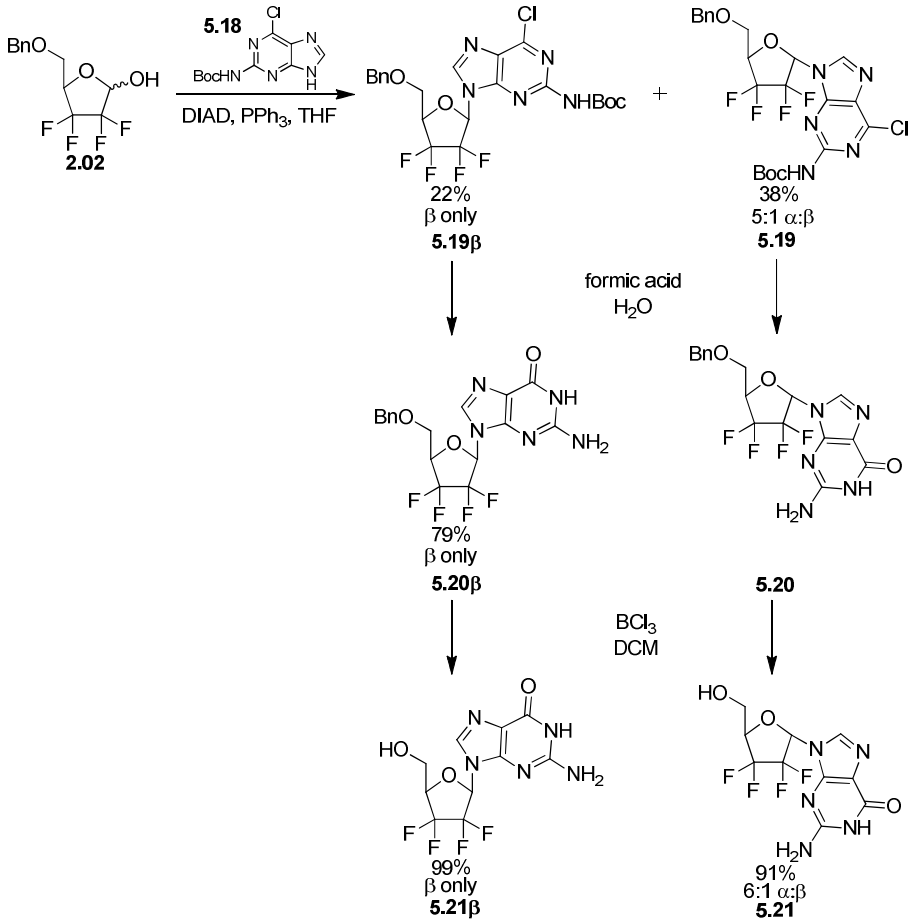
Reactions with guanines are typically found to be problematic owing to their insolubility in organic solvents and polyfunctionality. We were however attracted to a recent publication by Fletcher *et al* which provided a solution to the solubility problem. [113] They were able to access a range of substituted guanines *via* Mitsunobu chemistry with a selection of primary and secondary alcohols, using a more soluble N2-Boc purine **5.18**. These reactions were found to be high yielding and exhibited good N7/N9 regioselectivity. Hence it was decided to apply this methodology to our synthesis of tetrafluoropurines.

Synthesis of the N2-Boc purine can be easily undertaken from 2-amino-6-chloropurine **5.16** through Boc protection of N7, followed by NaH mediated Boc migration to N2, to furnish bis-Boc-purine **5.18** (Scheme 5.6).



Scheme 5.6: Synthesis of protected purine derivative **5.18**.[114]

Use of this protected purine derivative in the Mitsunobu reaction with tetrafluororibose **2.02** resulted in a greatly enhanced 60% yield of **5.19**. HPLC purification allowed for the partial separation of the 2 anomers, resulting in 22% of the pure β anomer, whilst the remaining material was enriched in favour of the α anomer (Scheme 5.7). Pleasingly formation of the N9 derivative was not observed.



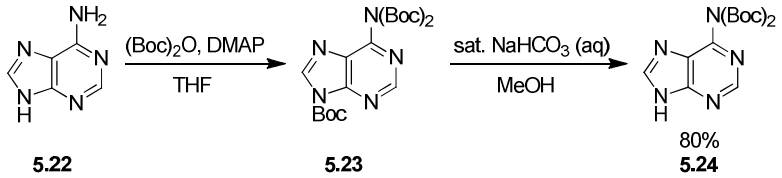
Scheme 5.7: Tetrafluoroguanidine **5.21** synthesis.

From here simultaneous Boc deprotection and dechlorination proceeds smoothly affording protected tetrafluoroguanidine **5.20**. Finally boron trichloride

debenzylation is utilised to furnish both the pure β and the α enriched tetrafluoroguanidine **5.21**.

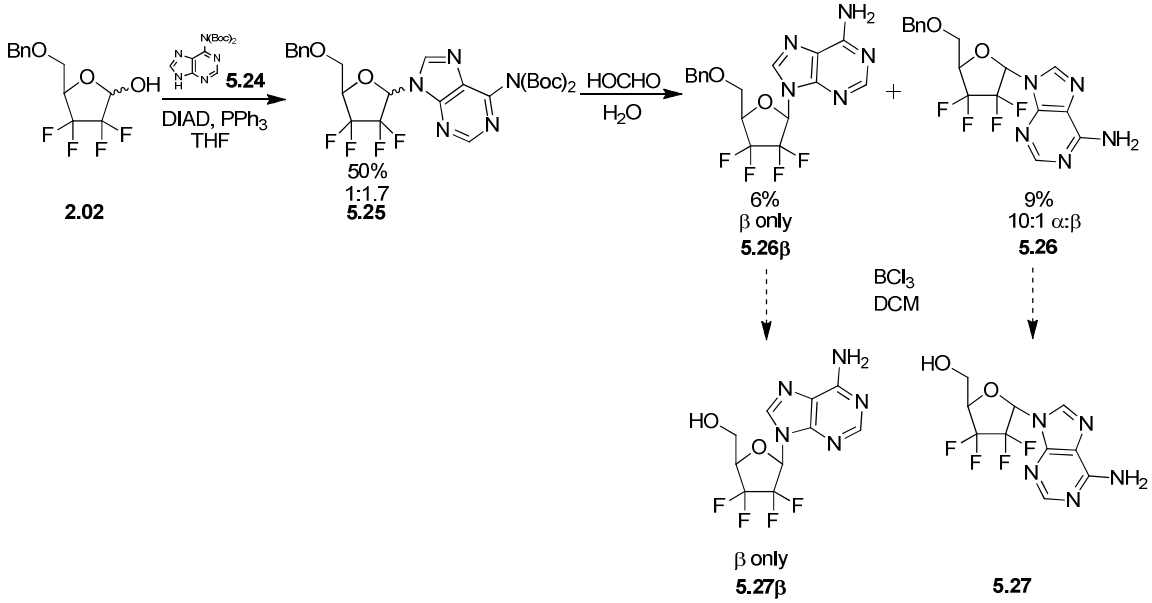
*5.2.2 Tetrafluoroadenosine **5.27***

An analogous method to that of the tetrafluoroguanosine **5.21** synthesis was utilised in the synthesis of tetrafluoroadenosine **5.27**. The more soluble di-Boc protected adenine **5.24** was synthesised from adenine **5.22** *via* the tri-Boc protected species **5.23**, followed by selective N7 Boc deprotection (Scheme 5.8).[115]



Scheme 5.8: Synthesis of protected adenine **5.24**.

Use of the more soluble bis-Boc-adenine **5.24**, resulted in a 50% conversion to **5.25** *via* Mitsunobu reaction. The subsequent deprotection step requires optimisation, as after HPLC purification to separate the anomers, a disappointing 15% overall yield of **5.26** was obtained (Scheme 5.9).



Scheme 5.9: Tetrafluoroadenosine **5.27** synthesis.

5.3 AZT Analogue 5.28

Azidothymidine (AZT) **1.01** is a thymidine analogue, in which the 3′OH is replaced by an azide. First approved by the FDA in 1987 it is marketed under the tradename of Retrovir and used in the treatment of HIV. Acting *via* the inhibition of reverse transcriptase it inhibits the translation of single stranded RNA into double stranded DNA. The presence of the azide increases the lipophilicity of the molecule, aiding the crossing of cell membranes.[116] We undertook a synthesis of the 2′,2′-difluorinated analogue **5.36** (Figure 5.1).

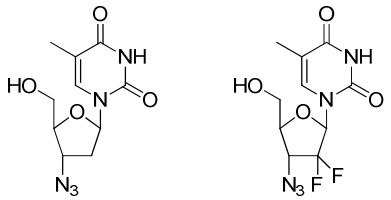
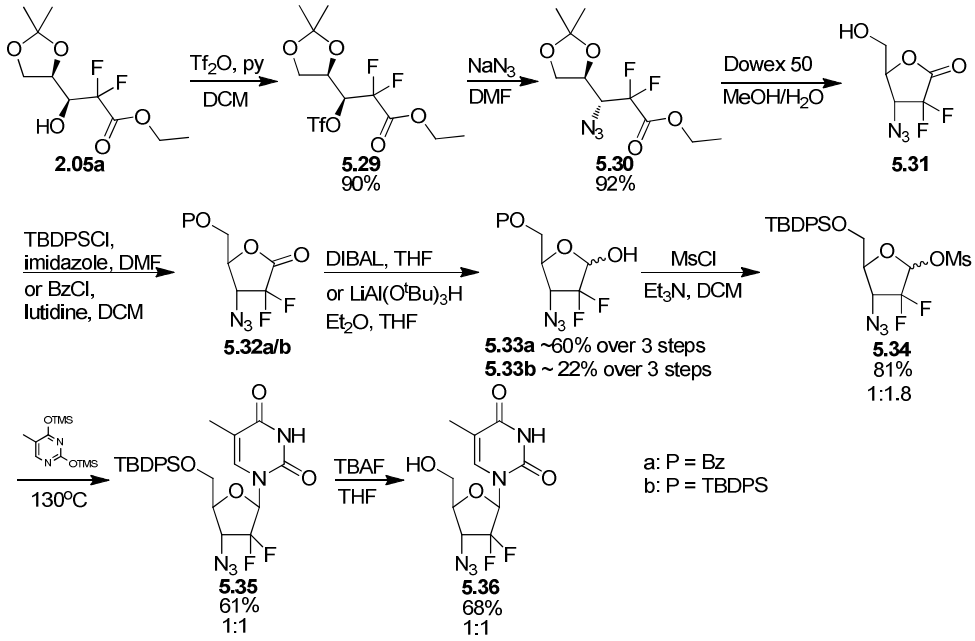


Figure 5.1: AZT **1.01** and its difluorinated analogue **5.36**.

Starting from the undesired *syn* diastereomer **2.05a** obtained from the Reformatsky reaction in the synthesis of gemcitabine **1.08**, triflation followed by displacement with NaN_3 furnishes the desired azide **5.30** with the required inversion of stereochemistry.



Scheme 5.10: AZT analogue **5.36** synthesis.

Cyclisation to the γ-lactone **5.31** was undertaken with Dowex 50, before 5OH protection as the benzoyl or TBDPS ether and subsequent reduction to the lactol **5.32**. As with the 2,2-difluororibose in the synthesis of gemcitabine, 5-O-silyl protection resulted in the best overall yield. Conversion to mesylate **5.34** allowed the introduction of the thymine nucleobase, affording protected nucleoside **5.35** as a 1:1 anomeric ratio. Finally TBAF mediated desilylation furnished the difluorinated AZT analogue **5.36** (Scheme 5.10).

5.4 Conclusions

The synthesis of pyrimidine analogues tetrafluorocytidine **4.40**, tetrafluorothymidine **5.04** and tetrafluoro-5-fluorouridine **5.05** *via* mesylate displacement chemistry has been realised. Tetrafluoroguanidine **5.21** and tetrafluoroadenosine **5.27** have been synthesised *via* Mitsunobu chemistry. The 2′,2′-difluoro AZT analogue **5.36** has also been successfully synthesised.

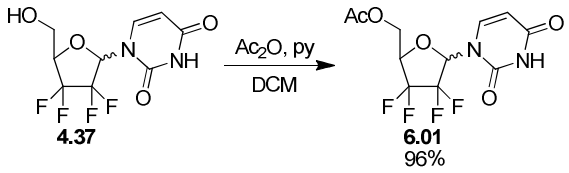
6 Separation and Characterisation of the Pure Nucleoside Anomers

6.1 Anomeric Separation

All the fluorinated nucleosides were synthesised as anomeric mixtures, which were found to be inseparable by silica gel column chromatography. Therefore investigations into their anomeric separation by other means were conducted.

6.1.1 Via 5-O-derivatisation

Neither tetrafluorouridine **4.37** nor the 5-O-benzyl derivative **3.36** were separable by chromatography. Gourverneur *et al* found 5-O-acetate protection enabled anomeric separation of their tetrafluoro-C-nucleoside analogues.[68] Therefore 5-O-acetate protection of tetrafluorouridine **4.37** was trialled.



Scheme 6.1: 5-O-acetate protection.

The 5-O-acetate **6.01** was found to be very insoluble, hampering purification, however partial separation was obtained by column chromatography to furnish two samples, one with a 4.7:1 (A) anomeric ratio and the other of 20.7:1 (B) (Figure 6.1). It was not possible however to effect complete separation by HPLC due to the insolubility.

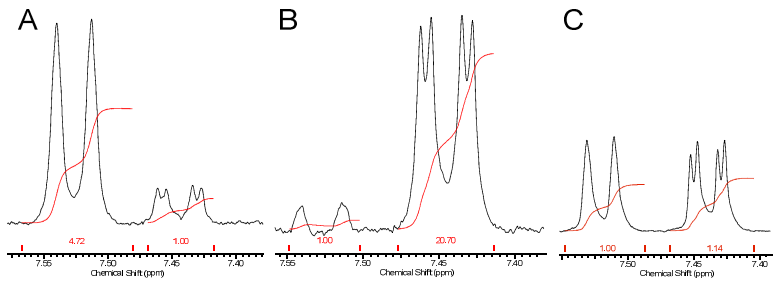
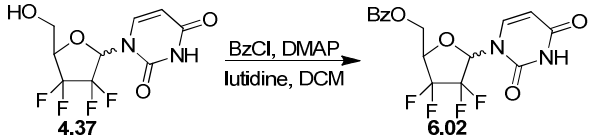


Figure 6.1: ^{1}H NMR of H6 of **6.01** (A 4.7:1; B 1:20.7; C 1:1.14).

The 5-O-acetate was therefore replaced by a 5-O-benzoate to afford **6.02**, which was found to be even more insoluble than the 5-O-acetate derivative **6.01**.



Scheme 6.2: 5-O-benzoate protection.

Nevertheless anomeric separation of the 5-O-benzoate **6.02** was achieved by fractional crystallisation. It can be deduced from the ^{19}F NMR chemical shift pattern (section 6.2.2) that spectrum A most likely corresponds to the β anomer and spectrum B to the α anomer (Figure 6.2).

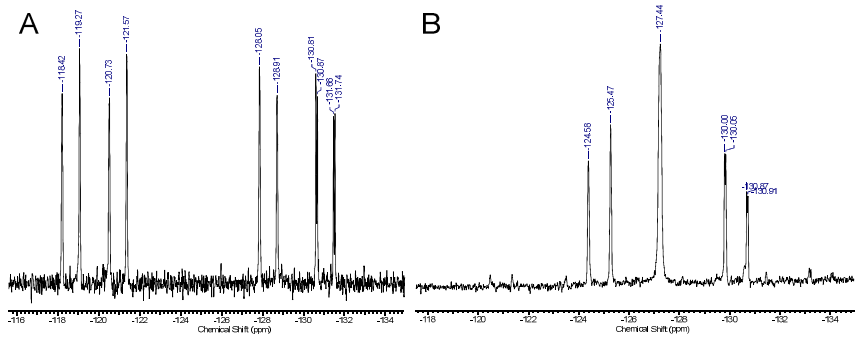


Figure 6.2: ^{19}F NMR of precipitated **6.02**.

6.1.2 Via RP-HPLC

Anomeric separation of the nucleosides shown in Figure 6.3 was acheived using preparative RP-HPLC. Run times of up to hour, using a solvent gradient were required to achieve baseline separation.

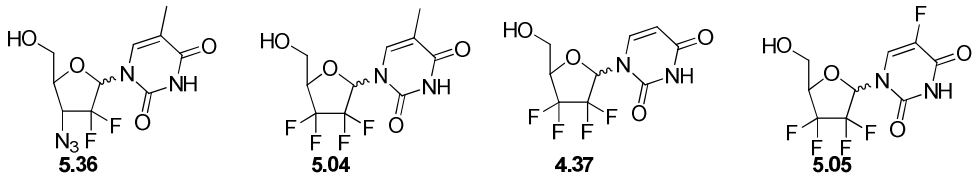


Figure 6.3: Nucleosides separated by RP-HPLC.

6.2 Anomeric Assignment

6.2.1 Via GOESY NMR

GOESY ^{1}H NMR was utilised to assign the separated nucleoside anomers. Figure 6.4 shows that when H4′ of **5.05α** was irradiated no NOE response was seen at H1′, however an NOE response was seen at H6 proving this to be the α anomer. The expected response at H5′ was also visible.

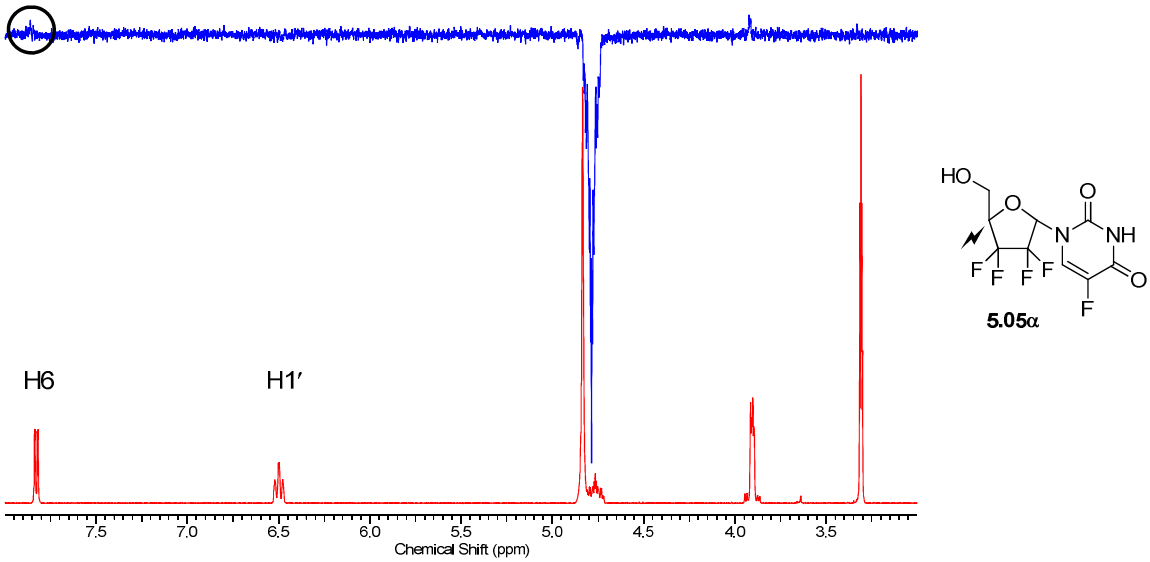


Figure 6.4: GOESY of 5.05α

Figure 6.5 shows when H4′ of **5.05β** was irradiated an NOE response was seen at H1′, whilst no NOE response was seen at H6 proving this to be the β anomer. The expected response at H5′ was also visible.

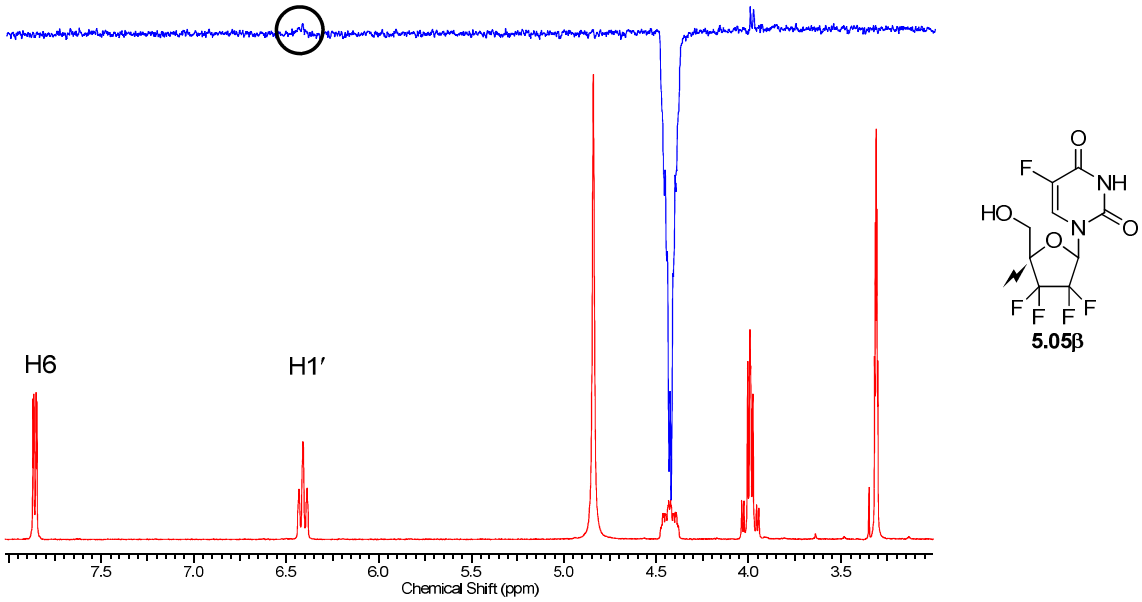


Figure 6.5: GOESY of **5.05β**.

Figure 6.6 shows for the difluorinated analogue of AZT **5.36α** irradiation at H4′ gave an NOE response at H6, but not at H1′ proving this to be the α anomer. The expected response at H5′ was also visible. However GOESY NMR of the other anomer, to reconfirm this result, was not possible as the peaks for H4′ overlap with those for H5′. The α anomer eluted 2nd from the RP-HPLC column for this difluorinated nucleoside, the reverse to the order of elution seen for the tetrafluorinated nucleosides.

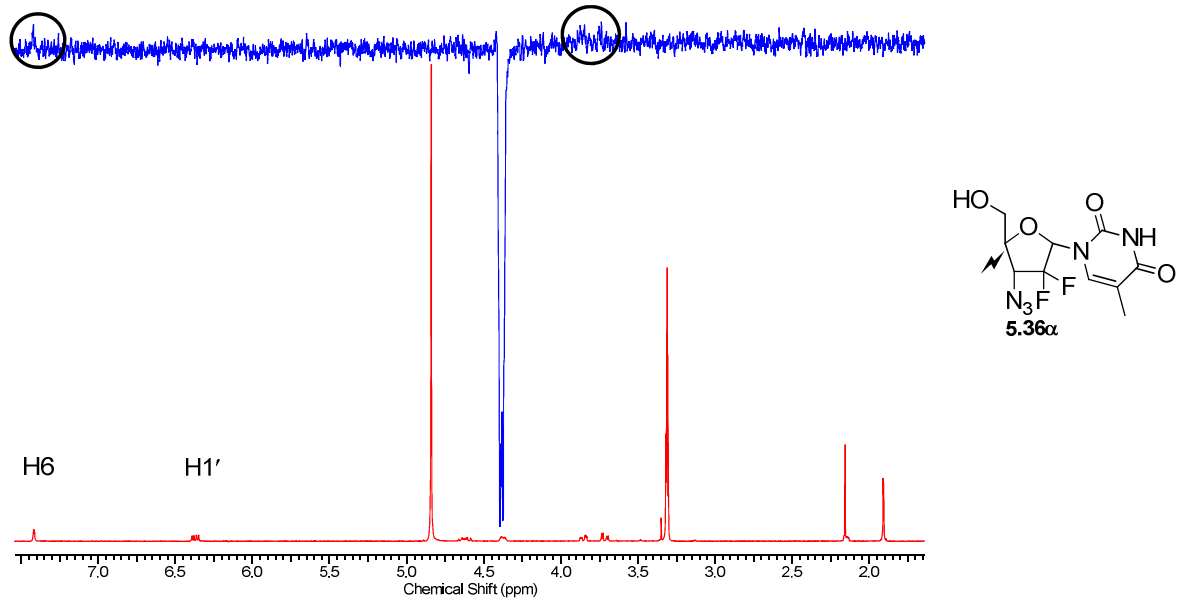


Figure 6.6: GOESY of **5.36α**.

6.2.2 ^{19}F NMR Chemical Shift Pattern

A characteristic shift pattern emerged for the tetrafluorinated nucleosides. In the α anomer coalescence of two of the fluorines was observed. In contrast the chemical shift pattern for the β anomers was found to be much more evenly spaced (Figure 6.7).

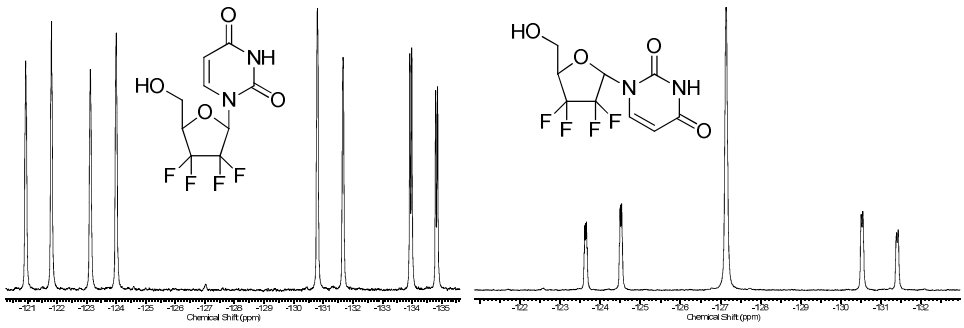


Figure 6.7: ^{19}F NMR for **4.37**.

This chemical shift pattern was seen for all the tetrafluorinated nucleosides synthesised and in all cases the α anomer was found to elute 1st from the RP-HPLC column.

The ^{19}F NMR coupling pattern in the difluorinated AZT analogue **5.36** was the reverse of that seen for the tetrafluorinated nucleosides, with peak coalescence seen in the spectrum of the β anomer and the more evenly spaced peaks seen for the α anomer (Figure 6.8).

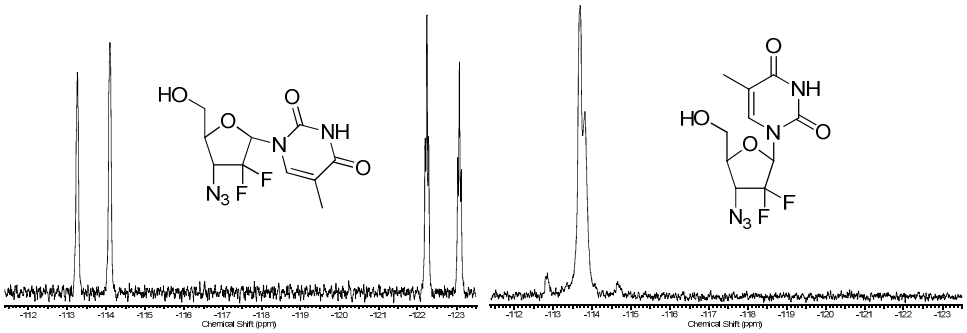


Figure 6.8: ^{19}F NMR of **5.36**.

6.3 Intramolecular C–F - H–C Interactions

Interactions between F2′ and H8 in some purine nucleosides have been observed by NMR. Watts *et al* have presented evidence to suggest the F2′–H8 interaction in their 2′-deoxy-2′-fluoroarabinoadenosine (2′F-araA) derivatives is due to a favourable pseudohydrogen bonding interaction, rather than that of a 5-bond coupling.[117,118]

A 2 Hz coupling is seen for H8 in 2′F-araA **6.03**. In contrast, no coupling is seen for H8 in the 3′,5′-O-disiloxane tethered **6.04**. If **6.03** adopts a southeast sugar pucker, the F2′ will be orientated such that a F2′–H8 interaction would be possible. However, if the sugar was constrained by an O3′,O5′ tether as in **6.04**, the sugar would be forced to adopt a northern pucker conformation. This change in conformation would no longer allow for a F2′–H8 interaction to occur.

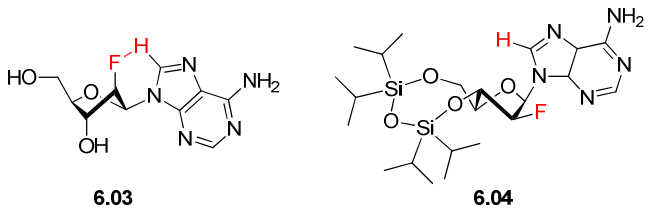


Figure 6.9: 2′F nucleoside conformation.

Further support of the F2′–H8 interaction can be derived from the decreased rate of deuterium exchange exhibited by H8. Acidic protons of this nature will undergo slow exchange with D_2O over a number of days. The rate of exchange for 2′F-araA was found to be markedly slower than that observed in other adenosine nucleosides. It is most likely this reduced exchange rate is due to stabilisation from participation in the F2′–H8 interaction.[119]

It has been found that oligonucleotide sequences containing 2′F-araA are stabilised in comparison to their non-fluorinated counterparts. Melting temperatures were found to increase by up to 12.6 °C. This increased stability is also thought to relate to F2′–H8 interactions providing stabilisation to the duplex.

*6.3.1 Protected β-Tetrafluoroadenosine **5.26β***

We have also observed similar long range H–F couplings. An interaction between F2′ and H8 is present in 5′-O-benzyl-β-tetrafluoroadenosine **5.26β**. The interaction is clearly demonstrated by the cross peak in the ^{1}H-^{19}F COSY NMR (Figure 6.10).

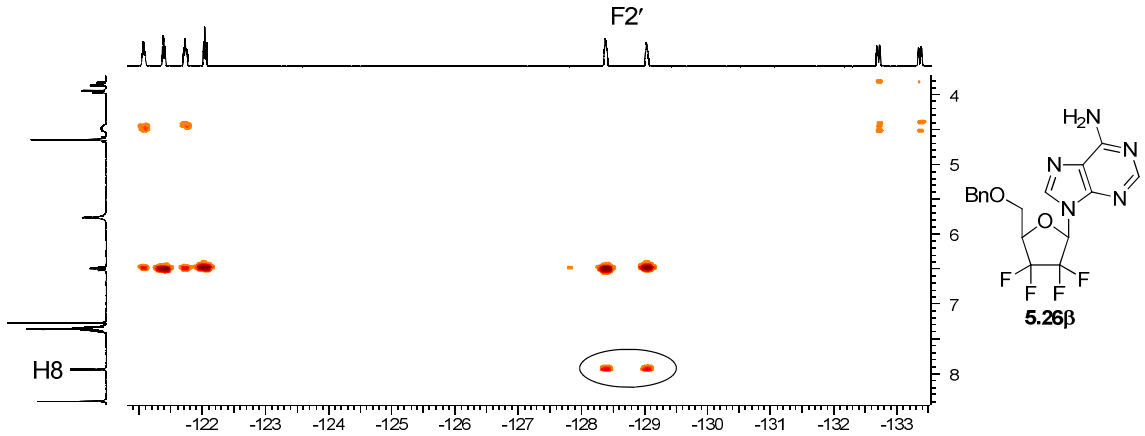


Figure 6.10: ^{1}H-^{19}F COSY for 5′-O-benzyl-β-tetrafluoroadenosine **5.26β**.

The coupling was of 1.6 Hz and was seen to disappear in the $^{1}H\{^{19}F\}$ NMR (Figure 6.11), further confirming the origin of the coupling to be an interaction with fluorine.

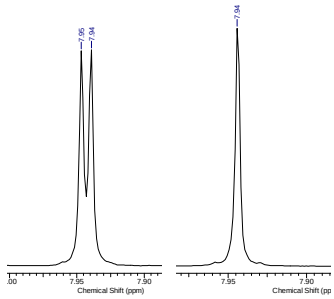


Figure 6.11: ^{1}H and $^{1}H\{^{19}F\}$ spectra for H8 of **5.26β**.

*6.3.2 β-Tetrafluorouracil **4.37β***

An interaction was also observed between F2′ and H6 in the β-tetrafluorouridine **4.37β**. The interaction was clearly demonstrated by the cross peak in the ^{1}H-^{19}F COSY NMR (Figure 6.12).

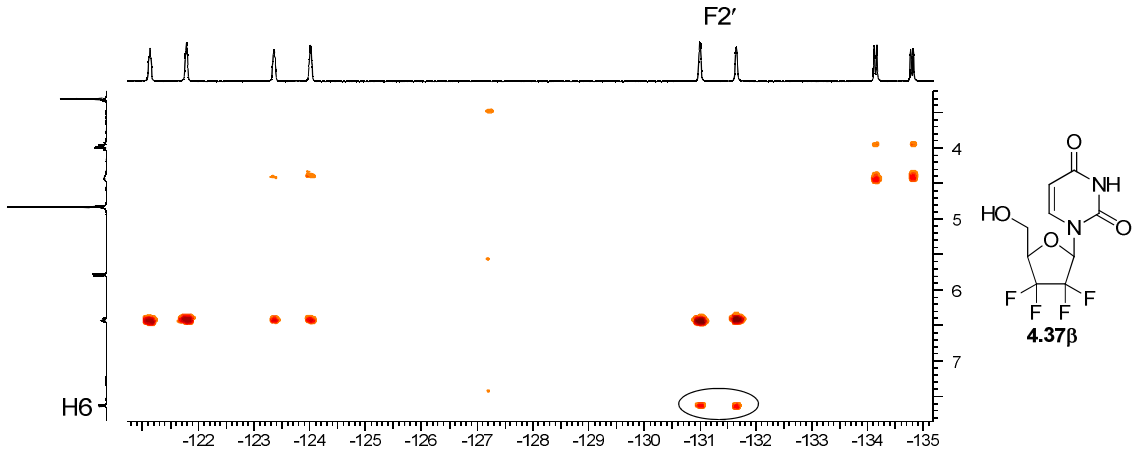


Figure 6.12: ^{1}H-^{19}F COSY for β-tetrafluorouridine **4.37β**.

The coupling was of 2.1 Hz and was seen to disappear in the $^{1}H\{^{19}F\}$ NMR spectrum (Figure 6.13), further confirming the origin of the coupling to be an interaction with fluorine.

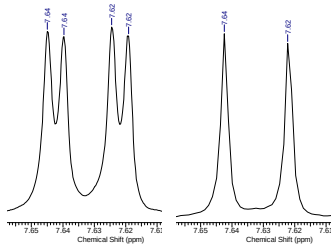


Figure 6.13: ^{1}H and $^{1}H\{^{19}F\}$ spectra for H6 in **4.37β**.

Several of the nucleosides synthesised displayed an interaction between F2′ and H8 in the case of the purines and H6 in the pyrimidines. Those that did display an interaction of this nature are shown in Figure 6.14.

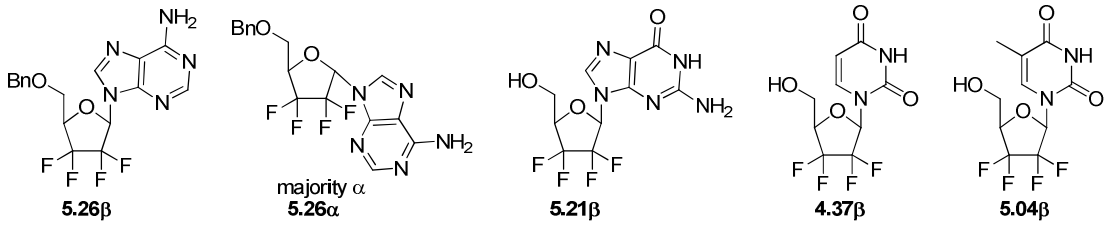


Figure 6.14: Nucleosides displaying coupling between F2′ and the nucleobase.

6.4 Conclusions

Anomeric separation and assignment was successfully undertaken for tetrafluorouridine **4.37**, tetrafluorothyimidine **5.04**, tetrafluoro-5-fluorouridine **5.05** and the difluorinated AZT analogue **5.36**.The presence of long range H–F coupling, between the sugar and the nucleobases, was also identified.

7 Project Summary

In summary the main aims of the project have been achieved. The synthesis of gemcitabine *via* novel aminoglycosylation chemistry and subsequent linear nucleobase construction has been realised. However it did not prove to be possible to crystallise or effect anomeric separation of the early stage intermediates in the synthesis. Moreover, the lack of stereochemical integrity at the anomeric centre during nucleobase construction further reduces any advantage of our newly developed methodology over the existing methods of gemicitabine synthesis.

The stability and structure of the aminoglycosides synthesised during the development of the aminoglycosylation methodology was investigated. Surprisingly these were seen to readily undergo hydrolysis when subjected to acidic conditions. This reactivity was surprising due to the extra stability expected to be imparted by the 2,2-difluorination.

A range of novel tetrafluorinated nucleoside analogues has been constructed, making use of both our newly developed aminoglycosylation methodology as well as more established methods of nucleobase introduction *via* mesylate displacement and Mitsunobu chemistry. In this context, we have improved the yield of purine introduction *via* the Mitsunobu reaction. In addition the synthesis of a novel 2′,2′-difluorinated AZT analogue was also undertaken.

Anomeric separation of the novel nucleosides was effected *via* RP-HPLC, enabling the possibility of further analysis of the structure of these molecules and additionally allowing the evaluation of their biological activity. The structure of most nucleoside anomers was proven by NMR.

8 Experimental

General Experimental

Reaction vessels were flame dried under vacuum and cooled under N_2 prior to use. Water sensitive reactions were carried out under nitrogen atmosphere, using dry solvents. For reactions carried out at low temperature, dry ice was used as the cryogenic substance.

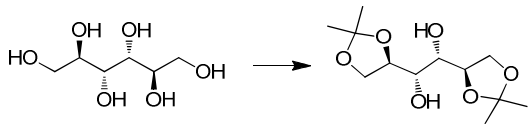
THF and Et_2O were distilled from Na/benzophenone. DCM, Et_3N and pyridine were distilled from CaH. Toluene was distilled from Na. MeCN was dried over molecular sieves. Chemical reagents were ordered from Aldrich or Alfa Aeser.

Reactions were monitored by TLC (Kiesegel 60 F_{254} MERCK Art 5735 aluminium sheet). The TLC dye is a solution of *p*-anisaldehyde (186 mL EtOH, 6.9 mL H_2SO_4, 2.1 mL AcOH, 5.1 mL *p*-anisaldehyde). Flash column chromatography was performed on silica gel (60 Å, 35-70 microns).

NMR spectra were recorded on a BRUCKER AV300 at 300 MHz (^{1}H), 75 MHz (^{13}C) and 282 MHz (^{19}F), or on a BRUCKER AV400 at 400 MHz (^{1}H), 100 MHz (^{13}C) using residual solvents as the internal standard. The coupling constants (*J*) are expressed in Hertz, the chemical shift in ppm. IR spectra were recorded on a THERMO MATSON Fourier Transform spectrometer. The wave numbers (ν) are given in cm^{-1}.

LRMS spectra were accomplished with ThermoQuest Trace MS, single quadrupol GC. This instrument was used for electronionisation (EI) and chemical ionisation (CI) spectra. HRMS spectra were recorded on a VG Analytical 70-250-SE, normal geometry, double focusing.

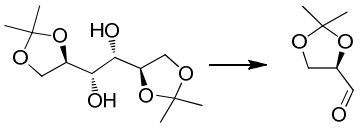
(1*S*,2*S*)-1,2-Bis[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethane-1,2-diol, 1.35a[59]



To a stirring suspension of D-mannitol **1.34** (300 g, 1.65 mol) and molecular sieves (32 g) in DMSO (600 mL) was added PTSA (0.05 equiv, 82.5 mmol, 15.7 g) and 2,2-dimethoxypropane (2.5 equiv, 4.12 mol, 506 mL). The reaction mixture was stirred at RT for 48 h then poured into 3% $NaHCO_3$ (aq) and extracted with EtOAc (3×1 L). The organic extracts were washed with water, then brine before drying over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude white solid which was refluxed in a small volume of EtOAc before addition of hot petrol. This was left overnight to recrystallise to yield **1.35a** as a white solid (280 g, 65%).

Mp: 104–109 ℃ (EtOAc/hexane), lit [59] 115–119 ℃ (Et_2O/hexane).
[α]$_D$ +16.6 (c 1.2, MeOH, 24 ℃), lit [120] +2.1 (c 2.1, MeOH, 25 ℃).
IR (film) 3268 (br), 2978 (m), 2894 (m), 1382 (s), 1372 (s) cm^{-1}.
LRMS (ESI^+) *m*/*z* 285.2 $(M+Na)^+$ (100).
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24–4.11 (4 H, m, 2×CH_2), 4.01–3.96 (2 H, m, 2×CH), 3.79–3.73 (2 H, m, 2×CH), 2.58 (2 H, d, *J* = 6.7 Hz, 2×OH), 1.43 (6 H, s, 2×CH_3), 1.37 (6 H, s, 2×CH_3) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 109.4 (2×C), 76.3 (2×CH), 71.2 (2×CH), 66.7 (2×CH_2), 26.7 (2×CH_3), 25.2 (2×CH_3) ppm.
Data corresponds to the literature.[121]

(4*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde, 2.03a[121]

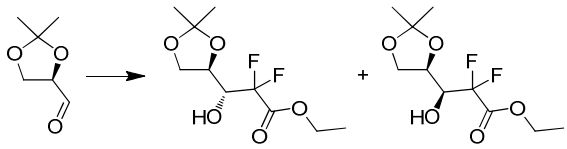


To a stirring solution of **1.35a** (90.1 g, 0.342 mol) in DCM (760 mL) and sat. $NaHCO_3$ (aq) (35 mL) at 0 ℃ was added sodium metaperiodate (2 equiv, 0.684 mmol, 148 g) portionwise over 45 min. The reaction mixture was stirred

vigorously at 0 ℃ for a further 3.25 h. The precip itate was removed by filtration, the filtrate dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo* to yield a crude yellow oil. This was purified by vacuum distillation (b.p. 48–52 ℃, 18 mmHg) to yield **2.03a** as a pale yellow oil (68.4 g, 76%).

[α_D] +13.3 (c 0.2, benzene, 24 ℃), lit [31] +12.6 (c 15.19, benzene, 20 ℃).
IR (film): 3413 (s.br), 2989 (m), 2935 (w), 2357 (w), 1375 (w), 1071 (s) cm^{-1}.
LRMS (ESI^+) *m*/*z* 185.2 $(M+Na+MeOH)^+$ (100).
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (1 H, dd, *J* = 1.8, 0.3 Hz, CHO), 4.40 (1 H, ddd, *J* = 7.2, 4.8, 1.9 Hz, OCH), 4.19 (1 H, ddd, *J* = 8.8, 7.3, 0.3 Hz, CHH), 4.11 (1 H, dd, *J* = 8.8, 4.6 Hz, CHH), 1.51 (3 H, q, *J* = 0.7 Hz, CH_3), 1.43 (3 H, q, *J* = 0.7 Hz, CH_3) ppm.
^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 201.8 (CHO), 111.3 (C), 79.8 (CH), 65.6 (CH_2), 26.2 (CH_3), 25.1 (CH_3) ppm.
A more detailed ^{1}H NMR assignment is given here than in the literature.[121]

(*R*)-ethyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propanoate, 2.04a
(*S*)-ethyl-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-difluoro-3-hydroxy propanoate, 2.05a



A solution of **2.03a** (11.3 g, 86.8 mmol) and ethyl bromodifluoroacetate (1.5 equiv, 130.2 mmol, 16.7 mL) in 1:1 THF/Et_2O (120 mL) was added, dropwise at a rate to maintain a gentle reflux, to activated zinc powder (2 equiv, 173.7 mmol, 11.4 g) under anhydrous conditions, whilst maintaining a gentle reflux. The reaction mixture was stirred for a further 30 min at 50 ℃. The reaction mixture was cooled and poured into 1 M HCl/ice (70 mL/70 g) and stirred until the ice had melted. The aqueous phase was extracted with Et_2O (2×150 mL), washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a colourless oil which was purified by column

chromatography on silica gel (0.5:99.5–1.5:98.5 MeOH/DCM) to yield **2.04a** and **2.05a** as colourless oil (16.0 g, 72%).[62]

2.04a

[α_D] –2.8 (c 4.2, $CHCl_3$, 24 ℃).

IR (film) 3425 (br), 2989 (m), 1759 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40–4.25 (4 H, m, CH_2, 2×CH), 4.11–4.09 (2 H, m, OCH_2), 2.64 (1 H, d, *J* = 3.8 Hz, OH), 1.40–1.34 (9 H, m, 3×CH_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 162.8 (C=O), 113.9 (dd, *J* = 256.0, 253.8 Hz, CF_2), 109.6 (C), 73.4 (CH), 71.7 (dd, *J* = 25.4, 23.2 Hz, CH), 65.5 (d, *J* = 3.3 Hz, OCH_2), 63.1 ($\underline{C}H_2CH_3$), 26.2 (CH_3), 25.0 (CH_3), 13.8 ($CH_2\underline{C}H_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –117.6 (1 F, dd, *J* = 262.2, 12.9 Hz, C$\underline{F}$F), –120.2 (1 F, dd, *J* = 262.2, 12.9 Hz, CF$\underline{F}$) ppm.

2.05a

[α_D] +9.6 (c 0.9, $CHCl_3$, 24 ℃).

IR (film) 3479 (br), 2988 (m), 1759 (s) cm^{-1}.

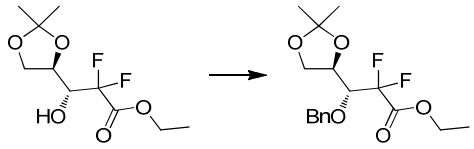
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (1 H, m, CH), 4.36 (2 H, q, *J* = 7.1 Hz, $C\underline{H}_2CH_3$) 4.15 (1 H, dd, *J* = 8.4, 6.6 Hz, HOCH), 4.05–3.86 (2 H, m, 2×CH), 2.91 (1 H, d, *J* = 8.5 Hz, OH), 1.44 (3 H, s, CH_3), 1.41–1.33 (6 H, m, 2×CH_3) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 163.0 (C=O), 113.6 (dd, *J* = 259.3, 252.7 Hz, CF_2), 110.3 (C), 72.2 (CH), 70.9 (dd, *J* = 28.2, 26.0 Hz, CH), 66.3 (CH_2), 63.2 ($\underline{C}H_2CH_3$), 26.2 (CH_3), 25.3 (CH_3), 13.9 ($CH_2\underline{C}H_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –112.5 (1 F, dd, *J* = 265.4, 5.4 Hz, C$\underline{F}$F), –122.3 (1 F, dd, *J* = 265.4, 16.1 Hz, CF$\underline{F}$) ppm.

A more detailed ^{1}H NMR assignment is given here than in the literature.[30]

Ethyl-(3*R*)-3-(benzyloxy)-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoropropanoate, 2.06a



To a stirring solution of **2.04a** (1.832 g, 7.21 mmol) in DMF (40 mL) at 0 ℃ was added sodium hydride (60% dispersion in mineral oil, 1.2 equiv, 8.65 mmol, 346 mg). The reaction mixture was stirred at 0 ℃ f or 1 h, before the addition of tetrabutylammonium iodide (0.1 equiv, 0.72 mmol, 266 mg) and benzyl bromide (1.3 equiv, 9.37 mmol, 1.11 mL). The reaction mixture was stirred at RT in the dark for 18 h, quenched with sat. NH_4Cl (aq) and stirred for 5 min before dilution with water and extraction into Et_2O (3×60 mL). The combined organic extracts were washed with water and brine before drying over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude oil which was purified by column chromatography on silica gel (10:90 acetone/petrol) to yield **2.06a** as colourless oil (2.17 g). This product contained a small amount of co-running impurity visible by ^{19}F NMR.

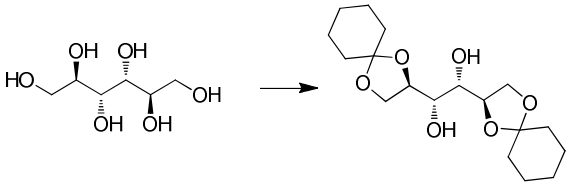
IR (film) 2987 (m), 2938 (w), 1777 (s), 1757 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.31 (5 H, m, 5×ArH), 4.81 (2 H, s, OCH_2Ar), 4.38–4.16 (4 H, m, 2×CH_2), 4.10–3.96 (2 H, m, 2×CH), 1.41 (3 H, s, CH_3), 1.35 (3 H, s, CH_3), 1.31 (3 H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 204.0 (C), 159.8 (C), 137.1 (C), 128.5 (2×CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (2×CH_{Ar}), 78.2 (dd, *J* = 24.3, 21.0 Hz, CH), 75.9 (d, *J* = 2.2 Hz, CH_2), 73.7 (d, *J* = 3.3 Hz, CH), 65.4 (CH_2), 63.0 (CH_2), 26.2 (CH_3), 25.0 (CH_3), 13.9 (CH_3) ppm (CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –115.2 (1 F, dd, *J* = 266, 12.9 Hz, C$\underline{F}$F), –116.9 (1 F, dd, *J* = 266, 12.9 Hz, CF$\underline{F}$) ppm.

(1*S*,2*S*)-1,2-Di-(*R*)-1,4-dioxa-spiro[4.5]dec-2-yl-ethane-1,2-diol, 1.35b[60]



To a stirring suspension of D-mannitol **1.34** (20.00 g, 109.8 mmol) in DMSO (40 mL), was added cyclohexanone (3 equiv, 329.4 mmol, 31.88 mL), triethylorthoformate (1.01 equiv, 110.9 mmol, 18.44 mL) and boron trifluoride diethyl etherate (0.08 equiv, 8.78 mmol, 1.08 mL) dropwise. The reaction was stirred at RT for 3 d then poured into ice cold 10% $NaHCO_3$ (aq) (200 mL). The aqueous phase was extracted with Et_2O (3×80 mL) and the combined organic phases washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to yield an orange oil which was recrystallised overnight from 2:1 hexane/Et_2O to yield 7.00 g as a white solid. A 2nd and 3rd crop were obtained to give a further 19.20 g. Total yield **1.35b** 26.20 g, 70%.

Mp: 100–103 ℃ (Et_2O/hexane), lit[60] 105–106 ℃ (Et_2O/hexane).

[α]$_D$: +2.3 (c 0.8, MeOH, 24 ℃), lit [60] +2.1 (c 5, MeOH, 20 ℃).

IR (film): 3282 (br), 2933 (s), 2852 (m), 1096 (s) cm^{-1}.

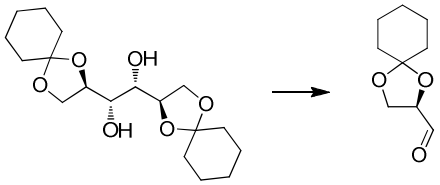
LRMS (ESI$^+$) *m/z* 365.4 (M+Na)$^+$ (100).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29–4.06 (4 H, m, 2×OCH_2), 4.03–3.87 (2 H, m, 2×CH), 3.83–3.65 (2 H, m, 2×CH), 2.61 (2 H, d, *J* = 6.7 Hz, 2×OH), 1.74–1.47 (16 H, m, 8×CH_2), 1.41 (4 H, br s, 2×CH_2) ppm.

^{13}C NMR + DEPT (75 MHz, $CDCl_3$) δ 110.0 (2×C), 76.0 (2×OCH), 71.4 (2×OCH), 66.4 (2×OCH_2), 36.4 (2×CH_2), 34.6 (2×CH_2), 25.1 (2×CH_2), 24.0 (2×CH_2), 23.8 (2×CH_2) ppm.

A more detailed ^{1}H NMR assignment is given here than in the literature.[60]

1,4-Dioxaspiro[4.5]decane-2-carbaldehyde, 2.03b[122]

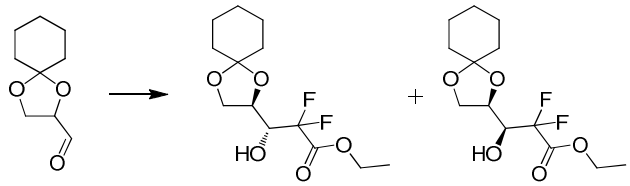


To a stirring suspension of **1.35b** (17.21 g, 50.6 mmol) in 60:40 MeCN/water (125 mL) under N_2 at 0–10 ℃ was added sodium (meta)periodate (2 equiv, 101 mmol, 21.63 g) portionwise over 40 min. The reaction mixture was stirred for a further 1 h then filtered and the filtrate diluted with water before extraction with $CHCl_3$. The organic phase was washed successively with water, then brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude colourless oil which was purified by vacuum distillation (b.p. 56–62 ℃, 0.5 mmHg) to yield **2.03b** as a colourless oil (8.61 g, 50%).

$[\alpha]_D$: +37.5 (c 1.4, benzene, 24 ℃), lit [122] +60.5 (c 3.5, benzene, 23 ℃).
IR (film) 3404 (br), 2935 (s), 2860 (w), 1736 (w), 1096 (s) cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1 H, d, *J* = 1.9 Hz, CHO), 4.38 (1 H, ddd, *J* = 7.1, 4.9, 1.9 Hz, OCH) 4.21–4.03 (2 H, m, OCH_2) 1.75–1.52 (8 H, m, 4×CH_2), 1.44 (2 H, d, *J* = 5.1 Hz, CH_2) ppm.
^{13}C NMR +DEPT (75 MHz, $CDCl_3$) δ 202.1 (CHO), 111.9 (C), 79.5 (CH), 65.2 (OCH_2), 35.9 (CH_2), 34.6 (CH_2), 25.0 (CH_2), 23.9 (CH_2), 23.8 (CH_2) ppm.
A more detailed ^{1}H NMR assignment is given here than in the literature.[122]

(*R*)-ethyl-2,2-difluoro-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl) propanoate, 2.04b

(*S*)-ethyl-2,2-difluoro-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl) propanoate, 2.05b



A solution of **2.03b** (3.158 g, 18.6 mmol) and ethyl bromodifluoroacetate (2 equiv, 37.1 mmol, 4.76 mL) in 1:1 THF/Et_2O (26 mL) was added, dropwise over 20 min, to activated zinc powder (2 equiv, 37.1 mmol, 2.43 g) under anhydrous conditions, whilst maintaining a gentle reflux, then stirred for a further 30 min at 50 ℃. The reaction mixture was c ooled and poured into 1 M HCl/ice (22 mL/22 g) and stirred until the ice had melted. The aqueous phase was extracted with Et_2O (2×50 mL) and the combined organic phases washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a colourless oil which was purified by column chromatography on silica gel (5:95 EtOAc/DCM) to yield **2.04b** and **2.05b** as colourless oil (2.65 g, 48%).

Data for **2.04b**

[α_D] +0.4 (c 2.9, $CHCl_3$, 24 ℃).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43–4.16 (4 H, m, OC$\underline{H}_2$CH and C$\underline{H}_2$CH$_3$), 4.16–4.01 (2 H, m, C$\underline{H}$OH + OC$\underline{H}$), 2.54 (1 H, d, *J* = 4.0 Hz, OH), 1.65–1.50 (8 H, m, 4×CH_2), 1.43–1.39 (2 H, m, CH_2), 1.37 (3 H, t, *J* = 7.2 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (t, *J* = 31.1 Hz, C=O), 113.9 (dd, *J* = 256.6, 254.6 Hz, CF_2), 110.3 (C), 73.1 (OCH), 71.9 (dd, *J* = 25.3, 23.3 Hz, $\underline{C}$HCF$_2$), 65.2 (d, *J* = 3.9 Hz, OCH_2), 63.1 (OCH_2), 36.0 (CH_2), 34.5 (CH_2), 25.1 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 13.9 (CH_3) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –117.5 (1 F, dd, *J* = 262.2, 12.9 Hz, C$\underline{F}$F), –120.0 (1 F, dd, *J* = 262.2 Hz, 12.9 CF$\underline{F}$) ppm.

Data for **2.05b**

[α_D] –13.4 (c 0.5, $CHCl_3$, 22 ℃).

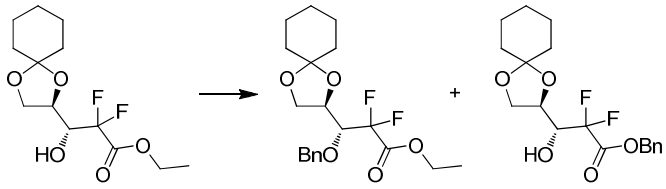
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (1 H, m, $CH_2C\underline{H}O$), 4.37 (2 H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 4.14 (1 H, dd, *J* = 8.4, 6.6 Hz, C<u>H</u>HCH), 3.96 (1 H, m, C<u>H</u>OH), 3.90 (1 H, dd, *J* = 9.3, 6.9 Hz, CH<u>H</u>CH), 2.93 (1 H, d, *J* = 8.5 Hz, OH), 1.66–1.55 (8 H, m, 4×CH_2), 1.43–1.37 (2 H, m, CH_2), 1.38 (3 H, t, *J* = 7.1 Hz, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (t, *J* = 30.7 Hz, C=O), 113.6 (dd, *J* = 260.5, 253.2 Hz, CF_2), 110.9 (C), 71.8 ($CH_2\underline{C}HO$), 70.9 (t, *J* = 26.3 Hz, CHOH), 66.0 ($\underline{C}H_2CHO$), 63.2 ($\underline{C}H_2CH_3$), 35.8 (CH_2), 34.8 (CH_2), 25.0 (CH_2), 23.9 (CH_2), 23.7 (CH_2), 13.9 (CH_3) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –112.2 (1 F, d, *J* = 270.8 Hz, C<u>F</u>F), –122.1 (1 F, dd, *J* = 266.5, 17.2 Hz, CF<u>F</u>) ppm.

(*R*)-3-Benzyloxy-3-(*R*)-1,4-dioxa-spiro[4.5]dec-2-yl-2,2-difluoro-propionic acid ethyl ester, 2.06b

(*R*)-benzyl-2,2-difluoro-3-hydroxy-3-((*R*)-1,4-dioxaspiro[4.5]decan-2-yl)propanoate, 2.07



To a stirring solution of **2.06b** (2.505 g, 8.50 mmol) in DMF (50 mL) at 0 ℃ was added sodium hydride (60% dispersion in mineral oil, 1.2 equiv, 10.2 mmol, 408 mg). The reaction mixture was stirred at 0 °C for 1 h, before the addition of tetrabutylammonium iodide (0.1 equiv, 0.85 mmol, 314 mg) and benzyl bromide (1.3 equiv, 11.1 mmol, 1.31 mL). The reaction mixture was stirred at RT for 18 h, quenched with sat. NH_4Cl (aq) and stirred for 5 min before dilution with water and extraction into Et_2O (3×50 mL). The combined organic extracts were washed water, then brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude oil which was purified by column chromatography on silica gel (10:90 EtOAc/petrol) to yield **2.06b** as colourless oil (2.92 g). This product contained a small amount of co-running impurity visible by ^{19}F NMR.

Data for **2.06b**:

IR (film) 2936 (m), 2862 (w), 1777 (s), 1758 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.30 (5 H, m, 5×ArH), 4.81 (2 H, s, CH_2Ph), 4.70–4.17 (4 H, m, 2×CH_2), 4.09–3.94 (2 H, m, 2×CH), 1.61–1.57 (10 H, m, 4×CH_2), 1.32 (3 H, t, *J* = 7.2 Hz, CH_3) ppm.

^{13}C NMR + DEPT (300 MHz, $CDCl_3$) δ 137.1 (C_{Ar}), 128.4 (2×CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (2×CH_{Ar}), 110.0 (d, *J* = 3.3 Hz, C), 78.2 (dd, *J* = 24.3, 22.1 Hz, CH), 75.8 (CH_2), 73.3 (d, *J* = 2.2 Hz, CH), 65.0 (d, *J* = 3.3 Hz, CH_2), 63.0 (CH_2), 35.9 (CH_2), 34.4 (CH_2), 25.1 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 13.9 (CH_3) ppm (C=O and CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –115.2 (1 F, dd, *J* = 264.3, 12.9 Hz, C<u>F</u>F), –120.0 (1 F, dd, *J* = 264.3, 12.9 Hz, CF<u>F</u>) ppm.

Data for **2.07**:

IR (film) 3416 (br), 2937 (m), 2860 (w), 1760 (s) cm^{-1}.

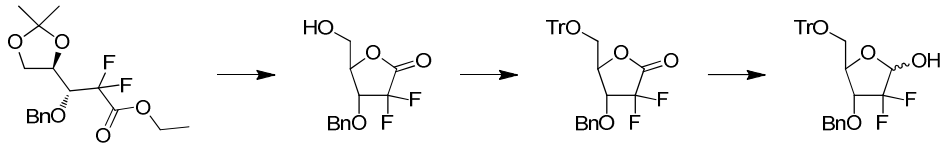
LRMS (ESI^+) *m*/*z* 379.2 $(M+Na)^+$ (100).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.36 (5 H, m, 5×ArH), 5.31 (2 H, dd, *J* = 31.6, 12.2 Hz, CH_2Ph), 4.30–4.23 (2 H, m, CH_2), 4.11–4.04 (2 H, m, 2×CH), 2.46 (1 H, d, *J* = 2.5 Hz, OH), 1.63–1.53 (10 H, m, 4×CH_2) ppm.

^{13}C NMR + DEPT (400 MHz, $CDCl_3$) δ 162.7 (t, *J* = 32.1 Hz, C=O), 134.1 (C_{Ar}), 128.8 (CH_{Ar}), 128.7 (2×CH_{Ar}), 128.3 (2×CH_{Ar}), 114.0 (dd, *J* = 256.1, 253.1 Hz, CF_2), 110.3 (C), 73.0 (CH), 71.9 (dd, *J* = 24.8, 22.8 Hz, CH), 68.5 (CH_2), 65.2 (d, *J* = 3.9 Hz, CH_2), 35.9 (CH_2), 34.4 (CH_2), 25.0 (CH_2), 23.9 (CH_2), 23.7 (CH_2) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –117.1 (1 F, dd, *J* = 262.2, 12.9 Hz, C<u>F</u>F), –120.0 (1 F, dd, *J* = 262.2, 12.9 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-4-Benzyloxy-3,3-difluoro-5-trityloxymethyl-tetrahydrofuran-2-ol, 2.12c[62]



To benzylated alcohol **2.06a** (662 mg, 1.92 mmol), in 2:1 MeOH/water (10.5 mL) was added Dowex 50 (5 g). The reaction mixture was stirred at RT for 3 d, the Dowex 50 filtered off and the solvents reduced *in vacuo*. The resulting crude residue was taken up in water and extracted with Et_2O (3×15 mL). The organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude residue, **2.10**.

^{19}F NMR (282 MHz, $CDCl_3$) δ –114.2 (1 F, dd, *J* = 279.0, 6.4 Hz, C<u>F</u>F), –121.9 (1 F, dd, *J* = 281.2, 15.0 Hz, CF<u>F</u>) ppm.

The crude residue **2.10**, was stirred in DCM (4 mL) with trityl chloride (1.1 equiv, 1.64 mmol, 458 mg), triethylamine (1.5 equiv, 2.24 mmol, 0.31 mL) and DMAP (0.1 equiv, 0.15 mmol, 18 mg). The reaction mixture was stirred at RT for 18 h, then diluted with brine and extracted with DCM (3×15 mL). The organic extracts were washed with water, then brine before drying over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield **2.11c** as a crude residue.

The crude residue **2.11c**, in toluene (6 mL) at –80 ℃ was treated with DIBAL (1 M in hexanes, 2 equiv, 2.98 mmol, 2.98 mL). The reaction mixture was stirred at –65 ℃ for 2 h, quenched with $Na_2SO_4 \cdot 10H_2O$, stirred for 10 min then filtered. The filtrate was diluted with water and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to yield a crude residue which was purified first by column chromatography on silica gel (15:85 acetone/hexane) then by HPLC (30:70 acetone/hexane) to yield **2.12c** as colourless oil as a 1:1 mixture of anomers (180 mg, 19% over 3 steps).

IR (film) 3393 (br), 3059 (w), 2928 (w), 1693 (s), 1597 (w), 1491 (m), 1449 (m), 1365 (w), 1318 (w), 1247 (m), 1221 (m), 1070 (s), 1030 (s) cm^{-1}.

LRMS (ESI^+) *m*/*z* 557.3 $(M+Na+MeOH)^+$ (100), 525.3 $(M+Na)^+$ (45).

HRMS (ESI^+) for $C_{31}H_{28}O_4F_2$ $(M+Na)^+$ calcd: 525.1848, found: 525.1852.

Anomer X

^{1}H NMR (400 MHz, acetone-d_6) δ 7.52–7.46 (6 H, m, 6×ArH), 7.35–7.26 (14 H, m, 14×ArH), 6.23 (1 H, d, *J* = 6.0 Hz, OH), 5.42 (1 H, t, *J* = 7.0 Hz, C<u>H</u>OH), 4.77 (1 H, d, *J* = 11.7 Hz, C<u>H</u>HPh)[a], 4.59 (1 H, d, *J* = 11.7 Hz, CH<u>H</u>Ph)[a], 4.14–4.03 (2 H, m, 2×CH), 3.38 (1 H, m, C<u>H</u>HOTr)[a], 3.22 (1 H, dd, *J* = 10.2, 4.9 Hz, CH<u>H</u>OTr)[a] ppm.

Anomer Z

^{1}H NMR (400 MHz, acetone-d_6) δ 7.52–7.46 (6 H, m, 6×ArH), 7.35–7.26 (14 H, m, 14×ArH), 6.46 (1 H, d, *J* = 6.1 Hz, OH), 5.25 (1 H, dd, *J* = 8.2, 6.4 Hz, C<u>H</u>OH), 4.77 (1 H, d, *J* = 11.8 Hz, C<u>H</u>HPh)[a], 4.56 (1 H, d, *J* = 11.8 Hz, CH<u>H</u>Ph)[a], 4.38–4.30 (2 H, m, 2×CH), 3.36 (1 H, m, C<u>H</u>HOTr)[a], 3.21 (1 H, dd, *J* = 10.4, 4.7 Hz, CH<u>H</u>OTr)[a] ppm.

[a] Unable to ascertain which CHHPh peaks belong to each of anomer X and anomer Z, therefore one arbitrarily assigned to each.

^{13}C NMR + DEPT (100 MHz, acetone-d_6) δ 144.9 (C_{Ar}), 144.8 (C_{Ar}), 138.4 (C_{Ar}), 138.3 (C_{Ar}), 129.6 (CH_{Ar}), 129.5 (CH_{Ar}), 129.2 (CH_{Ar}), 128.7 (CH_{Ar}), 128.0 (CH_{Ar}), 128.0 (CH_{Ar}), 124.3 (dd, *J* = 268.2, 248.8 Hz, 0.5×CF_2), 123.8 (dd, *J* = 263.4, 251.7 Hz, 0.5×CF_2), 97.1 (dd, *J* = 55.4, 22.4 Hz, 0.5×CHOH), 96.7 (dd, *J* = 51.5, 22.4 Hz, 0.5×CHOH), 80.7 (dd, *J* = 5.8, 1.9 Hz, 0.5×<u>C</u>HCH_2), 79.0 (d, *J* = 9.7 Hz, 0.5×<u>C</u>HCH_2), 78.8 (dd, *J* = 30.1, 18.5 Hz, 0.5×CHOBn), 77.5 (dd, *J* = 25.3, 16.5 Hz, 0.5×CHOBn), 73.5 (0.5×CH_2Ph), 73.3 (0.5×CH_2Ph), 64.9 (0.5×CH_2OTr), 63.8 (0.5×CH_2OTr) ppm (some C_{Ar}, CH_{Ar} overlap).

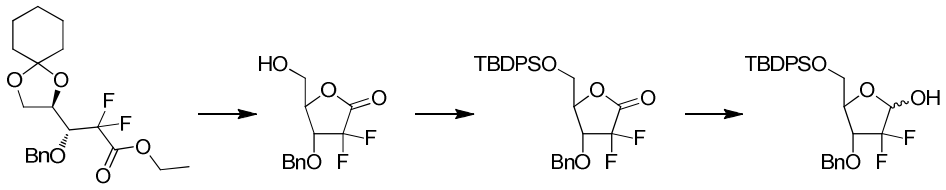
Anomer X:

^{19}F NMR (376 MHz, acetone-d_6) δ –105.9 (1 F, dq, *J* = 242.9, 17.2, 8.6 Hz, C<u>F</u>F), –125.5 (1 F, dd, *J* = 242.9, 4.3 Hz, CF<u>F</u>) ppm.

Anomer Z:

^{19}F NMR (376 MHz, acetone-d_6) δ –121.0 (1 F, dd, *J* = 234.3, 8.6 Hz, C<u>F</u>F), –126.1 (1 F, dq, *J* = 234.3, 15.0, 8.6 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-(tert-butyldiphenylsilyloxymethyl)-3,3-difluorotetrahydrofuran-2-ol, 2.12d[62]



To benzylated alcohol **2.06b** (1.135 g, 2.95 mmol) in 2:1 MeOH/water (12 mL) was added Dowex 50 (8.5 g). The reaction mixture was stirred at RT for 3 d, the Dowex 50 filtered off and the solvents reduced *in vacuo*. The resulting crude residue was taken up in water and extracted with Et_2O (3×25 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield **2.10** as a crude residue.

^{19}F NMR (282 MHz, $CDCl_3$) δ –114.2 (1 F, dd, *J* = 279.0, 6.4 Hz, C<u>F</u>F), –121.9 (1 F, dd, *J* = 281.2, 15.0 Hz, CF<u>F</u>) ppm.

The crude residue **2.10** was stirred in DMF (8 mL) with TBDPSCl (1.5 equiv, 4.43 mmol, 1.16 mL) and imidazole (2.2 equiv, 6.49 mmol, 442 mg) at RT for 20 h, then 40 ℃ for 24 h, then 70 ℃ for 20 h. The solvents were reduced *in vacuo* and the crude residue taken up in water and extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield **2.11d** as a crude residue.

^{19}F NMR (282 MHz, $CDCl_3$) δ –113.1 (1 F, d, *J* = 283.7 Hz, C<u>F</u>F), –121.4 (1 F, d, *J* = 285.4 Hz, CF<u>F</u>) ppm.

The crude residue **2.11d** in toluene (15 mL) at –80 ℃ was treated with DIBAL (1 M in hexanes, 2 equiv, 5.90 mmol, 5.90 mL), stirred at –65 ℃ for 2.5 h then quenched with MeOH (2 mL). The reaction mixture was stirred for 10 min then diliuted with 1 M HCl (aq) and extracted with Et_2O (3×25 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (aq), then brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude

residue which was purified first by column chromatography on silica gel (15:85 acetone/hexane) then by HPLC (25:75 acetone/hexane) to yield **2.12d** as colourless oil as a 1:1 mixture of anomers (1.257 g, 85% over 3 steps).

IR (film) 3414 (br), 3070 (w), 2931 (m), 2858 (m) cm^{-1}.

LRMS (ESI^+) *m*/*z* 521.4 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{28}H_{32}F_2O_4Si$ $(M+Na)^+$ calcd 521.1936, found 521.1922.

^{1}H NMR (300 MHz, acetone-d_6) δ 7.59–7.82 (4 H, m, 4×ArH), 7.21–7.55 (11 H, m, 11×ArH), 6.26 (0.5 H, d, *J* = 6.4 Hz, 0.5×OH), 6.13 (0.5 H, dd, *J* = 6.2, 0.8 Hz, 0.5×OH), 5.37 (0.5 H, t, *J* = 7 Hz, 0.5×C<u>H</u>OH), 5.21 (0.5 H, t, *J* = 5.9 Hz, 0.5×C<u>H</u>OH), 4.85 (0.5 H, d, *J* = 15.7 Hz, 0.5×C<u>H</u>HPh), 4.83 (0.5 H, d, *J* = 15.5 Hz, 0.5×CH<u>H</u>Ph), 4.66 (0.5 H, *J* = 14.8 Hz, 0.5×CH<u>H</u>Ph), 4.62 (0.5 H, d, *J* = 15.6 Hz, 0.5×C<u>H</u>HPh), 4.14–4.44 (1.5 H, m, 1.5×CH), 3.93–4.07 (0.5 H, m, 0.5×CH), 3.71–3.93 (2 H, m, CH_2), 1.03 (4.5 H, s, 0.5×$C(CH_3)_3$), 1.01 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (75 MHz, acetone-d_6) δ 139.0 (C_{Ar}), 138.9 (C_{Ar}), 134.1 (C_{Ar}), 134.0 (C_{Ar}), 136.8 (CH_{Ar}), 138.7 (CH_{Ar}), 130.8 (CH_{Ar}), 129.3 (CH_{Ar}), 129.9 (CH_{Ar}), 128.7 (CH_{Ar}), 97.3 (dd, *J* = 41.8, 22.4 Hz, 0.5×CHOH), 96.7 (dd, *J* = 37.9, 23.3 Hz, 0.5×CHOH), 82.1 (d, *J* = 4.9 Hz, 0.5×<u>C</u>HCH_2), 80.6 (d, *J* = 8.8 Hz, 0.5×<u>C</u>HCH_2), 78.1 (dd, *J* = 30.1, 17.5 Hz, 0.5×CHOBn), 77.5 (dd, *J* = 25.3, 16.5 Hz, 0.5×CHOBn), 73.6 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 73.4 (0.5×CH_2Ph), 65.2 (0.5×CH_2), 63.7 (0.5×CH_2), 27.3 (0.5×C(<u>C</u>$H_3)_3$), 27.2 (0.5×C(<u>C</u>$H_3)_3$), 19.9 (<u>C</u>$(CH_3)_3$) ppm (some C_{Ar}/CH_{Ar} overlap, CF_2 not visible).

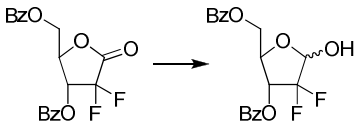
Anomer X:

^{19}F NMR (282 MHz, acetone-d_6) δ –106.1 (1 F, dq, *J* = 241.8, 15.0, 7.5 Hz, C<u>F</u>F), –125.5 (1 F, dd, *J* = 241.8, 3.2 Hz, CF<u>F</u>) ppm.

Anomer Z:

^{19}F NMR (282 MHz, acetone-d_6) δ –120.5 (1 F, dd, *J* = 235.3, 8.6 Hz, C<u>F</u>F), –125.7 (1 F, dq, *J* = 235.3, 14.0, 8.6 Hz, CF<u>F</u>) ppm.

[(2*R*,3*R*)-3-(Benzoyloxy)-4,4-difluoro-5-hydroxytetrahydrofuran-2-yl]methylbenzoate, 1.51



To lactone **1.50** (819 mg, 2.18 mmol) in THF (20 mL) at –30 ℃ was slowly added Vitride (65% wt solution in toluene, 1.0 equiv, 2.18 mmol, 0.68 mL) over 45 min. The reaction mixture was stirred at –20 ℃ for 45 min before addition of MeOH (0.4 mL), stirred 0℃ for a further 5 min, 10% HCl (aq) was added and the reaction mixture stirred for 30 min. The reaction mixture was poured into 10% HCl (aq) and extracted with EtOAc (3×25 mL), the combined organic extracts were washed with 5% $NaHCO_3$ (aq), then brine, then dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude oil which was purified by column chromatography on silica gel (10:90–20:80 acetone/petrol) to yield the lactol **1.51** as a colourless oil as a 1:1.75 anomeric mixture (580 mg, 70%).

IR (film) 3447 (br), 1724 (s), 1269 (s) 1097 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10–8.03 (4 H, m, 4×CH_{Ar}), 7.64–7.38 (6 H, m, 6×CH_{Ar}), 5.75 (0.36 H, ddd, *J* = 10.8, 9.7, 6.3 Hz, C<u>H</u>OH_{Minor}), 5.53–5.47 (1.28 H, m, $CHOBz_{Major}$ + $CHOH_{Major}$), 5.36 (0.36 H, dd, *J* = 6.4, 1.4 Hz, $CHOBz_{Minor}$), 4.79–4.72 (2.64 H, C<u>H</u>CH_{2Major} + CH_2), 4.47 (0.36 H, dd, *J* = 10.9, 5.1 Hz, C<u>H</u>CH_{2Minor}), 4.07 (0.36 H, br. s., OH_{Minor}), 3.86 (0.64 H, br. s, OH_{Major}) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 166.4 ($C{=}O_{Minor}$), 166.2 ($C{=}O_{Major}$), 165.2 ($C{=}O_{Minor}$), 165.5 ($C{=}O_{Major}$), 133.94 (CH_{Ar}), 133.87 (CH_{Ar}), 133.3 (CH_{Ar}), 130.0 (CH_{Ar}), 129.8 (CH_{Ar}), 128.59 (CH_{Ar}), 128.57 (CH_{Ar}), 128.4 (CH_{Ar}), 129.4 (C_{Ar}), 128.3 (C_{Ar}), 121.5 (dd, *J* = 271.2, 248.8 Hz, CF_{2Major}), 121.0 (dd, *J* = 263.4, 255.6, CF_{2Minor}), 96.1 (dd, *J* = 41.8, 23.3 Hz, $CHOH_{Major}$), 95.8 (dd, *J* = 36.9, 24.3 Hz, $CHOH_{Minor}$), 79.5 (t, *J* = 2.9 Hz, <u>C</u>HCH_{2Major}), 77.3 (d, *J* = 7.8 Hz, <u>C</u>HCH_{2Minor}), 77.9 (dd, *J* = 36.0, 18.5 Hz, $CHOBz_{Major}$), 71.3 (dd, *J* = 29.2, 16.5 Hz, $CHOBz_{Minor}$), 64.2 (CH_{2Minor}), 63.2 (CH_{2Major}) ppm (some C_{Ar}/CH_{Ar} overlap).

Major anomer:

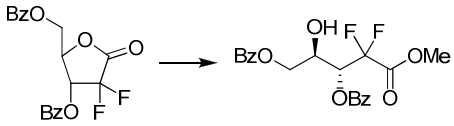
^{19}F NMR (282 MHz, $CDCl_3$) δ –123.7 (1 F, dd, *J* = 241.4, 9.5 Hz, C<u>F</u>F), –125.5 (1 F, ddd, *J* = 240.5, 10.3, 6.0 Hz, CF<u>F</u>) ppm.

Minor anomer:

^{19}F NMR (282 MHz, $CDCl_3$) δ –109.3 (1 F, ddd, *J* = 250.9, 16.4, 6.9 Hz, C<u>F</u>F), –125.3 (1 F, d, *J* = 251.7 Hz, CF<u>F</u>) ppm.

Data matches the literature.[43]

(3*R*,4*R*)-5-(Benzoyloxy)-2,2-difluoro-4-hydroxy-1-methoxy-1-oxopentan-3-yl benzoate, 2.13



To lactone **1.50** (150 mg, 0.40 mmol) in toluene (3.5 mL) at –78 ℃ was added DIBAL (1 M in hexanes, 1.0 equiv, 0.40 mmol, 0.40 mL) dropwise. The reaction mixture was stirred at –78 ℃ for 6 h before addition of MeOH (0.2 mL). The reaction mixture was stirred for 10 min whilst warming slowly to RT, then poured into 1 M HCl (aq) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a colourless oil which was purified by column chromatography on silica gel (10:90–20:80 acetone/petrol) to yield methyl ester **2.13** (131 mg, 80%), this slowly epimerised over time in $CDCl_3$ to give a 1:6.9 diastereomeric mixture.

Data for major diastereoisomer:

IR (film) 3481 (br), 1767 (m), 1725 (s), 1316 (m), 1267 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 472.2 $(M+Na+MeCN)^+$ (100), 431.2 $(M+Na)^+$ (80).

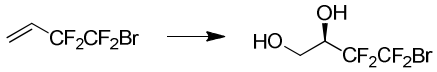
HRMS (ESI^+) for $C_{20}H_{18}F_2O_7$ $(M+Na)^+$ calcd 431.0913, found 431.0911.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.01 (4 H, m, 4×CH_{Ar}), 7.64–7.56 (2 H, m, 2×CH_{Ar}), 7.52–7.42 (4 H, m, 4×CH_{Ar}), 5.95 (1 H, ddd, *J* = 17.2, 8.3, 6.7 Hz, CHOBz), 4.63 (1 H, ddd, *J* = 11.9, 2.4, 0.8 Hz, C<u>H</u>H), 4.47 (1 H, ddd, *J* = 8.1, 5.5, 2.5 Hz, C<u>H</u>OH), 4.40 (1 H, dd, *J* = 12.0, 5.4 Hz, CH<u>H</u>), 3.88 (3 H, s, CH_3), 3.10 (1 H, br. s, OH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 167.0 (C=O), 164.7 (C=O), 163.0 (dd, *J* = 32.1, 30.1 Hz, CF_2C=O), 133.9 (CH_{Ar}), 133.5 (CH_{Ar}), 130.1 (2×CH_{Ar}), 129.8 (2×CH_{Ar}), 129.2 (C_{Ar}), 128.6 (2×CH_{Ar}), 128.5 (2×CH_{Ar}), 128.3 (C_{Ar}), 122.9 (dd, *J* = 258.5, 253.7 Hz, CF_2), 70.9 (t, *J* = 22.4 Hz, CHOBz), 68.1 (CHOH), 65.5 (CH_2), 53.6 (CH_3) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –113.4 (1 F, d, *J* = 270.8 Hz, CF<u>F</u>), –121.1 (1 F, dd, *J* = 266.5, 21.5 Hz, CF<u>F</u>) ppm.

(2*R*)-4-Bromo-3,3,4,4-tetrafluorobutane-1,2-diol, 2.15



Enantioselective conditions:

To potassium ferrocyanide (3 equiv, 176.9 mmol, 58.23 g), potassium carbonate (3 equiv, 176.9 mmol, 24.45 g), potassium osmate (VI) dihydrate (0.02 equiv, 1.18 mmol, 434 mg) and $(DHQ)_2PYR$ (0.02 equiv, 1.18 mmol, 1.04 g) was added *tert*-butanol (300 mL) and water (300 mL). The reaction mixture was stirred until complete dissolution occurred, then cooled to 4 ℃ and 4-bromo-3,3,4,4-tetrafluorobut-1-ene **2.14** (7.5 mL, 59.0 mmol) was added and the reaction mixture stirred at 4 ℃ for 10 days. Sodium sulphite (86 g) was added and the reaction mixture was warmed to RT over 2 h, diluted with water (60 mL) and Et_2O (210 mL). The phases were separated and the aqueous phase extracted with Et_2O (2×100 mL). The combined organic extracts were washed with 2 M HCl (2×90 mL), then brine, then dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a crude oil which was purified by vacuum distillation (68–72 ℃, 0.5 mmHg) to yield the desired diol **2.15** as colourless oil (12.35 g, 87 %).

(*ee* lit[66] 78%. *ee* not determined here, however *ee* of 78% confirmed by ^{1}H NMR of crude naproxen ester **2.18**).

To recover the $(DHQ)_2PYR$ the HCl (aq) extracts were neutralised with 2 M NaOH, extracted with EtOAc (2×100 mL) and the combined organic extracts dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a crude white solid which was recrystallised from EtOAc to give the recovered $(DHQ)_2PYR$.

Racemic conditions:

To citric acid (0.75 equiv, 0.181 mol, 34.77 g) in *tert*-butanol (140 mL) and water (140 mL) was added 4-bromo-3,3,4,4-tetrafluorobutan-1-ol **2.14** (50 g, 0.242 mol), potassium osmate (IV) dihydrate (0.001 equiv, 0.24 mmol, 89 mg) and 4-methylmorpholine-*N*-oxide (1.14 equiv, 0.275 mol, 32.2 g). The reaction mixture was stirred at RT for 4 d. The solvents were reduced *in vacuo* to yield a crude residue which was taken up in 2 M HCl (aq) and extracted with Et_2O (3×200 mL), the combined organic extracts were dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield the desired diol **rac-2.15** as a colourless oil (56.9 g, 97%).

IR (film) 3356 (br), 1132 (m), 1110 (m), 1082 (s) cm^{-1}.

^{1}H NMR (300 MHz, CD_3CN) δ 4.20 (1 H, m, C<u>H</u>OH), 3.99 (1 H, d, *J* = 7.6 Hz, CHO<u>H</u>), 3.78 (1 H, m, C<u>H</u>HOH), 3.66 (1 H, dt, *J* = 12.1, 6.1 Hz, CH<u>H</u>OH), 3.07 (1 H, dd, *J* = 6.6, 5.6 Hz, CH_2O<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 117.0 (tt, *J* = 311.8, 39.5 Hz, CF_2Br), 114.3 (ddt, *J* = 260.5, 257.6, 32.2 Hz, CF_2), 69.5 (dd, *J* = 27.8, 22.0 Hz, CHOH), 60.5 (CH_2) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –63.3 (1 F, dd, *J* = 180.5, 8.6 Hz, C<u>F</u>FBr), –64.2 (1 F, d, *J* = 180.5 Hz, CF<u>F</u>Br), –116.2 (1 F, d, *J* = 270.8 Hz, C<u>F</u>FCF_2Br), –123.1 (1 F, ddd, *J* = 270.8, 17.2, 8.6 Hz, CF<u>F</u>CF_2Br) ppm.

Data consistent with literature.[66]

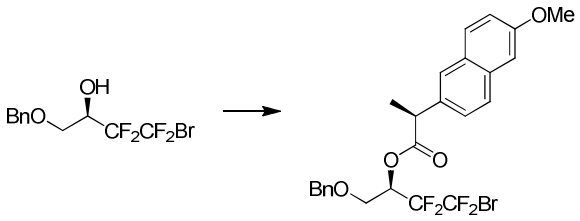
(2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-ol, 2.16

A stirring suspension of diol **2.15** (12.33 g, 51.2 mmol) and dibutyltin oxide (1.2 equiv, 61.4 mmol, 15.29 g) was refluxed in toluene (180 mL), with a Dean and Stark condenser, for 7 h. Benzyl bromide (1.2 equiv, 61.4 mmol, 7.30 mL) and tetrabutylammonium iodide (0.25 equiv, 12.8 mmol, 4.73 g) were added and the reaction mixture stirred at reflux for 18 h. The reaction mixture was cooled to RT, diluted with Et_2O (210 mL), washed with 10% w/v potassium fluoride (aq) (2×60 mL). The combined organic extracts were dried over

anhydrous $MgSO_4$ and reduced *in vacuo* to yield a crude yellow residue which was purified by flash chromatography on silica gel (20:80 Et_2O/petrol) to give benzyl alcohol **2.16** as a yellow oil (16.26 g, 88%).

[α]$_D$: +9.4 (c 1.3, $CHCl_3$, 26 ℃) (for enantiopure material).
IR (film) 3438 (br), 3033 (w), 2874 (w), 2359 (w), 1455 (w), 1366 (w), 1208 (m), 1083 (s), 1027 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (5 H, m, 5×CH_{Ar}), 4.62 (2 H, s, CH_2Ph), 4.37 (1 H, dt, *J* = 18.3, 5.1 Hz, C<u>H</u>OH), 3.83–3.73 (2 H, m, CHC<u>H</u>$_2$), 3.03 (1 H, m, OH) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.0 (C_{Ar}), 128.6 (2×CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (2×CH_{Ar}), 73.8 (CH_2Ph), 68.4 (dd, *J* = 28.8, 22.1 Hz, CHOH), 67.5 (CH<u>C</u>H$_2$) ppm (2×CF_2 not observed).
^{19}F NMR (282 MHz, $CDCl_3$) δ –63.0 (1 F, dd, *J* = 180.5, 8.6 Hz, C<u>F</u>FBr), –63.9 (1 F, d, *J* = 180.5 Hz, CF<u>F</u>Br), –115.3 (1 F, d, *J* = 270.8 Hz, C<u>F</u>FCF_2Br), –123.9 (1 F, ddd, *J* = 270.8, 17.2, 8.6 Hz, CF<u>F</u>CF_2Br) ppm.
Data consistant with literature.[66]

(*S*)-2-(6-Methoxy-naphthalen-2-yl)-propionic acid (*R*)-1-benzyloxymethyl-3-bromo-2,2,3,3-tetrafluoro-propyl ester, 2.18



To a stirring solution of **2.16** (10.33 g, 28.7 mmol) in DCM (145 mL) was added DCC (1.1 equiv, 31.6 mmol, 6.52 g) and DMAP (0.1 equiv, 2.87 mmol, 351 mg). The reaction mixture was stirred at RT until complete dissolution was obtained, (*S*)-naproxen (1.1 equiv, 31.6 mmol, 7.28 g) was added and the reaction mixture stirred at RT for 18 h. The white precipitate was removed by filtration and washed with DCM (20 mL). The resultant filtrate was reduced *in vacuo* to yield a crude suspension which was purified by column chromatography on silica gel (15:85 acetone/petrol) to yield a yellow solid as a mixture of

diastereomers. The desired major diastereomer **2.18** was then recrystallised from hexane as an off-white solid (14.58 g, 77%).

Mp: 69–71 ℃ (hexane).

[α]$_D$: +33.2 (c 0.9, $CHCl_3$, 26 ℃).

IR (film) 2938 (br), 1754 (s), 1633 (w), 1606 (m), 1506 (w), 1485 (w), 1454 (w), 1140 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 565.3 and 567.2 $(M+Na)^+$ 100:92 ratio.

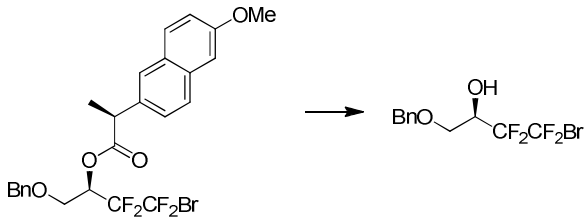
HRMS (ESI^+) for $C_{25}H_{23}{}^{79}BrF_4O_4$ $(M+Na)^+$ calcd 565.0614, found 565.0605.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (3 H, m, 3×CH_{Ar}), 7.40 (1 H, dd, *J* = 8.5, 1.7 Hz, CH_{Ar}), 7.24–7.10 (5 H, m, 5× CH_{Ar}), 7.01 (2 H, d, *J* = 6.7 Hz, 2× CH_{Ar}), 5.86 (1 H, dtd, *J* = 16.4, 7.5, 3.2 Hz, $CHCF_2$), 4.31 (1 H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.22 (1 H, d, *J* = 11.9 Hz, CH<u>H</u>Ph), 4.00–3.92 (4 H, m, C<u>H</u>CH_3, OCH_3), 3.76 (1 H, ddd, *J* = 11.2, 3.2, 2.0 Hz, C<u>H</u>HOBn), 3.60 (1 H, dd, *J* = 11.0, 7.8 Hz, CH<u>H</u>OBn), 1.62 (1 H, d, *J* = 7.2 Hz, CHC<u>H</u>$_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 172.7 (C=O), 157.7 (C_{Ar}), 137.1 (C_{Ar}), 134.6 (C_{Ar}), 133.8 (C_{Ar}), 129.3 (CH_{Ar}), 128.9 (C_{Ar}), 128.2 (2×CH_{Ar}), 127.6 (CH_{Ar}), 127.3 (2×CH_{Ar}), 127.2 (CH_{Ar}), 126.2 (CH_{Ar}), 126.1 (CH_{Ar}), 119.0 (CH_{Ar}), 105.6 (CH_{Ar}), 73.2 (CH_2Ph), 67.8 (dd, *J* = 29.7, 21.9 Hz, <u>C</u>HCF_2), 66.5 (CHOBn), 55.3 (CH<u>C</u>H_3), 45.1 (<u>C</u>CH_3), 18.4 (OCH_3) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –64.2 (2 F, s, CF_2Br), –114.0 (1 F, d, *J* = 275.1 Hz, CHCF<u>F</u>), –119.5 (1 F, dd, *J* = 275.1, 17.2 Hz, CHC<u>F</u>F) ppm.

(2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-ol, 2.16

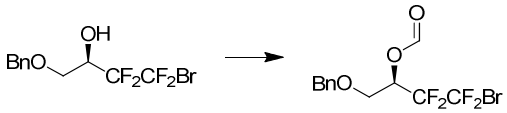


To **2.18** (17.70 g, 32.6 mmol) in THF (215 mL) was added sodium hydroxide (11 equiv, 358.0 mmol, 14.33 g). The reaction mixture was stirred at reflux for 3 h. The solvents were reduced *in vacuo* to yield a crude residue which was was taken up in sat. $NaHCO_3$ (aq) and extracted with Et_2O (3×100 mL). The

combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude waxy solid which was purified by column chromatography on silica gel (20:80 Et_2O/petrol) to yield benzyl alcohol **2.16** (10.37 g, 96%).

[α]$_D$: +9.4 (c 1.3, $CHCl_3$, 26 ℃).
Other data as for enantioenriched material.

(1*R*)-1-[(Benzyloxy)methyl]-3-bromo-2,2,3,3-tetrafluoropropyl formate, 2.17



To a stirring solution of **2.16** (10.35 g, 31.3 mmol) in DCM (175 mL) was added DCC (1.1 equiv, 34.4 mmol, 7.09 mg) and DMAP (0.1 equiv, 3.13 mmol, 382 mg). The reaction mixture was stirred until complete dissolution occurred, formic acid (1.1 equiv, 34.4 mmol, 1.32 mL) was then added. The reaction mixture was stirred at RT for 22 h, diluted with hexane, the precipitate removed by filtration and the residue washed with hexane. The filtrate was reduced *in vacuo* to yield a crude slurry which was purified by column chromatography on silica gel (10:90 Et_2O/petrol) to yield **2.17** as a colourless oil (10.57 g, 94%).

[α]$_D$: +11.2 (c 1.0, $CHCl_3$, 23 ℃).
IR (film) 2947 (br), 2360 (w), 1742 (s), 1147 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (1 H, s, HC=O), 7.39–7.30 (5 H, m, CH_{Ar}), 5.91 (1 H, dtd, *J* = 15.4, 7.8, 3.2 Hz, CHO), 4.62 (1 H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.54 (1 H, d, *J* = 11.9 Hz, CH<u>H</u>Ph), 3.89 (1 H, dt, *J* = 11.2, 2.6 Hz, CHC<u>H</u>H), 3.80 (1 H, dd, *J* = 11.2, 7.8 Hz, CHCH<u>H</u>) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 158.6 (CH=O), 136.9 (C_{Ar}), 128.5 (2×CH_{Ar}), 128.0 (CH_{Ar}), 127.7 (2×CH_{Ar}), 73.4 (CH_2Ph), 66.9 (dd, *J* = 29.2, 22.4 Hz, CHO), 66.2 (CH<u>C</u>H$_2$) ppm (2×CF_2 not visible).
^{19}F NMR (282 MHz, $CDCl_3$) δ –64.2 (2 F, s, CF_2Br), –114.3 (1 F, d, *J* = 275.1 Hz, C<u>F</u>FCH), –119.0 (1 F, dd, *J* = 275.1, 12.9 Hz, CF<u>F</u>CH) ppm.
Data consistant with literature.[66]

(5*R*)-5-[(Benzyloxy)methyl]-3,3,4,4-tetrafluorotetrahydrofuran-2-ol, 2.02

Formate **2.17** (1.829 g, 5.09 mmol) was taken up in dry DCM and filtered through a plug of $MgSO_4$, the solvents were blown off with a stream of dry N_2 and the resultant oil was left under high vacuum for 16 h. To the formate in THF (50 mL) at –78 ℃ was added methyl lithium (1.6 M in Et_2O, 1 equiv, 5.09 mmol, 3.18 mL) dropwise. The reaction mixture was stirred at –78 ℃ for 4 h before quenching with sat NH_4Cl (aq) (15 mL). The reaction mixture was slowly warmed to RT, diluted with water and extracted with Et_2O (3×30 mL). The combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were removed *in vacuo* to yield a crude oil which was purified by column chromatography (15:85–25:75 EtOAc/petrol) to yield lactol **2.02** as a colourless oil as a 1:1.4 mixture of anomers (884 mg, 62%).

IR (film) 3354 (br), 2875 (w), 1497 (w), 1455 (m), 1369 (m), 1239 (m), 1201 (m), 1143 (s), 1019 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (5 H, m, 5×CH_{Ar}), 5.41 (0.4 H, dd, *J* = 7.3, 2.5 Hz, C<u>H</u>OH_{Minor}), 5.28 (0.6 H, d, *J* = 8.2 Hz, C<u>H</u>OH_{Major}), 4.67–4.52 (3 H, m, CH_2Ph, C<u>H</u>CH_{2Minor}, OH_{Major}), 4.42 (0.6 H, m, C<u>H</u>CH_{2Major}), 3.82–3.67 (2.4 H, m, CHC<u>H_2</u>, OH_{Minor}) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 136.8 (0.5×C_{Ar}), 136.0 (0.5×C_{Ar}), 128.7 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 127.0 (CH_{Ar}), 118.3–113.0 (2×CF_2), 96.1 (m, 0.5×CHOH), 94.7 (dd, *J* = 39.5, 22.0 Hz, 0.5×CHOH), 79.1 (m, 0.5×<u>C</u>HCH_2), 77.1 (t, *J* = 26.3 Hz, 0.5×<u>C</u>HCH_2), 74.2 (0.5×CH_2Ph), 73.9 (0.5×CH_2Ph), 66.4–66.3 (CH_2OBn) ppm (some CH_{Ar} overlap).

Major anomer

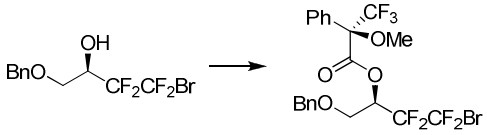
^{19}F NMR (282 MHz, $CDCl_3$) δ –119.01 (1 F, dddd, *J* = 247.4, 15.5, 5.2, 1.7 Hz, C<u>F</u>F), –124.72 (1 F, dtd, *J* = 247.4, 6.9, 3.4 Hz, CF<u>F</u>), –125.66 (1 F, ddd, *J* = 248.3, 8.6, 4.3 Hz, C<u>F</u>F), –127.76 (1 F, dt, *J* = 249.1, 6.0 Hz, CF<u>F</u>) ppm.

Minor Anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –117.0 (1 F, m, C<u>F</u>F), –127.9 (1 F, m, CF<u>F</u>), –131.1 (1 F, dt, *J* = 246.6, 5.2 Hz, C<u>F</u>F), –134.1 (1 F, ddt, *J* = 245.7, 14.7, 3.4 Hz, CF<u>F</u>) ppm.

Data consistant with literature.[66]

(2*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluoro-1-hydroxybutan-2-yl-(2*R*)-3-3,3-trifluoro-2-methoxy-2-phenylpropanoate, 2.19



To monobenzylalcohol **2.16** (19 mg, 0.057 mmol) in pyridine (0.4 mL) was added DMAP (trace) and (*S*)-α-methoxyl-α-(trifluoromethyl)phenylacetylchloride (2 equiv, 0.11 mmol, 0.029 mL). The reaction mixture was stirred at RT for 36 h then water (0.5 mL) and Et_2O (5 mL) were added, the phases were separated and the organic phase washed with 2 M HCl (4×3 mL), sat $NaHCO_3$ (aq) (2×3 mL) and dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a colourless oil (33 mg) which showed complete conversion by NMR. This oil was purified by column chromatography on silica gel (10:90 Et_2O/petrol) to yield the Mosher ester derivative **2.19** as colourless oil (27 mg).

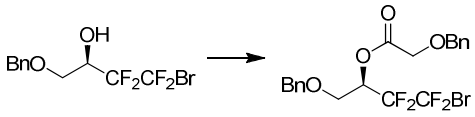
IR (film) 2954 (w), 1765 (s), 1267 (m), 1237 (m), 1151 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (2 H, d, *J* = 7.7 Hz, 2×CH_{Ar}), 7.09–7.35 (8 H, m, 8×CH_{Ar}), 5.95 (1 H, tdd, *J* = 11.2, 8.7, 2.8 Hz, CHO), 4.37 (2 H, dd, *J* = 25.4, 11.9 Hz, CH_2Ph), 3.77 (1 H, d, *J* = 10.9 Hz, C<u>H</u>HCH), 3.62 (1 H, dd, *J* = 10.9, 8.8 Hz, CH<u>H</u>CH), 3.44 (3 H, s, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 165.3 (C=O), 136.8 (C_{Ar}), 131.4 (C_{Ar}), 129.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.0 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 123.0 (q, *J* = 288.7 Hz, CF_3), 119.9–112.7 (m, 2×CF_2), 85.0 (q, *J* = 28.2 Hz, <u>C</u>CF_3), 73.4 (CH_2Ph), 69.6 (t, *J* = 25.3 Hz, CH), 66.2 (CH<u>C</u>H_2), 55.6 (CH_3) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –64.3 (2 F, s, C<u>F</u>FBr), –72.1 (3 F, s, CF_3), –115.0 (1 F, dd, *J* = 275.1, 8.6 Hz, C<u>F</u>FCH), –116.1 (1 F, dd, *J* = 275.1, 12.9 Hz, CF<u>F</u>CH) ppm.

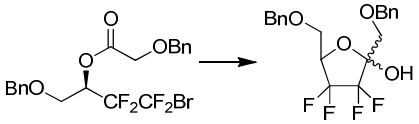
(*R*)-1-(Benzyloxy)-4-bromo-3,3,4,4-tetrafluorobutan-2-yl-2-(benzyloxy) acetate, 2.22



To benzylalcohol **2.16** (521 mg, 1.57 mmol) in DCM (5 mL) was added triethylamine (1.01 equiv, 1.59 mmol, 0.22 mL) and DMAP (0.09 equiv, 0.14 mmol, 18 mg). The reaction mixture was stirred at RT for 5 min and benzyloxyacetyl chloride (1.38 equiv, 2.17 mmol, 0.26 mL) was added dropwise. The reaction mixture was stirred at RT for 6 h, diluted with DCM (10 mL), washed with 1 M HCl (aq) (10 mL), dried over anhydrous $MgSO_4$ and the solvents removed *in vacuo* to yield a crude oil. This oil was purified by column chromatography (10:90 acetone/petrol) to yield the desired ester **2.22** as a colourless oil (737 mg, 98%).

$[\alpha]_D$: +19.6 (c 0.8, $CHCl_3$, 27 ℃).
IR (film) 3032 (w), 2871 (w), 1776 (m), 1117 (s), 1079 (m) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (10 H, m, 10×CH_{Ar}), 5.93 (1 H, dtd, *J* = 16.0, 8.0, 3.2 Hz, CHO), 4.66–4.61 (3 H, m, CH_2Ph, C<u>H</u>HCO_2), 4.52 (1 H, d, *J* = 12.1 Hz, CH<u>H</u>CO_2), 4.23–4.19 (2 H, m, CH_2Ph), 3.88 (1 H, dd, *J* = 11.2, 2.3 Hz, CHCH<u>H</u>), 3.78 (1 H, dd, *J* = 11.1, 8.0 Hz, CHC<u>H</u>H) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 168.6 (C=O), 137.0 (C_{Ar}), 136.8 (C_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.7 (CH_{Ar}), 73.3 (2×CH_2Ph), 67.6 (dd, *J* = 29.3, 22.0 Hz, CHO), 66.5 (CH_2OBn), 66.2 (<u>C</u>H_2CH) ppm (2×CF_2 not visible).
^{19}F NMR (282 MHz, $CDCl_3$) δ –64.4 (2 F, s, CF_2Br), –114.3 (1 F, d, *J* = 275.1 Hz, C<u>F</u>FCH), –119.5 (1 F, dd, *J* = 275.1, 17.2 Hz, CF<u>F</u>CH) ppm.
Data matches that for the enatioenriched material in the literature[66]

(5*R*)-2,5-Bis((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-ol, 2.23



To ester **2.22** (500 mg, 1.04 mmol) in THF (10 mL) at –78 ℃ was added methyllithium (1.6 M solution in Et_2O, 1.0 equiv, 1.04 mmol, 0.65 mL). The reaction mixture was stirred at –78 ℃ for 4.5 h then quenched with sat. NH_4Cl (aq) (3 mL). The reaction mixture was slowly warmed to RT, diluted with H_2O and extracted with Et_2O (3×15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvents reduced *in vacuo* to yield a crude oil. Purification by flash chromatography on silica gel (15:85–20:80 acetone/petrol) yielded the desired product **2.23** as a colourless oil as a mixture of anomers (165 mg, 40%).

IR (film) 3388 (br), 3032 (w), 2872 (w), 1454 (m), 1259 (m), 1208 (w), 1147 (m), 1100 (s), 1028 (m) cm^{-1}.

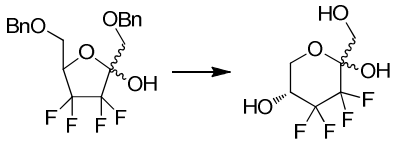
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.31 (20 H, m, 20×CH_{Ar}), 4.71–4.53 (10 H, m,), 4.26 (1 H, br. s), 3.86–3.64 (8 H, m) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.3 ($C_{ArMajor}$), 136.94 ($C_{ArMinor}$), 136.85 ($C_{ArMinor}$), 136.6 ($C_{ArMajor}$), 128.6 (CH_{Ar}), 128.54 (CH_{Ar}), 128.45 (CH_{Ar}), 128.3 (CH_{Ar}), 128.13 (CH_{Ar}), 128.06 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.7 (CH_{Ar}), 100.0–98.5 (m, CF_2), 78.2 (dd, *J* = 27.8, 23.4 Hz, CH_{Minor}), 77.2 (dd, *J* = 29.3, 22.0 Hz, CH_{Major}), 74.12 (CH_2Ph_{Major}), 74.05 (CH_2Ph_{Minor}), 73.8 (CH_2Ph_{Minor}), 73.7 (CH_2Ph_{Major}), 68.6 (CH_{2Minor}), 68.1 (d, *J* = 4.4 Hz, CH_{2Major}), 67.3 (dd, *J* = 6.6, 3.7 Hz, CH_{2Minor}), 66.1 (d, *J* = 8.8 Hz, CH_{2Major}) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –111.9 (1 F, dd, *J* = 245.0, 12.9 Hz, C<u>F</u>F), –122.7 (1 F, ddt, *J* = 247.1, 12.9, 5.4 Hz, CFF), –124.1 (1 F, ddt, *J* = 246.1, 10.7, 5.4 Hz, CFF), –129.8 (1 F, dt, *J* = 240.7, 5.4 Hz, CFF), –131.6—132.5 (3 F, m, 3×CFF), –134.5 (1 F, ddd, *J* = 243.9, 14.0, 5.4 Hz, CFF) ppm.

Data matches that in the literature[66]

(5*R*)-3,3,4,4-Tetrafluoro-2-(hydroxymethyl)tetrahydro-2H-pyran-2,5-diol, 2.24



Furanose **2.23** (132 mg, 0.33 mmol) was stirred with $Pd(OH)_2/C$ (20% w/w Pd/C, 53 mg) in EtOAc (mL) under a H_2 atmosphere (1 atm) at RT for 18 h. The reaction mixture was filtered through celite and the filtrate was reduced *in vacuo* to yield a colourless oil. Purification by flash chromatography (40:60 acetone/petrol) yielded the desired fructose derivative **2.24** as a colourless oil as a 1:7 anomeric mixture (73 mg, quantitative yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.83 (0.8 H, br. s. COH_{Major}), 6.70 (0.2 H br. s. COH_{Minor}), 6.11 (0.8 H, d, *J* = 6.8 Hz, $CHO\underline{H}_{Major}$), 5.98 (0.2 H, d, *J* = 5.1 Hz, $CHO\underline{H}_{Major}$), 5.13 (0.8 H, dd, *J* = 6.8, 5.9 Hz, $CH_2O\underline{H}_{Major}$), 5.09 (0.2 H, dd, *J* = 6.9, 5.9 Hz, $CH_2O\underline{H}_{Minor}$), 4.09 (0.2 H, m, $C\underline{H}HOH_{Minor}$), 3.90 (1 H, m, $C\underline{H}OH$, $CH\underline{H}OH_{Minor}$), 3.76 (0.8 H, t, *J* = 10.9 Hz, $CHC\underline{H}H_{Major}$), 3.65 (1 H, m, $CHC\underline{H}H$), 3.58 (1 H, dd, *J* = 11.6, 7.1 Hz, $C\underline{H}HOH_{Major}$), 3.53 (0.2 H, m, $CH\underline{H}OH_{Minor}$), 3.48 (0.8 H, ddd, *J* = 11.6, 5.6, 2.5 Hz, $C\underline{H}HOH_{Major}$) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d_6) δ 95.5 (dd, *J* = 30.7, 23.4 Hz, $\underline{C}CF_2$), 65.9 (t, *J* = 19.8 Hz, $\underline{C}HCF_2$), 61.6 (CH_2OH), 59.4 (d, *J* = 7.3 Hz, $\underline{C}H_2OC$) ppm. (2×CF_2 not visible, assignment for major anomer only, signals for minor isomer anomer obscured)

Major anomer

^{19}F NMR (282 MHz, DMSO-d_6) δ –124.5 (1 F, m, *J* = 261.6 Hz can be observed, $C\underline{F}F$), –128.2 (1 F, m, *J* = 248.1 Hz can be observed, $CF\underline{F}$), –129.4 (1 F, dddd, *J* = 248.1, 19.6, 14.4, 5.6 Hz, $C\underline{F}F$), –133.9 (1 F, ddd, *J* = 261.9, 4.9, 11.0 Hz, $CF\underline{F}$) ppm.

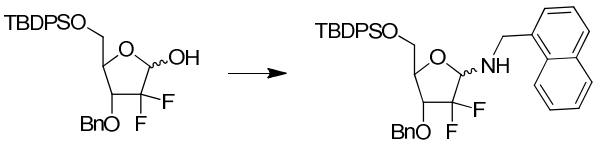
Minor anomer

^{19}F NMR (282 MHz, DMSO-d_6) δ –115.8 (1 F, m, *J* = 261.2 Hz can be observed, $C\underline{F}F$), –123.8 (1 F, m, *J* = 260.6 Hz can be observed, $CF\underline{F}$), –128.2 (1 F, m, $C\underline{F}F$), –132.3 (1 F, m, *J* = 262.5 Hz can be observed, $CF\underline{F}$) ppm.

General Procedure for Aminoglycosylations

To protected lactol in MeOH (0.02–0.05 M) was added amine (3 equiv) and PTSA (1 equiv). The reaction mixture was stirred at reflux, cooled to RT and diluted with DCM (3×MeOH volume) before filtration through a plug consisting of (from top to bottom) Na_2SO_4, $NaHCO_3$ and silica (approx 2 cm total depth, pretreated with 2 mL 1:10 Et_3N/DCM) and washed with DCM. The solvents were reduced *in vacuo* to yield a residue which was purified by column chromatography on silica gel to provide an inseparable mixture of anomers unless otherwise stated.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-(naphthalen-1-ylmethyl)tetrahydrofuran-2-amine, 3.22a



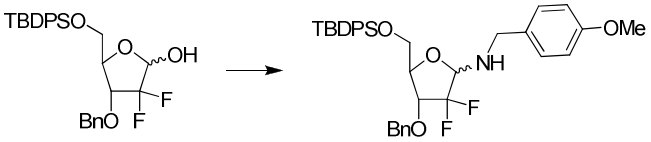
Following the general procedure:- lactol **2.01** (106 mg, 0.21 mmol), MeOH (1 mL), 1-napthylamine (3 equiv, 0.62 mmol, 0.09 mL) and PTSA (1 equiv, 0.21 mmol, 40 mg). Stir for 4 h. Column chromatography: (10:90 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22a** as (colourless oil) a 1:1 anomeric mixture (115 mg, 85%).

IR (film) 2929 (m), 2857 (m), 1691 (m), 1112 (s) cm^{-1}.
LRMS (ESI$^+$) *m/z* 660.5 $(M+Na)^+$ (100).
HRMS (ESI$^+$) for $C_{39}H_{41}F_2NO_3Si$ $(M+H)^+$ calcd 638.2897, found 638.2888.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–7.33 (22 H, m, CH_{Ar}), 4.98 (0.5 H, t, *J* = 6.7 Hz, 0.5×CHN), 4.86 (1 H, d, *J* = 11.5 Hz, C<u>H</u>HPh), 4.75 (0.5 H, m, 0.5×CHN), 4.62–4.57 (2 H, m, CH<u>H</u>Ph, 0.5×NCH_2), 4.41–4.31 (1.5 H, m, 0.5×NCH_2, 0.5×CHOBn), 4.12–4.16 (1 H, m, 0.5×CHOBn, 0.5×C<u>H</u>CH_2), 3.88–3.81 (2 H, m, CHC<u>H_2</u>), 3.75 (0.5 H, dd, *J* = 11.3, 3.0 Hz, 0.5×C<u>H</u>CH_2), 2.42 (0.5 H, br. s, 0.5×NH), 2.25 (0.5 H, br. s, 0.5×NH), 1.06 (4.5 H, s, 0.5×$C(CH_3)_3$), 1.03 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.04 (C_{Ar}), 137.00 (C_{Ar}), 136.6 (CH_{Ar}), 135.7 (CH_{Ar}), 135.6 (CH_{Ar}), 135.3 (CH_{Ar}), 134.6 (C_{Ar}), 133.8 (C_{Ar}), 133.3 (C_{Ar}), 133.26 (C_{Ar}), 133.17 (C_{Ar}), 133.12 (C_{Ar}), 133.06 (C_{Ar}), 131.7 (C_{Ar}), 131.4 (C_{Ar}), 129.8 (CH_{Ar}), 129.1 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.7 (CH_{Ar}), 127.0 (CH_{Ar}), 126.3 (CH_{Ar}), 126.2 (CH_{Ar}), 126.1 (CH_{Ar}), 125.6 (CH_{Ar}), 125.4 (CH_{Ar}), 124.9 (CH_{Ar}), 123.8 (CH_{Ar}), 89.5–89.0 (m, CHN), 79.6–78.8 (m, $\underline{C}HCH_2$), 78.0–77.1 (m, CHOBn), 73.0 (0.5×CH_2Ph), 72.8 (0.5×CH_2Ph), 63.3 (0.5×CH$\underline{C}H_2$), 62.7 (0.5×CH$\underline{C}H_2$), 47.5 (0.5×NCH_2), 47.0 (0.5×NCH_2), 26.8 (C($\underline{C}H_3)_3$), 19.3 (0.5×$\underline{C}(CH_3)_3$), 19.2 (0.5×$\underline{C}(CH_3)_3$) ppm (some C_{Ar}/CH_{Ar} overlap, CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –112.9 (0.5 F, dt, *J* = 238.5, 8.6 Hz, 0.5×C$\underline{F}$F), –116.5 (0.5 F, *J* = 240.7, 12.9 Hz, 0.5×C$\underline{F}$F), –122.7 (0.5 F, dd, *J* = 242.8, 6.5 Hz, 0.5×CF$\underline{F}$), –132.0 (0.5 F, dt, *J* = 238.5, 8.6 Hz, 0.5×CF$\underline{F}$) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-(4-methoxybenzyl)tetrahydrofuran-2-amine, 3.22b



Following the general procedure:- lactol **2.01** (89 mg, 0.18 mmol), MeOH (1 mL), *p*-methoxybenzylamine (3 equiv, 0.53 mmol, 0.07 mL) and PTSA (1 equiv, 0.18 mmol, 34 mg). Stir for 5 h. Column chromatography: (10:90 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22b** as (colourless oil) a 1:1 anomeric mixture (109 mg, 98%).

IR (film) 2930 (w), 2857 (w), 1512 (m), 1104 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 640.2 $(M+Na)^+$ (100).

HRMS (ESI$^+$) for $C_{36}H_{41}F_2NO_4Si$ $(M+Na)^+$ calcd 640.2671, found 640.2679.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.55 (4 H, m, 4×CH_{Ar}), 7.40–7.23 (13 H, m, 13×CH_{Ar}), 6.82–6.78 (2 H, m, 2×CH_{Ar}), 4.80 (0.5 H, d, *J* = 11.8 Hz, 0.5×C$\underline{H}$HPh), 4.79 (0.5 H, d, *J* = 11.4 Hz, 0.5×C$\underline{H}$HPh), 4.52 (0.5 H, d, *J* = 11.7 Hz, 0.5×CH$\underline{H}$Ph), 4.51 (0.5 H, d, *J* = 11.5 Hz, 0.5×CH$\underline{H}$Ph), 4.80 (0.5 H, m, 0.5×CHN), 4.57 (0.5 H, dd, *J* = 12.2, 7.7 Hz, 0.5×CHN), 4.27 (0.5 H, td, *J* =

10.2, 6.5 Hz, 0.5×CHOBn), 4.00–3.97 (2 H, m, 0.5×C<u>H</u>CH_2, NC<u>H</u>H, 0.5×CHOBn), 3.85–3.75 (3 H, m, 0.5×C<u>H</u>CH_2, 0.5×CHC<u>H</u>H, CHCH<u>H</u>, NCH<u>H</u>), 3.73 (1.5 H, s, 1.5×OMe), 3.72 (1.5 H, s, 1.5×OMe), 3.64 (0.5 H, dd, *J* = 11.3, 3.0 Hz, 0.5×CHC<u>H</u>H), 2.21 (0.5 H, br. s, 0.5×NH), 2.06 (0.5 H, br. s, 0.5×NH), 0.98 (4.5 H, s, 0.5×C$(CH_3)_3$), 0.95 (4.5 H, s, 0.5×C$(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 158.81 (0.5×C_{Ar}), 158.78 (0.5×C_{Ar}), 137.03 (0.5×C_{Ar}), 137.00 (0.5×C_{Ar}), 135.64 (CH_{Ar}), 135.58 (CH_{Ar}), 135.6 (CH_{Ar}), 133.2 (0.5×C_{Ar}), 133.15 (0.5×C_{Ar}), 133.08 (0.5×C_{Ar}), 133.0 (0.5×C_{Ar}), 131.3 (0.5×C_{Ar}), 131.2 (0.5×C_{Ar}), 129.8 (CH_{Ar}), 129.7 (CH_{Ar}), 129.41 (CH_{Ar}), 129.36 (CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.02 (CH_{Ar}), 128.00 (CH_{Ar}), 127.72 (CH_{Ar}), 127.69 (CH_{Ar}), 127.6 (CH_{Ar}), 113.8 (CH_{Ar}), 122.7 (dd, *J* = 261.4, 255.6 Hz, 0.5×CF_2), 122.5 (dd, *J* = 261.4, 255.6 Hz, 0.5×CF_2), 88.8 (dd, *J* = 32.1, 21.4 Hz, 0.5×CHN), 88.7 (dd, *J* = 32.1, 18.5 Hz, 0.5×CHN), 79.3 (d, *J* = 7.8 Hz, 0.5×<u>C</u>HCH_2), 78.5 (dd, *J* = 5.8, 2.9 Hz, 0.5×<u>C</u>HCH_2), 77.6 (dd, *J* = 30.1, 16.5 Hz, 0.5×CHOBn), 76.8 (dd, *J* = 25.3, 17.5 Hz, 0.5×CHOBn), 73.0 (0.5×CH_2Ph), 72.8 (0.5×CH_2Ph), 63.3 (0.5×CH<u>C</u>H_2), 62.7 (0.5×CH<u>C</u>H_2), 55.2 (OMe), 49.1 (0.5×NCH_2), 48.6 (0.5×NCH_2), 26.7 (C(<u>C</u>$H_3)_3$), 19.3 (0.5×<u>C</u>$(CH_3)_3$), 19.2 (0.5×<u>C</u>$(CH_3)_3$) ppm (some CH_{Ar} overlap).

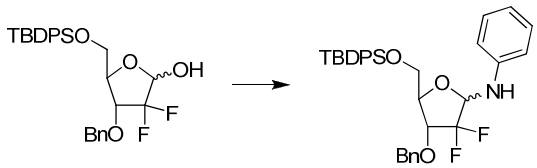
Anomer X:

^{19}F NMR (376 MHz, $CDCl_3$) δ –113.3 (1 F, dt, *J* = 237.5, 8.2 Hz, C<u>F</u>F), –132.2 (1 F, dt, *J* = 237.5, 9.9 Hz, CF<u>F</u>) ppm.

Anomer Z:

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.3 (1 F, dt, *J* = 242.5, 14.8 Hz, C<u>F</u>F), –122.7 (1 F, dt, *J* = 242.5, 4.9 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-phenyltetrahydrofuran-2-amine, 3.22c



Following the general procedure:- lactol **2.01** (79 mg, 0.16 mmol), MeOH (1 mL), aniline (3 equiv, 0.48 mmol, 0.044 mL) and PTSA (1 equiv, 0.16 mmol,

30 mg). Stir for 4.5 h. Column chromatography: (10:90 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22c** as (colourless oil) a 1:1 anomeric mixture (77 mg, 98%).

IR (film) 3069 (w), 2930 (w), 2857 (w), 1604 (m), 1104 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 596.3 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{34}H_{37}F_2O_3NSi$ $(M+H)^+$ calcd 574.2589, found 574.2584.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.51 (4 H, m, 4×CH_{Ar}), 7.37–7.11 (13 H, m, 13×CH_{Ar}), 6.81–6.68 (3 H, m, 3×CH_{Ar}), 5.46 (0.5 H, dd, *J* = 16.9, 7.8 Hz, 0.5×CHN), 5.23 (0.5 H, td, *J* = 10.9, 7.5 Hz, CHN), 4.81 (0.5 H, d, *J* = 11.4 Hz, 0.5×C<u>H</u>HPh), 4.80 (0.5 H, d, *J* = 11.4 Hz, 0.5×C<u>H</u>HPh), 4.66 (0.5 H, d, *J* = 9.4 Hz, 0.5×NH), 4.55 (0.5 H, d, *J* = 11.8 Hz, 0.5×CH<u>H</u>Ph), 4.53 (0.5, d, *J* = 11.4 Hz, 0.5×CH<u>H</u>Ph), 4.40–4.34 (1 H, m, 0.5×NH, 0.5×CHOBn), 4.08 (0.5 H, ddd, *J* = 15.3, 5.6, 3.4 Hz, 0.5×CHOBn), 4.01 (0.5 H, ddd, *J* = 6.2, 3.0, 2.8 Hz, 0.5×C<u>H</u>CH_2), 3.85 (0.5 H, dtd, *J* = 5.5, 4.2, 1.2 Hz, 0.5×C<u>H</u>CH_2), 3.77 (0.5 H, ddd, *J* = 11.3, 3.3, 1.5 Hz, 0.5×CHC<u>H</u>H), 3.71 (1 H, d, *J* = 4.0 Hz, CHC<u>H</u>H), 3.64 (0.5 H, dd, *J* = 11.5, 2.8 Hz, 0.5×CHC<u>H</u>H), 0.96 (4.5 H, s, 0.5×$C(CH_3)_3$), 0.94 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 144.24 (C_{Ar}), 144.16 (C_{Ar}), 136.9 (C_{Ar}), 136.8 (C_{Ar}), 135.64 (CH_{Ar}), 135.58 (CH_{Ar}), 133.04 (C_{Ar}), 133.00 (C_{Ar}), 132.9 (C_{Ar}), 129.84 (CH_{Ar}), 129.77 (CH_{Ar}), 129.7 (CH_{Ar}), 129.3 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.21 (CH_{Ar}), 128.16 (CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (CH_{Ar}), 127.74 (CH_{Ar}), 127.70 (CH_{Ar}), 127.6 (CH_{Ar}), 120.1 (CH_{Ar}), 119.9 (CH_{Ar}), 114.9 (CH_{Ar}), 114.7 (CH_{Ar}), 125.5–120.3 (m, CF_2), 85.3–84.4 (m, CHN), 79.8 (d, *J* = 6.8 Hz, 0.5×<u>C</u>HCH_2), 78.9 (dd, *J* = 5.4, 2.4 Hz, 0.5×<u>C</u>HCH_2), 77.1 (dd, *J* = 30.1, 16.5 Hz, 0.5×CHOBn), 76.6 (dd, *J* = 26.2, 17.5 Hz, 0.5×CHOBn), 73.1 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 73.0 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 62.8 (0.5×CH<u>C</u>H_2), 62.5 (0.5×CH<u>C</u>H_2), 26.8 ($C(\underline{C}H_3)_3$), 19.2 ($\underline{C}(CH_3)_3$) ppm. (some C_{Ar}/CH_{Ar} overlap)

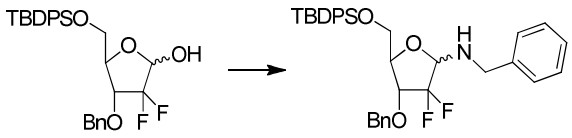
Anomer X:

^{19}F NMR (376 MHz, $CDCl_3$) δ –111.9 (1 F, dt, *J* = 237.5, 9.9 Hz, C<u>F</u>F), –130.3 (1 F, dt, *J* = 237.5, 8.3 Hz, CF<u>F</u>) ppm.

Anomer Z:

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.2 (1 F, dt, *J* = 240.8, 13.2 Hz, C<u>F</u>F), –122.2 (1 F, dd, *J* = 240.8, 4.9 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-*N*-Benzyl-4-(benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-amine, 3.22d



Following the general procedure:- lactol **2.01** (99 mg, 0.20 mmol), MeOH (0.75 mL), benzylamine (3 equiv, 0.60 mmol, 0.065 mL) and PTSA (1 equiv, 0.20 mmol, 38 mg). Stir for 5 h. Column chromatography: (15:85–20:80 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22d** as (colourless oil) a 1:1.3 anomeric mixture (114 mg, 98%).

IR (film) 3030 (w), 2930 (w), 2857 (w), 1428 (m), 1104 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 610.4 $(M+Na)^+$ (100), 588.4 $(M+H)^+$ (60).

HRMS (ESI^+) for $C_{35}H_{39}F_2NO_3Si$ $(M+H)^+$ calcd 588.2740, found 588.2752.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.55 (4 H, m, 4×CH_{Ar}), 7.39–7.14 (16 H, m, 16×CH_{Ar}), 4.81–4.75 (1.5 H, m, 0.5×OCH_2Ph, 0.5×CHN), 4.59 (0.5 H, m, 0.5×CHN), 4.54–4.49 (1 H, m, 0.5×OCH_2Ph), 4.28 (0.5 H, m, 0.5×CHOBn), 4.06–3.98 (2 H, m, 0.5×NHC$\underline{H}_2$, 0.5×C$\underline{H}CH_2$, 0.5×CHOBn), 3.92–3.84 (1 H, m, 0.5×NHC$\underline{H}_2$), 3.78–3.72 (2 H, m, 0.5×C$\underline{H}CH_2$, 0.75×CHC$\underline{H}_2$), 3.65 (0.5 H, m, 0.25×CHC$\underline{H}_2$), 2.28 (0.5 H, br.s, 0.5×NH), 2.09 (0.5 H, br.s, 0.5×NH), 0.99–0.94 (9 H, m, $C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 139.22 (0.5×C_{Ar}), 139.19 (0.5×C_{Ar}), 137.04 (0.5×C_{Ar}), 136.96 (0.5×C_{Ar}), 135.65 (CH_{Ar}), 135.56 (CH_{Ar}), 133.2 (0.5×C_{Ar}), 133.14 (0.5×C_{Ar}), 133.09 (0.5×C_{Ar}), 133.0 (0.5×C_{Ar}), 129.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.02 (CH_{Ar}), 127.99 (CH_{Ar}), 127.70 (CH_{Ar}), 127.65 (CH_{Ar}), 127.2 (CH_{Ar}), 127.1 (CH_{Ar}), 122.8 (dd, *J* = 261.4, 255.6 Hz, 0.5×CF_2), 122.5 (dd, *J* = 261.4, 255.6 Hz, 0.5×CF_2), 89.3–88.7 (m, CHN), 79.4 (d, *J* = 7.8 Hz, 0.5×$\underline{C}HCH_2$), 78.5 (d, *J* = 5.8, 2.9 Hz, 0.5×$\underline{C}HCH_2$), 77.6 (dd, *J* = 31.1, 17.5 Hz, 0.5×CHOBn), 76.8 (dd, *J* = 26.2, 17.5 Hz, 0.5×CHOBn), 73.0 (d, *J* = 1.9 Hz, 0.5×OCH_2Ph), 72.7 (0.5×OCH_2Ph), 63.3 (0.5×CH$\underline{C}H_2$), 62.7 (0.5×CH$\underline{C}H_2$), 49.7 (0.5×$NHCH_2$), 49.2 (0.5×$NHCH_2$), 26.7 ($C(\underline{C}H_3)_3$), 19.3 (0.5×$\underline{C}(CH_3)_3$), 19.2 (0.5×$\underline{C}(CH_3)_3$) ppm (some CH_{Ar} overlap).

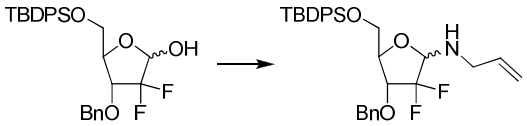
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.5 (1 F, dt, *J* = 240.7, 12.9 Hz, C<u>F</u>F), –122.8 (1 F, d, *J* = 240.7 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –113.3 (1 F, d, *J* = 236.4 Hz, C<u>F</u>F), –132.3 (1 F, d, *J* = 240.7 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-*N*-Allyl-4-(benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-amine, 3.22e



Following the general procedure:- lactol **2.01** (86 mg, 0.17 mmol), MeOH (1 mL), allylamine (3 equiv, 0.52 mmol, 0.039 mL) and PTSA (1 equiv, 0.17 mmol, 33 mg). Stir for 5 h. Column chromatography: (5:95 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22e** as (colourless oil) a 1:1 anomeric mixture (82 mg, 88%).

IR (film) 3071 (w), 2930 (m), 2858 (w), 1428 (m), 1105 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 560.4 $(M+Na)^+$ (93), 538.3 $(M+H)^+$ (100).

HRMS (ESI^+) for $C_{31}H_{37}F_2O_3NSi$ $(M+H)^+$ calcd 538.2584, found 538.2593.

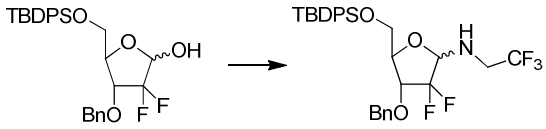
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.63 (4 H, m, 4×CH_{Ar}), 7.48–7.36 (11 H, m, 11×CH_{Ar}), 5.99–5.90 (1 H, m, <u>H</u>C=CH_2), 5.25 (1 H, m, 0.5×HC=C<u>H</u>$_2$), 5.14 (1 H, m, 0.5×HC=C<u>H</u>$_2$), 4.88 (0.5 H, d, *J* = 11.5 Hz, 0.5×C<u>H</u>HPh), 4.87 (0.5 H, d, *J* = 11.5 Hz, 0.5×C<u>H</u>HPh), 4.86 (0.5 H, m, 0.5×CHN), 4.68–4.56 (0.5 H, m, 0.5×CHN), 4.61 (0.5 H, d, *J* = 11.5 Hz, 0.5×CH<u>H</u>Ph), 4.59 (0.5 H, d, *J* = 11.5 Hz, 0.5×CH<u>H</u>Ph), 4.37 (0.5 H, td, *J* = 10.3, 6.5 Hz, 0.5×CHOBn), 4.09–4.04 (1 H, m, 0.5×CHOBn, 0.5×C<u>H</u>CH_2), 3.85–3.76 (2.5 H, m, 0.5×C<u>H</u>CH_2, CHC<u>H</u>H, 0.5×CHC<u>H</u>H), 3.71 (0.5 H, dd, *J* = 11.3, 2.9 Hz, 0.5×CHCH<u>H</u>), 3.58–3.53 (1 H, m, 0.5×NCH_2), 3.46–3.38 (1 H, m, 0.5×NCH_2), 2.11 (0.5 H, br. s, 0.5×NH), 1.91 (0.5 H, br. s, 0.5×NH), 1.06–1.05 (9 H, m, 0.5×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.1 (0.5×C_{Ar}), 137.0 (0.5×C_{Ar}), 136.2 (0.5×H<u>C</u>=CH_2), 136.1 (0.5×H<u>C</u>=CH_2), 135.64 (CH_{Ar}), 135.57 (CH_{Ar}), 133.23

(0.5×C_{Ar}), 133.15 (0.5×C_{Ar}), 133.1 (0.5×C_{Ar}), 133.0 (0.5×C_{Ar}), 129.8 (CH_{Ar}), 129.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.03 (CH_{Ar}), 128.00 (CH_{Ar}), 127.74 (CH_{Ar}), 127.69 (CH_{Ar}), 127.6 (CH_{Ar}), 122.9 (dd, *J* = 261.4, 255.6 Hz, CF_2), 116.5 (0.5×HC=$\underline{C}H_2$), 116.4 (0.5×HC=$\underline{C}H_2$), 89.2 (dd, *J* = 33.0, 21.4 Hz, 0.5×CHN), 89.1 (dd, *J* = 32.0, 19.4 Hz, 0.5×CHN), 79.3 (d, *J* = 7.8 Hz, 0.5×$\underline{C}HCH_2$), 78.6 (dd, *J* = 5.4, 3.4 Hz, 0.5×$\underline{C}HCH_2$), 78.5 (dd, *J* = 31.1, 17.5 Hz, 0.5×CHOBn), 77.7 (dd, *J* = 25.3, 17.5 Hz, 0.5×CHOBn), 73.0 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 72.8 (0.5×CH_2Ph), 63.3 (0.5×CH$\underline{C}H_2$), 62.7 (0.5×CH$\underline{C}H_2$), 48.8 (0.5×NCH_2), 48.3 (0.5×NCH_2), 26.8 (C($\underline{C}H_3$)$_3$), 19.3 ($\underline{C}(CH_3)_3$), 19.2 ($\underline{C}(CH_3)_3$) ppm. (some CH_{Ar} overlap)

^{19}F NMR (376 MHz, $CDCl_3$) δ –113.8 (0.5 F, ddd, *J* = 237.5, 9.2, 6.3 Hz, 0.5×C$\underline{F}$F), –116.8 (0.5 F, ddd, *J* = 242.1, 15.5, 11.5 Hz, 0.5×C$\underline{F}$F), –123.1 (0.5 F, ddd, *J* = 242.7, 7.5, 2.9 Hz, 0.5×CF$\underline{F}$), –132.7 (0.5 F, dt, *J* = 237.5, 10.3 Hz, 0.5×CF$\underline{F}$) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-(2,2,2-trifluoroethyl)tetrahydrofuran-2-amine, 3.22f



Following the general procedure:- lactol **2.01** (109 mg, 0.22 mmol), MeOH (0.5 mL), 2,2,2-trifluoroethylamine (3 equiv, 0.66 mmol, 0.05 mL) and PTSA (1 equiv, 0.22 mmol, 42 mg). Stir for 18 h. Column chromatography: (10:90 acetone/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22f** as (colourless oil) a 1:1.3 anomeric mixture (95 mg, 75%).

IR (film) 2931 (w), 2859 (w), 1272 (w), 1150 (m), 1112 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 602.3 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{30}H_{34}O_3F_5NSi$ $(M+H)^+$ calcd 602.2120, found 602.2126.

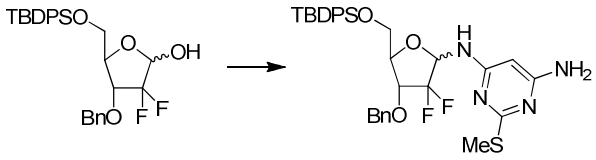
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (4 H, m, 4×CH_{Ar}), 7.39–7.24 (11 H, m, 11×CH_{Ar}), 4.88 (0.5 H, m, 0.5×CHN), 4.784 (0.5 H, d, *J* = 11.5 Hz, 0.5×C$\underline{H}$HPh), 4.780 (0.5 H, d, *J* = 11.4 Hz, 0.5×C$\underline{H}$HPh), 4.54 (0.5 H, m, 0.5×CHN), 4.51 (0.5 H, d, *J* = 11.7 Hz, 0.5×CH$\underline{H}$Ph), 4.49 (0.5 H, d, *J* = 11.5 Hz, 0.5×CH$\underline{H}$Ph),

4.26 (0.5 H, m, 0.5×CHOBn), 4.01–3.97 (1 H, m, 0.5×CHOBn, 0.5×C<u>H</u>CH_2), 3.76–3.67 (2 H, m, 0.5×C<u>H</u>CH_2, 0.75×CH_2OSi), 3.63 (0.5 H, dd, *J* = 11.4, 3.0 Hz, 0.25×CH_2Si), 3.40–3.15 (2 H, m, CH_2CF_3), 2.35 (0.5 H, m, NH), 2.14 (0.5 H, m, NH), 0.97 (9 H, s, C(CH_3)$_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 136.9 (0.5×C_{Ar}), 136.8 (0.5×C_{Ar}), 135.6 (CH_{Ar}), 135.6 (CH_{Ar}), 133.1 (0.5×C_{Ar}), 133.04 (0.5×C_{Ar}), 132.98 (0.5×C_{Ar}), 132.9 (0.5×C_{Ar}), 129.9 (CH_{Ar}), 129.8 (CH_{Ar}), 128.54 (CH_{Ar}), 128.52 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.73 (CH_{Ar}), 127.67 (CH_{Ar}), 126.3–119.5 (m, CF_2, CF_3), 89.4 (dd, *J* = 33.0, 21.4 Hz, 0.5×CHN), 89.5 (dd, *J* = 34.0, 20.0 Hz, 0.5×CHN), 79.9 (d, *J* = 6.8 Hz, 0.5×<u>C</u>HCH_2), 78.8 (dd, *J* = 5.8, 2.9 Hz, 0.5×C<u>H</u>CH_2), 77.1 (dd, *J* = 31.1, 17.5 Hz, 0.5×CHOBn), 76.7 (dd, *J* = 28.2, 17.5 Hz, 0.5×CHOBn), 73.1 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 72.9 (0.5×CH_2Ph), 63.1 (0.5×CH_2OSi), 62.5 (0.5×CH_2OSi), 47.5 (q, *J* = 33.0 Hz, 0.5×<u>C</u>H_2CF_3), 46.9 (q, *J* = 33.0 Hz, 0.5×<u>C</u>H_2CF_3), 26.7 (C(<u>C</u>H_3)$_3$), 19.23 (0.5×<u>C</u>(CH_3)$_3$), 19.20 (0.5×<u>C</u>(CH_3)$_3$) ppm (some CH_{Ar} overlap).

^{19}F NMR (282 MHz, $CDCl_3$) δ –73.1 (1.5 F, t, *J* = 8.6 Hz, 0.5×CF_3), –73.4 (1.5 F, t, *J* = 8.6 Hz, 0.5×CF_3), –113.1 (0.5 F, dt, *J* = 239.6, 9.7 Hz, 0.5×C<u>F</u>F), –116.9 (0.5 F, dt, *J* = 242.9, 12.9 Hz, 0.5×C<u>F</u>F), –123.4 (0.5 F, dd, *J* = 242.9, 5.4 Hz, 0.5×CF<u>F</u>), –131.7 (0.5 F, dt, *J* = 239.6, 8.6 Hz, 0.5×CF<u>F</u>) ppm.

N^4-((4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-2-(methylthio)pyrimidine-4,6-diamine, 3.22g



Lactol **2.01** (70 mg, 0.14 mmol), 4,6-diamino-2-(thiomethyl)-pyrimidine (5 equiv, 0.70 mmol, 110 mg) and PTSA (1 equiv, 0.14 mmol, 27 mg) were stirred in MeOH (0.5 mL) at reflux for 3 d. The reaction mixture was cooled to RT, and poured into sat. $NaHCO_3$ (aq). The aqueous phase was extracted with DCM (3×5 mL), the combined organic phases were washed with water, then brine then dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel

(20:80–30:70 acetone/hexane + 0.5% Et_3N) to yield the desired product **3.22g** as a colourless oil, as a 1:1.2 mixture of anomers (63 mg, 70%).

IR (film) 3381 (br), 2929 (w), 2857 (w), 1586 (s), 1496 (m), 1292 (m), 1104 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 637.2 $(M+H)^+$ (100).

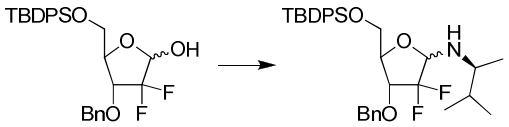
HRMS (ESI^+) for $C_{33}H_{38}F_2N_4O_3SSi$ $(M+H)^+$ Calcd 637.2475; Found 637.2469.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.60 (4 H, m, 4×CH_{Ar}), 7.47–7.33 (11 H, m, 11×CH_{Ar}), 5.88 (0.5 H, m, 0.5×CHN), 5.86 (0.5 H, m, 0.5×CHN), 5.52 (0.5 H, d, *J* = 9.5 Hz, 0.5×NH), 5.27 (0.5 H, s, 0.5×CH_{Ar}), 5.22 (0.5 H, d, *J* = 9.8 Hz, 0.5×NH), 5.14 (0.5 H, s, 0.5×CH_{Ar}), 4.88 (1 H, d, C<u>H</u>HPh), 4.64–4.55 (3 H, m, CH<u>H</u>Ph, NH_2), 4.41 (0.5 H, ddd, *J* = 10.8, 8.2, 6.1, 0.5×CHOBn), 4.20 (0.5 H, ddd, *J* = 14.4, 5.7, 4.4 Hz, 0.5×CHOBn), 4.14 (0.5 H, m, 0.5×C<u>H</u>CH_2), 3.96 (0.5 H, m, 0.5×C<u>H</u>CH_2), 3.85–3.72 (2 H, m, CHC<u>H_2</u>), 2.47 (1.5 H, s, 0.5×SMe), 2.44 (1.5 H, s, 0.5×SMe), 1.05 (4.5 H, s, 0.5×$C(CH_3)_3$), 1.04 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 171.42 (C_{Ar}), 171.37 (C_{Ar}), 163.1 (C_{Ar}), 161.3 (C_{Ar}), 161.2 (C_{Ar}), 136.73 (C_{Ar}), 136.66 (C_{Ar}), 135.6 (CH_{Ar}), 135.5 (CH_{Ar}), 133.1 (C_{Ar}), 132.82 (C_{Ar}), 132.80 (C_{Ar}), 129.91 (CH_{Ar}), 129.88 (CH_{Ar}), 129.83 (CH_{Ar}), 129.8 (CH_{Ar}), 128.59 (CH_{Ar}), 128.56 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.10 (CH_{Ar}), 128.05 (CH_{Ar}), 127.81 (CH_{Ar}), 127.78 (CH_{Ar}), 127.7 (CH_{Ar}), 122.8 (dd, *J* = 263.4, 257.6 Hz, 0.5×CF_2), 82.3–81.2 (m, CHN), 80.8 (d, *J* = 8.7 Hz, CH_{Ar}), 80.6 (d, *J* = 5.8 Hz, CH_{Ar}), 79.52 (0.5×C<u>H</u>CH_2), 79.48 (0.5×C<u>H</u>CH_2), 77.3–76.4 (m, CHOBn), 73.1 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 73.0 (0.5×CH_2Ph), 62.7 (0.5×CH<u>C</u>H_2), 62.4 (0.5×CH<u>C</u>H_2), 26.81 (0.5×C(<u>C</u>$H_3)_3$), 26.79 (0.5×C(<u>C</u>$H_3)_3$), 19.28 (0.5×<u>C</u>$(CH_3)_3$), 19.25 (0.5×<u>C</u>$(CH_3)_3$), 13.83 (0.5×SMe), 13.78 (0.5×SMe) ppm (some C_{Ar}/CH_{Ar} overlap, 0.5×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –112.1 (0.5 F, d, *J* = 239.7 Hz, C<u>F</u>F), –115.8 (0.5 F, dt, *J* = 241.4, 12.9 Hz, C<u>F</u>F), –122.9 (0.5 F, d, *J* = 241.4 Hz, CF<u>F</u>), –129.3 (0.5 F, dt, *J* = 239.7, 7.8 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-((*S*)-3-methylbutan-2-yl)tetrahydrofuran-2-amine, 3.22h



Following the general procedure:- lactol **2.01** (74 mg, 0.15 mmol), MeOH (1 mL), (*S*)-1,2-dimethylpropylamine (3 equiv, 0.45 mmol, 0.028 mL) and PTSA (1 equiv, 0.15 mmol, 28 mg). Stir for 22 h. Column chromatography: (10:90–20:80 Et_2O/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22h** as (colourless oil) a 1:1.5 anomeric mixture (39 mg, 46%).

IR (film) 2958 (m), 2930 (m), 2858 (m), 1105 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 590.4 $(M+Na)^+$ (100), 568.4 $(M+H)^+$ (35).

HRMS (ESI^+) for $C_{33}H_{43}F_2NO_3Si$ $(M+H)^+$ calcd 568.3053, found 568.3057.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.62 (4 H, m, 4×CH_{Ar}), 7.47–7.32 (11 H, m, 11×CH_{Ar}), 4.95 (0.5 H, dd, *J* = 9.9, 6.5 Hz, 0.5×OCHN), 4.88 (0.5 H, d, *J* = 11.7 Hz, 0.5×C<u>H</u>HPh), 4.86 (0.5 H, d, *J* = 11.4 Hz, 0.5×C<u>H</u>HPh), 4.65 (0.5 H, dd, *J* = 13.7, 6.8 Hz, 0.5×OCHN), 4.602 (0.5 H, d, *J* = 11.7 Hz, 0.5×CH<u>H</u>Ph), 4.598 (0.5 H, d, *J* = 11.4 Hz, 0.5×CH<u>H</u>Ph), 4.36 (0.5 H, td, *J* = 10.4, 6.4 Hz, 0.5×CHOBn), 4.04–4.00 (1 H, m, 0.5×CHOBn, 0.5×C<u>H</u>CH_2), 3.84–3.79 (2 H, m, 0.5xC<u>H</u>CH_2, CHC<u>H</u>H, 0.5×CHCH<u>H</u>), 3.70 (0.5 H, dd, *J* = 11.2, 2.9 Hz, 0.5×CHCH<u>H</u>), 2.85 (0.5 H, quin, *J* = 6.2 Hz, 0.5×NC<u>H</u>CH_3), 2.78 (0.5 H, quin, *J* = 6.2 Hz, 0.5×NC<u>H</u>CH_3), 1.71–1.65 (1 H, m, C<u>H</u>$(CH_3)_2$), 1.12–0.99 (3 H, m, NCHC<u>H</u>$_3$), 1.05 (9 H, s, $C(CH_3)_3$), 0.94–0.90 (6 H, m, $CH(C\underline{H}_3)_2$) ppm (NH not visible).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.2 (0.5×C_{Ar}), 137.1 (0.5×C_{Ar}), 135.7 (CH_{Ar}), 135.6 (CH_{Ar}), 133.4 (0.5×C_{Ar}), 133.2 (0.5×C_{Ar}), 133.1 (0.5×C_{Ar}), 133.0 (0.5×C_{Ar}), 129.8 (CH_{Ar}), 129.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.73 (CH_{Ar}), 127.67 (CH_{Ar}), 127.6 (CH_{Ar}) , 122.8 (dd, *J* = 261.4, 255.6 Hz, 0.5×CF_2), 122.3 (dd, *J* = 262.4, 254.6 Hz, 0.5×CF_2), 89.6 (dd, *J* = 31.1, 20.4 Hz, 0.5×OCHN), 87.9 (dd, *J* = 32.0, 18.5 Hz, 0.5×OCHN), 79.0 (d, *J* = 7.8 Hz, 0.5×<u>C</u>HCH_2), 78.2 (d, *J* = 3.9 Hz, 0.5×<u>C</u>HCH_2), 77.6 (dd, *J* = 32.0, 17.5 Hz, 0.5×CHOBn), 76.9 (dd, *J* = 25.3, 17.5 Hz, 0.5×CHOBn), 73.0 (d, *J* = 2.9 Hz, 0.5×CH_2Ph), 72.7

(0.5×CH_2Ph), 63.4 (0.5×CH<u>C</u>H_2), 62.8 (0.5×CH<u>C</u>H_2), 56.6 (0.5×N<u>C</u>HCH_3), 54.5 (0.5×N<u>C</u>HCH_3), 33.5 (0.5×<u>C</u>H(CH_3)$_2$), 33.0 (0.5×<u>C</u>H(CH_3)$_2$), 26.73 (0.5×C(<u>C</u>H_3)$_3$), 26.71 (0.5×C(<u>C</u>H_3)$_3$), 19.3 (0.5×<u>C</u>(CH_3)$_3$), 19.2 (0.5×<u>C</u>(CH_3)$_3$), 19.1 (0.5×CH_3), 18.7 (0.5×CH_3), 18.6 (0.5×CH_3), 17.5 (0.5×CH_3), 17.4 (0.5×CH_3), 15.8 (0.5×CH_3) ppm. (some CH_{Ar} overlap)

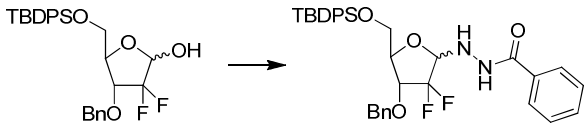
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.9 (1 F, dd, *J* = 245.0, 17.2 Hz, C<u>F</u>F), –123.6 (1 F, dd, *J* = 240.7, 8.6 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –113.9 (1 F, d, *J* = 236.4 Hz, C<u>F</u>F), –133.0 (1 F, d, *J* = 236.4 Hz, CF<u>F</u>) ppm.

N'-((4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)benzohydrazide, 3.22i



Following the general procedure:- lactol **2.01** (84 mg, 0.17 mmol), MeOH (0.5 mL), benzhydrazide (3 equiv, 0.51 mmol, 69 mg) and PTSA (1 equiv, 0.17 mmol, 32 mg). Stir for 4 h. Column chromatography: (30:70 acetone/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22i** as (colourless oil) a 1:2 anomeric mixture (94 mg, 90%).

IR (film) 3294 (br), 2930 (w), 2858 (w), 1659 (m), 1456 (m), 1426 (m), 1104 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 639.3 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{35}H_{38}O_4F_2N_2Si$ $(M+H)^+$ calcd 639.2461, found 639.2460.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.25 (20 H, m, 20×CH_{Ar}), 5.49 ($^2/_3$ H, br. s, NH_{Major}), 5.23 ($^1/_3$ H, br. s, NH_{Minor}), 4.93 ($^2/_3$ H, m, CHN_{Major}), 4.87 ($^1/_3$ H, m, CHN_{Minor}), 4.80 ($^2/_3$ H, d, *J* = 11.5 Hz, C<u>H</u>HPh$_{Major}$), 4.79 ($^1/_3$ H, d, *J* = 11.4 Hz, C<u>H</u>HPh$_{Minor}$), 4.521 ($^2/_3$ H, d, *J* = 11.5 Hz, CH<u>H</u>Ph$_{Major}$), 4.516 ($^1/_3$ H, d, *J* = 11.5 Hz, CH<u>H</u>Ph$_{Minor}$), 4.25–4.20 ($^2/_3$ H, m, C<u>H</u>CH$_{2Major}$), 4.19–4.12 (1 H, m, CHOBn), 3.90 ($^1/_3$ H, dt, *J* = 7.2, 3.3 Hz, C<u>H</u>CH$_{2Minor}$), 3.79 ($^1/_3$ H, ddd, *J* = 11.5,

3.8, 1.3 Hz, C<u>H</u>HOSi$_{Minor}$), 3.72–3.63 ($1^2/_3$, m, CH_2OSi_{Major}, CH<u>H</u>OSi), 0.94 (6 H, s, $C(CH_3)_{3Major}$), 0.93 (3 H, s, $C(CH_3)_{3Minor}$) ppm (1×NH not visible).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 167.1 (C=O), 136.8 (0.5×C_{Ar}), 136.7 (0.5×C_{Ar}), 135.6 (CH_{Ar}), 135.5 (CH_{Ar}), 133.04 (0.5×C_{Ar}), 132.98 (0.5×C_{Ar}), 132.93 (0.5×C_{Ar}), 132.87 (0.5×C_{Ar}), 132.2 (0.5×C_{Ar}), 131.9 (CH_{Ar}), 129.81 (CH_{Ar}), 129.76 (CH_{Ar}), 129.7 (CH_{Ar}), 128.61 (CH_{Ar}), 128.55 (CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.71 (CH_{Ar}), 127.67 (CH_{Ar}), 127.0 (CH_{Ar}), 123.8 (dd, *J* = 267.3, 254.6 Hz, CF_2), 90.7 (dd, *J* = 36.0, 19.4 Hz, 0.5×CHN), 89.8 (dd, *J* = 33.0, 20.4 Hz, 0.5×CHN), 82.4 (0.5×<u>C</u>HCH_2), 79.9 (d, *J* = 6.8 Hz, 0.5×<u>C</u>HCH_2), 77.6 (dd, *J* = 30.1, 17.5 Hz, 0.5×CHOBn), 76.6 (dd, *J* = 26.2, 16.5 Hz, 0.5×CHOBn), 73.4 (d, *J* = 1.9 Hz, 0.5×CH_2Ph), 72.9 (0.5×CH_2Ph), 62.6 (0.5×CH<u>C</u>H_2), 62.5 (0.5×CHCH_2), 26.7 (C(<u>C</u>$H_3)_3$), 19.2 (<u>C</u>$(CH_3)_3$) ppm. (some C_{Ar}/CH_{Ar} overlap)

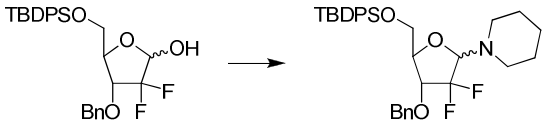
Major anomer:

^{19}F NMR (282 MHz, $CDCl_3$) δ –104.1 (1 F, dt, *J* = 249.3, 12.9 Hz, C<u>F</u>F), –126.2 (1 F, d, *J* = 249.3 Hz, CF<u>F</u>) ppm.

Minor anomer:

^{19}F NMR (282 MHz, $CDCl_3$) δ –118.0 (1 F, d, *J* = 240.7 Hz, C<u>F</u>F), –121.1 (1 F, d, *J* = 240.7, 8.6 Hz, CF<u>F</u>) ppm.

1-((4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)piperidine, 3.22j



Following the general procedure:- lactol **2.01** (81 mg, 0.16 mmol), MeOH (1 mL), piperidine (3 equiv, 0.49 mmol, 0.048 mL) and PTSA (1 equiv, 0.16 mmol, 31 mg). Stir for 22 h. Column chromatography: (5:95 acetone/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22j** as (colourless oil) a 1:3 anomeric mixture (67 mg, 73%).

IR (film) 3070 (w), 2931 (m), 2856 (m), 1428 (m), 1194 (m), 1105 (s), 1073 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 588.2 $(M+Na)^+$ (39), 566.3 $(M+H)^+$(100).

HRMS (ESI^+) for $C_{33}H_{41}F_2NO_3Si$ $(M+H)^+$ calcd 566.2897, found 566.2889.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.63 (4 H, m, 4×CH_{Ar}), 7.47–7.32 (11 H, m, 11×CH_{Ar}), 4.91 (0.75 H, d, *J* = 11.5 Hz, C<u>H</u>HPh$_{Major}$), 4.89 (0.25 H, d, *J* = 11.5 Hz, C<u>H</u>HPh$_{Minor}$), 4.69 (0.25 H, t, *J* = 11.1 Hz, CHN$_{Minor}$), 4.62 (0.75 H, d, *J* = 11.5 Hz, CH<u>H</u>Ph$_{Major}$), 4.64–4.57 (1 H, m, CH<u>H</u>Ph$_{Minor}$, CHN$_{Major}$), 4.35–4.28 (0.25 H, m, CHOBn$_{Minor}$), 4.20 (0.75 H, td, *J* = 11.6, 8.4 Hz, CHOBn$_{Major}$), 4.08 (0.25 H, ddd, *J* = 6.0, 3.2, 3.1 Hz, C<u>H</u>CH$_{2Minor}$), 3.96 (0.75 H, d, *J* = 11.5 Hz, C<u>H</u>HCH$_{Major}$), 3.86–3.70 (2 H, m, CH<u>H</u>CH$_{Major}$, C<u>H$_2$</u>CH$_{Minor}$, CH$_2$C<u>H</u>$_{Major}$), 2.99–2.94 (0.5 H, m, NCH$_{2Minor}$), 2.87–2.78 (3 H, m, N(CH$_2$)$_{2Major}$), 2.70–2.65 (0.5 H, m, NCH$_{2Minor}$), 1.65–1.57 (4 H, m, 2×NCH$_2$NC<u>H$_2$</u>), 1.51–1.45 (2 H, m, NCH$_2$CH$_2$C<u>H$_2$</u>), 1.05 (9 H, s, C(CH$_3$)$_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.1 (C_{Ar}), 135.6 (CH_{Ar}), 135.5 (CH_{Ar}), 133.1 (C_{Ar}), 129.7 (CH_{Ar}), 129.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.02 (CH_{Ar}), 127.96 (CH_{Ar}), 127.7 (CH_{Ar}), 127.6 (CH_{Ar}), 124.3 (dd, *J* = 267.2, 250.7 Hz, CF$_{2Minor}$), 124.0 (dd, *J* = 262.4, 253.6 Hz, CF$_{2Major}$), 96.2 (dd, *J* = 36.0, 20.4 Hz, CHN$_{Major}$), 96.2 (dd, *J* = 36.9, 17.5 Hz, CHN$_{Minor}$), 80.9 (d, *J* = 7.8 Hz, <u>C</u>HCH$_{2Minor}$), 77.5 (dd, *J* = 28.2, 17.5 Hz, CHOBn$_{Minor}$), 76.9 (dd, *J* = 24.3, 18.5 Hz, CHOBn$_{Major}$), 76.7 (d, *J* = 8.8 Hz, <u>C</u>HCH$_{2Major}$), 72.7 (CH$_2$Ph$_{Minor}$), 72.6 (CH$_2$Ph$_{Major}$), 63.2 (CH<u>C</u>H$_{2Minor}$), 61.9 (CH<u>C</u>H$_{2Major}$), 50.1 (N(CH$_2$)$_{2Minor}$), 49.7 (N(CH$_2$)$_{2Major}$), 26.7 (C(<u>C</u>H$_3$)$_3$), 26.1 (2×NCH$_2$<u>C</u>H$_2$), 24.4 (NCH$_2$CH$_2$<u>C</u>H$_2$), 19.2 (<u>C</u>(CH$_3$)$_3$) ppm. (some C_{Ar}/CH_{Ar} overlap)

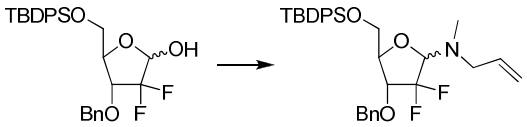
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –111.7 (ddd, *J* = 240.7, 16.1, 11.8 Hz, C<u>F</u>F), –113.1 (ddd, *J* = 240.7, 11.8, 8.6 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –103.4 (dt, *J* = 241.7, 11.8 Hz, C<u>F</u>F), –125.2 (dt, *J* = 240.7, 8.6 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-*N*-Allyl-4-(benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-methyltetrahydrofuran-2-amine, 3.22k



Following the general procedure:- lactol **2.01** (56 mg, 0.11 mmol), MeOH (1 mL), *N*-allylmethylamine (3 equiv, 0.34 mmol, 0.03 mL) and PTSA (1 equiv, 0.11 mmol, 21 mg). Stir for 22 h. Column chromatography: (10:90–15:85 EtOAc/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.22k** as (colourless oil) a 1:2.9 anomeric mixture (37 mg, 60%).

IR (film) 3071 (w), 2930 (m), 2858 (m), 1428 (m), 1112 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 574.2 $(M+Na)^+$ (18), 552.2 $(M+H)^+$ (100).

HRMS (ESI^+) for $C_{32}H_{39}F_2NO_3Si$ $(M+H)^+$ calcd 552.2740, found 552.2731.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.63 (4 H, m, 4×CH_{Ar}), 7.47–7.31 (11 H, m, 11×CH_{Ar}), 5.95–5.85 (1 H, m, C<u>H</u>=CH_2), 5.25–5.14 (2 H, m, CH=C<u>H</u>$_2$), 4.90 (0.75 H, d, *J* = 11.5 Hz, C<u>H</u>HPh), 4.89 (0.25 H, d, *J* = 11.7 Hz, C<u>H</u>HPh), 4.86–4.79 (0.25 H, m, CHN_{Minor}), 4.71 (0.75 H, dd, *J* = 15.0, 8.9 Hz, CHN_{Major}), 4.60 (0.75 H, d, *J* = 11.5 Hz, CH<u>H</u>Ph_{Major}), 4.59 (0.25 H, d, *J* = 11.7 Hz, CH<u>H</u>Ph_{Minor}), 4.36 (0.25 H, ddd, *J* = 11.3, 9.6, 6.9 Hz, $CHOBn_{Minor}$), 4.18 (0.75 H, ddd, *J* = 12.8, 10.0, 8.1 Hz, $CHOBn_{Major}$), 4.09–4.08 (0.25 H, m, CHC<u>H</u>H_{Minor}), 3.94 (0.75 H, m, CHC<u>H</u>H_{Major}), 3.86–3.69 (2 H, m, C<u>H</u>CH_2, CHCH<u>H</u>), 3.47–3.25 (2 H, m, NCH_2), 2.49 (0.75 H, m, NCH_{3Minor}), 2.47 (2.25 H, m, NCH_{3Major}), 1.04 (9 H, s, $C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.1 (C_{Ar}), 134.8 (C_{Ar}), 133.11 (C_{Ar}), 133.07 (C_{Ar}), 135.8 (<u>C</u>H=CH_{2Minor}), 135.6 (<u>C</u>H=CH_{2Major}), 129.8 (CH_{Ar}), 129.77 (CH_{Ar}), 129.66 (CH_{Ar}), 128.5 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.72 (CH_{Ar}), 127.66 (CH_{Ar}), 123.9 (dd, *J* = 261.4, 254.6 Hz, CF_{2Major}), 117.4 (CH=<u>C</u>H_2), 94.7 (dd, *J* = 35.0, 20.4 Hz, CHN_{Major}), 94.0 (dd, *J* = 36.9, 17.5 Hz, CHN_{Minor}), 80.4 (d, *J* = 8.8 Hz, <u>C</u>HCH_{2Minor}), 76.0–75.6 (m, <u>C</u>HCH_{2Major}, CHOBn), 72.7 (CH_2Ph_{Minor}), 72.6 (CH_2Ph_{Major}), 63.1 (CH<u>C</u>H_{2Minor}), 61.9 (CH<u>C</u>H_{2Major}), 57.8 (NCH_{2Minor}), 57.4 (NCH_{2Major}), 36.8 (d, *J* = 4.9 Hz, NCH_{3Minor}), 36.5 (d, *J* = 2.9 Hz, NCH_{3Major}), 26.7 ($C(\underline{C}H_3)_3$), 19.2 (<u>C</u>$(CH_3)_3$) ppm (some C_{Ar}/CH_{Ar} overlap, minor CF_2 not visible).

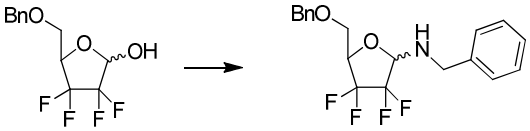
Major anomer

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.1 (1 F, ddd, *J* = 241.0, 12.0, 10.0 Hz, C<u>F</u>F), –113.2 (1 F, ddd, *J* = 241.0, 15.0, 10.0 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (376 MHz, $CDCl_3$) δ –106.7 (1 F, dt, *J* = 240.3, 10.5 Hz, C<u>F</u>F), –126.8 (1 F, dt, *J* = 241.0, 11.0 Hz, CF<u>F</u>) ppm.

(5*R*)-*N*-Benzyl-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-amine, 3.23a



Following the general procedure:- lactol **2.02** (51 mg, 0.18 mmol), MeOH (0.75 mL), benzylamine (3 equiv, 0.55 mmol, 0.060 mL) and PTSA (1 equiv, 0.18 mmol, 35 mg). Stir for 5 h. Column chromatography: (15:85–20:80 acetone/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.23a** as (colourless oil) a 1:1.5 anomeric mixture (53 mg, 79%).

IR (film) 3013 (w), 2869 (br), 1496 (m), 1454 (m), 1136 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 392.1 $(M+Na)^+$ (100), 370.1 $(M+H)^+$ (28).

HRMS (ESI^+) for $C_{19}H_{19}F_4NO_2$ $(M+H)^+$ Calcd. 370.1425; Found 370.1419.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (10 H, m, 10×CH_{Ar}), 4.85 (0.4 H, m, CHN_{Minor}), 4.63–4.47 (2.6 H, m, CHN_{Major}, OCH_2Ph), 4.30 (0.4 H, tdt, *J* = 14.7, 5.6, 2.6 Hz, C<u>H</u>CH_{2Minor}), 4.08–3.97 (1.6 H, m, C<u>H</u>CH_{2Major}, NC<u>H</u>H), 3.91–3.83 (1 H, m, NCH<u>H</u>), 3.71 (0.4 H, dd, *J* = 7.4, 5.0 Hz, CHC<u>H</u>H_{Minor}), 3.68 (0.6 H, dd, *J* = 7.3, 5.0 Hz, CHC<u>H</u>H_{Major}), 3.62–3.56 (1 H, m, CHCH<u>H</u>), 2.26–2.16 (1 H, m, NH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 138.6 (C_{Ar}), 137.4 ($C_{ArMinor}$), 137.3 ($C_{ArMajor}$), 128.52 (CH_{Ar}), 128.49 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.95 (CH_{Ar}), 127.89 (CH_{Ar}), 127.79 (CH_{Ar}), 127.7 (CH_{Ar}), 127.4 (CH_{Ar}), 88.3 (ddt, *J* = 31.1, 19.4, 2.9 Hz, CHN_{Major}), 87.6 (ddd, *J* = 29.2, 18.5, 3.9 Hz, CHN_{Minor}), 76.2–75.3 (m, <u>C</u>HCH_2), 73.74 (0.6×OCH_2Ph_{Major}), 73.70 (OCH_2Ph_{Minor}), 66.7 (d, *J* =

6.8 Hz, 0.4×CH<u>C</u>H$_{2Minor}$), 66.5 (d, *J* = 6.8 Hz, CH<u>C</u>H$_{2Major}$), 49.4 (NCH$_{2Major}$), 49.2 (NCH$_{2Minor}$) ppm (some CH$_{Ar}$ overlap, 2×CF$_2$ not visible).

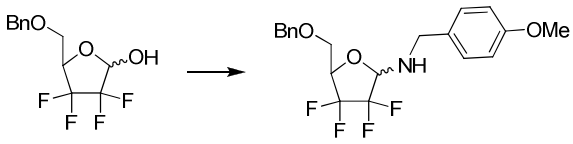
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.8 (1 F, dd, *J* = 245.0, 12.9 Hz, C<u>F</u>F), –125.5 (1 F, d, *J* = 245.0 Hz, C<u>F</u>F), –134.0 (1 F, dd, *J* = 245.0, 17.2 Hz, CF<u>F</u>), –135.6 (1 F, dd, *J* = 245.0, 8.6 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –125.6 (1 F, dt, *J* = 245.0, 10.7 Hz, C<u>F</u>F), –130.7 (1 F, ddd, *J* = 245.0, 17.2, 8.6 Hz, C<u>F</u>F), –132.2 (1 F, d, *J* = 245.0 Hz, CF<u>F</u>), –133.9 (1 F, dt, *J* = 245.0, 8.6 Hz, CF<u>F</u>) ppm.

(5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluoro-*N*-(4-methoxybenzyl) tetrahydrofuran-2-amine, 3.23b



Following the general procedure:- lactol **2.02** (49 mg, 0.15 mmol), MeOH (1 mL), *p*-methoxybenzylamine (3 equiv, 0.52 mmol, 0.07 mL) and PTSA (1 equiv, 0.15 mmol, 33 mg). Stir for 5 h. Column chromatography: (20:80 Et_2O/hexane + 0.5% Et_3N). Yield of aminoglycoside **3.23b** as (colourless oil) a 1:1 anomeric mixture (65 mg, 93%).

IR (film) 3351 (br), 2912 (w), 1612 (m), 1586 (w), 1513 (s), 1497 (m), 1455 (m), 1386 (m), 1285 (w), 1246 (s), 1205 (m), 1136 (s), 1029 (s), 1000 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 422.1 $(M+Na)^+$ (52), 400.1 $(M+H)^+$ (43).

HRMS (ESI^+) for $C_{20}H_{21}F_4NO_3$ $(M+Na)^+$ calcd 422.1350, found 422.1349.

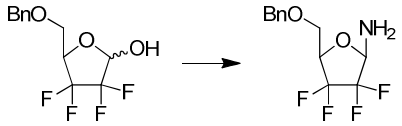
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.18 (7 H, m, 7×CH$_{Ar}$), 6.80–6.78 (2 H, m, 2×CH$_{Ar}$), 4.85 (0.5 H, m, 0.5×CHN), 4.58 (0.5 H, m, 0.5×CHN), 4.55 (0.5 H, d, *J* = 12.1 Hz, 0.5×C<u>H</u>HPh), 4.53 (0.5 H, d, *J* = 12.1 Hz, 0.5×CH<u>H</u>Ph), 4.50 (0.5 H, d, *J* = 12.1 Hz, 0.5×C<u>H</u>HPh), 4.49 (0.5 H, d, *J* = 12.1 Hz, 0.5×CH<u>H</u>Ph), 4.29 (0.5 H, m, 0.5×C<u>H</u>CH$_2$), 4.05–3.95 (1.5 H, m, 0.5×C<u>H</u>CH$_2$, NC<u>H</u>H), 3.85–3.77 (1 H, m, NCH<u>H</u>), 3.721 (1.5 H, s, 1.5×OMe), 3.717 (1.5 H, s,

1.5×OMe), 3.69–3.66 (1 H, m, CHHOBn), 3.62–3.58 (1 H, m, CHHOBn), 2.19–2.11 (1 H, m, NH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 159.0 (C_{Ar}), 137.4 (C_{Ar}), 137.3 (C_{Ar}), 130.6 (C_{Ar}), 129.4 (CH_{Ar}), 129.3 (CH_{Ar}), 128.5 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 113.9 (CH_{Ar}), 88.2 (dd, *J* = 31.1, 18.5 Hz, CHN), 75.8 (m, $\underline{C}HCH_2$), 73.8 (0.5×CH_2Ph), 73.7 (0.5×CH_2Ph), 66.7 (d, *J* = 6.8 Hz, 0.5×CH$\underline{C}H_2$), 66.6 (d, *J* = 6.8 Hz, 0.5×CH$\underline{C}H_2$), 55.3 (OCH_3), 48.8 (0.5×NCH_2), 48.7 (0.5×NCH_2) ppm (some C_{Ar}/CH_{Ar} overlap, 2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.8 (0.5 F, d, *J* = 245.0 Hz, 0.5×C$\underline{F}$F), –125.5 (0.5 F, d, *J* = 245.0 Hz, 0.5×C$\underline{F}$F), –125.8 (0.5 F, d, *J* = 245.0 Hz, 0.5×C$\underline{F}$F), –130.8 (0.5 F, ddd, *J* = 245.0, 17.2, 8.6 Hz, 0.5×C$\underline{F}$F), –132.8 (0.5 F, d, *J* = 245.0 Hz, 0.5×CF$\underline{F}$), –133.6 (0.5 F, dd, *J* = 38.7, 8.6 Hz, 0.5×CF$\underline{F}$), –134.5 (0.5 F, dd, *J* = 38.7, 12.9 Hz, 0.5×CF$\underline{F}$), –135.7 (0.5 F, dd, *J* = 245.0, 12.9 Hz, 0.5×CF$\underline{F}$) ppm.

(2*R*,5*R*)-5-(Benzyloxymethyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-amine, 3.24



To lactol **2.02** (73 mg, 0.26 mmol) in 1:1 MeOH/water (5 mL) was added NH_4HCO_3 until a saturated solution was obtained. The reaction mixture was stirred at RT for 7 d, with periodic addition of NH_4HCO_3, to maintain a saturated solution. The solvents were reduced *in vacuo* and the resultant residue taken up in $CHCl_3$, washed with water, then brine and dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a crude white solid which was recrystallised from DCM to yield the desired glycosylamine **3.24** as a white crystalline solid, exclusively the β anomer which anomerised over time in solution (71 mg, 98%).

Mp 128–132 ℃ (DCM).

IR (film) 3409 (m), 3344 (m), 2907 (w), 1455 (w), 1361 (w), 1287 (m), 1250 (m), 1198 (m), 1140 (s), 1099 (s), 1061 (s), 992 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 321.1 $(M+H+MeCN)^+$ (83), 280.1 $(M+H)^+$ (100).

HRMS (ESI$^+$) for $C_{12}H_{13}F_4O_2N$ $(M+H)^+$ Calcd: 280.0955; Found: 280.0963.

α anomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (5 H, m, 5×CH_{Ar}), 5.01 (1 H, dtdd, *J* = 12.7, 9.4, 6.1, 3.0 Hz, CHN), 4.62 (1 H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.58 (1 H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.40 (1 H, m, C<u>H</u>CH_2), 3.88 (1 H, m, C<u>H</u>HOBn), 3.69–3.65 (1 H, m, CH<u>H</u>OBn), 2.18 (2 H, d, *J* = 9.5 Hz, NH_2) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.3 (C_{Ar}), 127.9, 127.7 (5×CH_{Ar}, partially obscured), 84.0 (ddd, *J* = 29.3, 20.5, 4.4 Hz, CHN), 75.7 (dd, *J* = 29.3, 23.4 Hz, <u>C</u>HCH_2), 73.8 (CH_2Ph), 66.8 (d, *J* = 7.3 Hz, CH<u>C</u>H_2) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –126.3 (1 F, dtd, *J* = 245.5, 9.3, 4.5 Hz, C<u>F</u>F), –129.7 (1 F, dddd, *J* = 245.7, 16.8, 8.0, 2.6 Hz, CF<u>F</u>), –134.1 (1 F, dddd, *J* = 244.2, 8.6, 6.0, 4.5 Hz, C<u>F</u>F), –136.5 (1 F, dddd, *J* = 244.4, 13.1, 8.4, 3.0 Hz, CF<u>F</u>) ppm.

β anomer

$[\alpha]_D$ –7.2 (c 0.55, $CHCl_3$, 27 ℃) (Reading taken immediately after sample preparation.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.29 (5 H, m, 5×CH_{Ar}), 4.73 (1 H, m, CHN), 4.64 (1 H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.58 (1 H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 4.14 (1 H, m, C<u>H</u>CH_2), 3.78 (1 H, dd, *J* = 10.6, 4.7 Hz, C<u>H</u>HOBn), 3.67 (1 H, dd, *J* = 10.6, 6.7 Hz, CH<u>H</u>OBn), 2.22 (2 H, d, *J* = 9.0 Hz, NH_2) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 137.2 (C_{Ar}), 128.5 (2×CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (2×CH_{Ar}), 84.8 (dd, *J* = 32.2, 20.5 Hz, CHN), 76.1 (dd, *J* = 27.8, 23.4 Hz, <u>C</u>HCH_2), 73.8 (CH_2Ph), 66.5 (d, *J* = 7.3 Hz, CH<u>C</u>H_2) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –126.7 (1 F, ddddd, *J* = 244.0, 7.3, 5.6, 3.9, 1.7 Hz, C<u>F</u>F), –116.0 (1 F, ddddd, *J* = 245.3, 12.3, 5.5, 3.3, 1.7 Hz, CF<u>F</u>), –134.2 (1 F, ddd, *J* = 245.5, 14.2, 3.9 Hz, C<u>F</u>F), –137.5 (1 F, ddd, *J* = 244.0, 12.3, 3.0 Hz, CF<u>F</u>) ppm.

(4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluoro-*N*-(4-methoxybenzylidene)tetrahydrofuran-2-amine, 3.25

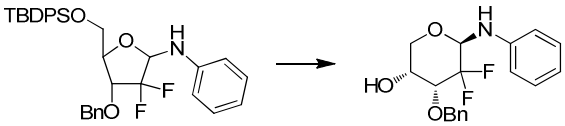
Glycosylamine **3.22b** (57 mg, 0.092 mmol) and DDQ (1.4 equiv, 0.13 mmol, 29 mg) in DCM (2 mL) and water (0.1 mL) were stirred at RT for 2 h. The reaction mixture was diluted with $CHCl_3$ and sat. $NaHCO_3$ (aq), the phases separated and the aqueous phase extracted with $CHCl_3$ (2×5 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude brown oil, which was stirred in Et_3N (2 mL) at RT for 18 h. The reaction mixture was diluted with water and extracted with $CHCl_3$ (3×5 mL), the combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude green oil which was purified by column chromatography on silica gel (15:85 acetone/hexane + 0.5% Et_3N) to yield imine **3.25** as a colourless oil as a 1:1.2 anomeric mixture (50 mg, 88%).

IR (film) 3070 (w), 2930 (m), 2858 (m), 1643 (m), 1606 (m) cm^{-1}.
LRMS (ESI$^+$) *m/z* 638.3 $(M+Na)^+$ (53), 616.3 $(M+H)^+$ (100).
HRMS (ESI$^+$) for $C_{36}H_{39}F_2O_4NSi$ $(M+Na)^+$ calcd: 638.2509, found: 638.2502.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (0.5 H, s, 0.5×N=CH), 8.42 (0.5 H, s, 0.5×N=CH), 7.80 (1 H, dd, *J* = 8.7, 1.6 Hz, CH_{Ar}), 7.72–7.64 (4 H, m, 4×CH_{Ar}), 7.35–7.33 (12 H, m, 12×CH_{Ar}), 6.98–6.91 (2 H, m, 2×CH_{Ar}), 5.54 (0.5 H, t, *J* = 7.7 Hz, 0.5×CHN), 5.43 (0.5 H, dd, *J* = 9.8, 8.2 Hz, 0.5×CHN), 4.93–4.87 (1 H, m, C<u>H</u>HPh), 4.62–4.58 (1 H, m, CH<u>H</u>Ph), 4.43 (0.5 H, m, 0.5×CHOBn), 4.32 (0.5 H, m, 0.5×C<u>H</u>CH_2), 4.26 (0.5, m, 0.5×CHOBn), 4.16 (0.5 H, m, C<u>H</u>CH_2), 3.97–3.80 (2 H, m, CHC<u>H</u>$_2$), 3.88 (1.5 H, s, 1.5×OMe), 3.86 (1.5 H, s, 1.5×OMe), 1.07–1.05 (9 H, m, $C(CH_3)_3$) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 162.31 (0.5×C_{Ar}), 162.29 (0.5×C_{Ar}), 161.3 (0.5×N=CH), 160.9 (0.5×N=CH), 137.12 (C_{Ar}), 137.08 (C_{Ar}), 133.2 (C_{Ar}), 133.0 (C_{Ar}), 135.64 (CH_{Ar}), 135.56 (CH_{Ar}), 130.62 (CH_{Ar}), 130.56 (CH_{Ar}), 129.8 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 128.03 (CH_{Ar}), 127.95 (CH_{Ar}), 127.7 (CH_{Ar}),

113.98 (CH_{Ar}), 113.95 (CH_{Ar}), 94.5 (dd, *J* = 35.0, 20.4 Hz, 0.5×CHN), 93.6 (dd, *J* = 32.1, 21.4 Hz, 0.5×CHN), 81.6 (d, *J* = 6.8 Hz, 0.5×$\underline{C}HCH_2$), 80.1 (d, *J* = 6.8 Hz, 0.5×$\underline{C}HCH_2$), 77.3 (t, *J* = 28.2 Hz, 0.5×CHOBn), 77.1 (t, *J* = 28.2 Hz, 0.5×CHOBn), 72.9 (0.5×CH_2Ph), 72.7 (0.5×CH_2Ph), 63.0 (0.5×CH$\underline{C}H_2$), 62.7 (0.5×CH$\underline{C}H_2$), 55.3 (OMe), 26.8 (C($\underline{C}H_3$)$_3$), 19.3 ($\underline{C}(CH_3)_3$) ppm (some CH_{Ar} overlap, CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –107.2 (0.5 F, dt, *J* = 236.4, 10.7 Hz, 0.5×C$\underline{F}$F), –115.4 (0.5 F, dt, *J* = 236.4, 8.6 Hz, 0.5×C$\underline{F}$F), –121.5 (0.5 F, dt, *J* = 236.4, 10.7 Hz, 0.5×CF$\underline{F}$), –125.7 (0.5 F, dt, *J* = 236.4, 8.6 Hz, 0.5×CF$\underline{F}$) ppm.

(3*R*,4*R*,6*R*)-4-(Benzyloxy)-5,5-difluoro-6-(phenylamino)tetrahydro-2H-pyran-3-ol, 3.27



Aminoglycoside **3.22c** (77 mg, 0.13 mmol) was stirred in TBAF (1 M in THF, 2 equiv, 0.26 mmol, 0.26 mL) at RT for 2.5 h. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (10:90–15:85 acetone/hexane + 0.5% Et_3N) to yield pyranose **3.27**, as a colourless oil as a 1:16 anomeric mixture (39 mg, 89%).

Data for major anomer only:

IR (film) 3410 (w), 3032 (w), 2925 (w), 1605 (m), 1106 (s), 1048 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 358.1 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{18}H_{19}F_2NO_3$ $(M+H)^+$ calcd: 336.1406; found: 336.1404.

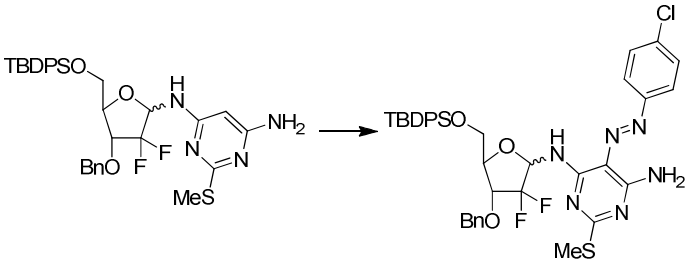
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.36 (5 H, m, 5×CH_{Ar}), 7.26–7.21 (2 H, m, 2×CH_{Ar}), 6.90–6.79 (3 H, m, 3×CH_{Ar}), 5.16 (1 H, dd, *J* = 17.8, 10.2 Hz, CHN), 5.01 (1 H, d, *J* = 11.2 Hz, C$\underline{H}$HPh), 4.66 (1 H, d, *J* = 11.2 Hz, CH$\underline{H}$Ph), 4.53 (1 H, d, *J* = 10.3 Hz, NH), 4.09 (1 H, dt, *J* = 6.7, 3.6 Hz, CHOBn), 4.04–3.94 (1 H, m, CHOH), 3.84 (1 H, dddd, *J* = 11.3, 5.3, 2.1, 1.0 Hz, CHC$\underline{H}$H), 3.63 (1 H, t, *J* = 10.9 Hz, CHCH$\underline{H}$), 2.21 (1 H, br. s, OH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 144.3 (C_{Ar}), 136.7 (C_{Ar}), 129.4 (CH_{Ar}), 128.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 120.2 (CH_{Ar}), 114.7 (CH_{Ar}), 117.0 (dd,

J = 260.4, 251.7 Hz, CF_2), 79.6 (dd, J = 26.2, 19.4 Hz, CHN), 77.2 (dd, J = 32.1, 19.4 Hz, CHOBn), 75.4 (d, J = 3.9 Hz, CH_2Ph), 66.1 (d, J = 4.9 Hz, CHOH), 64.7 ($CH\underline{C}H_2$) ppm (some CH_{Ar} overlap).

^{19}F NMR (282 MHz, $CDCl_3$) δ –114.6 (1 F, d, J = 257.9 Hz, C$\underline{F}$F), –127.4 (1 F, dd, J = 257.9, 12.9 Hz, CF$\underline{F}$) ppm.

4-(5*R*)-[4-Benzyloxy-5-[(*tert*-butyl(diphenyl)silyl)oxymethyl]-3,3-difluoro-tetrahydrofuran-2-yl]-5-(4-chlorophenyl)azo-2-methylsulfanyl-pyrimidine-4,6-diamine, 3.29



To 4-chloroaniline (1.1 equiv, 0.52 mmol, 66 mg) in 36% HCl (0.32 mL) and water (0.5 mL) at 0 ℃ was added sodium nitrite (1. 2 equiv, 0.57 mmol, 39 mg) in water (0.63 mL). The reaction mixture was stirred at 0 ℃ for 1 h, then added to a mixture of glycosylamine **3.22g** (295 mg, 0.46 mmol) and NaOAc (15 equiv, 6.95 mmol, 570 mg) in 1:1 AcOH/DMF (4.4 mL). The reaction mixture was left at RT for 4 d, with occasional agitation. The solvents were reduced *in vacuo* and water was added to form a yellow precipitate, which was removed by filtration, washed with water and dried under high vacuum before purification by flash chromatography on silica gel (20:80 acetone/petrol) to yield the desired product **3.29** as a yellow oil as a 1:1.1 anomeric mixture (305 mg, 84%).

IR (film) 3276 (w), 3069 (w), 2929 (w), 2857 (w), 1588 (m), 1570 (s), 1548 (s), 1482 (w), 1471 (w), 1427 (m), 1411 (w), 1359 (m), 1339 (m), 1298 (m), 1275 (m), 1227 (w), 1174 (w), 1088 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 799.4 $(M+Na)^+$ (35), 797.4 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{39}H_{41}F_2N_6O_3SSi^{35}Cl$ $(M+Na)^+$ calcd: 797.2284, found: 797.2328.

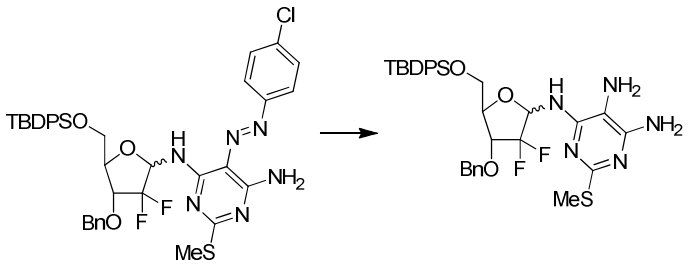
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.14 (19 H, m, 19×CH_{Ar}), 6.38 (0.5 H, td, J = 8.7, 5.8 Hz, 0.5×CHN), 6.18 (0.5 H, ddd, J = 12.9, 9.6, 6.8 Hz, 0.5×CHN), 4.83

(0.5 H, d, *J* = 12.1 Hz, 0.5×C<u>H</u>HPh), 4.80 (0.5 H, d, *J* = 11.1 Hz, 0.5×C<u>H</u>HPh), 4.59 (0.5 H, d, *J* = 12.1 Hz, 0.5×CH<u>H</u>Ph), 4.53 (0.5 H, d, *J* = 11.1 Hz, 0.5×CH<u>H</u>Ph), 4.34 (0.5 H, dt, *J* = 11.4, 5.9 Hz, 0.5×CHOBn), 4.16–4.11 (1 H, m, 0.5×CHOBn, 0.5×C<u>H</u>CH_2), 3.92 (0.5 H, q, *J* = 4.4 Hz, 0.5×C<u>H</u>CH_2), 3.78–3.68 (2 H, m, CHC<u>H_2</u>), 2.43 (1.5 H, s, 0.5×SCH_3), 2.37 (1.5 H, s, 0.5×SCH_3), 0.97 (4.5 H, s, 0.5×$C(CH_3)_3$), 0.93 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm (3×NH not visible).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 174.4 (C_{Ar}), 174.3 (C_{Ar}), 150.7 (C_{Ar}), 136.8 (C_{Ar}), 136.7 (C_{Ar}), 135.1 (C_{Ar}), 134.9 (C_{Ar}), 133.1 (C_{Ar}), 133.0 (C_{Ar}), 132.79 (C_{Ar}), 132.75 (C_{Ar}), 135.60 (CH_{Ar}), 135.57 (CH_{Ar}), 135.5 (CH_{Ar}), 129.84 (CH_{Ar}), 129.81 (CH_{Ar}), 129.75 (CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.74 (CH_{Ar}), 127.71 (CH_{Ar}), 127.67 (CH_{Ar}), 122.7 (CH_{Ar}), 122.6 (CH_{Ar}), 122.1 (C_{Ar}), 123.2 (dd, *J* = 263.5, 254.7 Hz, 0.5×CF_2), 122.9 (dd, *J* = 263.5, 256.1 Hz, 0.5×CF_2), 81.5 (d, *J* = 4.4 Hz, 0.5×<u>C</u>HCH_2), 80.6 (dd, *J* = 38.1, 22.0 Hz, 0.5×CHN), 80.2 (dd, *J* = 36.6, 20.5 Hz, 0.5×CHN), 79.7 (dd, *J* = 5.9, 2.9 Hz, 0.5×<u>C</u>HCH_2), 77.5–77.2 (m, CHOBn), 73.3 (0.5×CH_2Ph), 73.2 (0.5×CH_2Ph), 62.5 (0.5×CH_2OSi), 62.3 (0.5×CH_2OSi), 26.8 (0.5×C(<u>C</u>H_3)$_3$), 26.7 (0.5×C(<u>C</u>H_3)$_3$), 19.2 (<u>C</u>$(CH_3)_3$), 14.4 (0.5×SCH_3), 14.3 (0.5×SCH_3) ppm (some C_{Ar}/CH_{Ar} overlap).

^{19}F NMR (282 MHz, $CDCl_3$) δ –110.3 (1 F, d, *J* = 244.8 Hz, C<u>F</u>F), –113.1 (1 F, d, *J* = 244.0 Hz, C<u>F</u>F), –122.1 (1 F, dd, *J* = 242.2, 5.2 Hz, CF<u>F</u>), –126.5 (1 F, d, *J* = 244.8 Hz, CF<u>F</u>) ppm.

N4-((5*R*)-4-(Benzyloxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-2-(methylthio)pyrimidine-4,5,6-triamine, 3.30

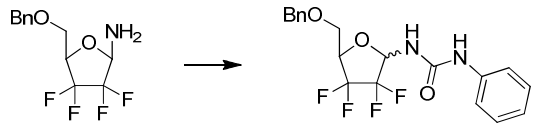


To diazo compound **3.29** (60.5 mg, 0.078 mmol) in 1:1 EtOH/water (2.4 mL) was added zinc powder (10 equiv, 0.78 mmol, 59 mg) and AcOH (0.03 mL). The reaction mixture was stirred at reflux for 40 min, filtered and the solvents

reduced *in vacuo* to yield a crude residue. Purification by flash chromatography on silica gel (0:100–5:95 MeOH/DCM) yielded the desired product contaminated with AcOH. This was taken up in DCM, washed with sat. $NaHCO_3$ (aq) and dried over anhydrous $MgSO_4$ to yield the desired product **3.30** as a yellow oil as a 1:1.1 anomeric ratio (25 mg, 49%).

IR (film) 3370 (br), 3073 (w), 2929 (m), 2857 (m), 1737 (w), 1614 (m), 1591 (m), 1557 (s), 1495 (m), 1428 (m), 1362 (m), 1306 (m), 1112 (s) cm^{-1}.
LRMS (ESI^+) *m/z* 674.5 $(M+Na)^+$ (29), 652.4 $(M+H)^+$ (100).
HRMS (ESI^+) for $C_{33}H_{39}F_2N_5O_3SSi$ $(M+H)^+$ Calcd: 652.2584; Found: 652.2598.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.62 (5 H, m, 5×CH_{Ar}), 7.46–7.33 (10 H, m, 10×CH_{Ar}), 6.33–6.24 (1 H, m, 0.5×CHN, 0.5×NH), 6.13 (0.5 H, ddd, *J* = 12.1, 10.4, 7.0 Hz, 0.5×CHN), 5.90 (0.5 H, d, *J* = 10.4 Hz, 0.5×NH), 4.89 (1 H, d, *J* = 11.5 Hz, CHHPh), 4.83–4.82 (2 H, m, NH_2), 4.67 (0.5 H, d, *J* = 11.5 Hz, 0.5×CHHPh), 4.61 (0.5 H, d, *J* = 11.5 Hz, 0.5×CHHPh), 4.44 (0.5 H, ddd, *J* = 9.6, 8.5, 5.6 Hz, 0.5×CHOBn), 4.22–4.16 (1 H, m, 0.5×CHOBn, 0.5×$CHCH_2$), 3.98 (0.5 H, dtd, *J* = 5.4, 4.1, 0.9 Hz, 0.5×$CHCH_2$), 3.88–3.75 (2 H, m, $CHCH_2$), 2.46 (1.5 H, s, 0.5×SCH_3), 2.38 (1.5 H, s, 0.5×SCH_3), 1.064 (4.5 H, s, 0.5×$C(CH_3)_3$), 1.055 (4.5 H, s, 0.5×$C(CH_3)_3$) ppm (NH_2 not visible).
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 165.8 (SC_{Ar}), 159.53 (C_{Ar}), 159.47 (C_{Ar}), 157.0 (C_{Ar}), 136.9 (C_{Ar}), 136.8 (C_{Ar}), 135.6 (CH_{Ar}), 135.5 (CH_{Ar}), 133.2 (C_{Ar}), 133.01 (C_{Ar}), 132.96 (C_{Ar}), 132.8 (C_{Ar}), 129.84 (CH_{Ar}), 129.81 (CH_{Ar}), 129.78 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.24 (CH_{Ar}), 128.15 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 99.1 (NC_{Ar}), 81.4–80.7 (m, CHN, 0.5×$\underline{C}HCH_2$), 79.2 (0.5×$\underline{C}HCH_2$), 77.4–76.7 (m, CHOBn), 73.1 (0.5×CH_2Ph), 73.0 (0.5×CH_2Ph), 62.6 (CH_2OSi), 26.8 ($C(\underline{C}H_3)_3$), 19.3 (0.5×$\underline{C}(CH_3)_3$), 19.2 (0.5×$\underline{C}(CH_3)_3$), 14.3 (0.5×SCH_3), 14.2 (0.5×SCH_3) ppm (CF_2 not visible).
^{19}F NMR (282 MHz, $CDCl_3$) δ –113.2 (0.5 F, ddd, *J* = 239.4, 10.1, 6.5 Hz, 0.5×C$\underline{F}$F), –115.2 (0.5 F, ddd, *J* = 241.4, 15.1, 12.3 Hz, 0.5×CF$\underline{F}$), –123.3 (0.5 F, ddd, *J* = 241.8, 7.3, 3.4 Hz, 0.5×C$\underline{F}$F), –129.7—128.7 (0.5 F, m, 0.5×CF$\underline{F}$) ppm.

1-(5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-3-phenylurea, 3.37



To glycosylamine **3.24β** (50 mg, 0.18 mmol) in MeCN (0.2 mL) was added phenylisocyanate (10 equiv, 1.79 mmol, 0.19 mL). The reaction mixture was stirred at 60 ℃ for 1 h. The solvents were reduced *in vacuo* to yield a crude residue which was purified by flash chromatography on silica gel (10:90–50:50 Et_2O/petrol) to yield the desired product **3.37** as a colourless oil as a 1:2.5 anomeric mixture (51 mg, 71%).

IR (film) 3338 (br), 3065 (w), 2872 (w), 1657 (m), 1600 (m), 1556 (s), 1499 (m), 1446 (m), 1366 (w), 1314 (w), 1286 (w), 1229 (m), 1138 (m), 1071 (w), 1002 (s) cm^{-1}.

LRMS (ESI^+) (m/z) 421.2 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{19}H_{18}F_4N_2O_3$ $(M+Na)^+$ Calcd: 421.1146; Found: 421.1152.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–6.94 (10 H, m, 10×CH_{Ar}), 6.68 (1 H, s, NHPh), 6.08 (0.3 H, d, *J* = 9.1 Hz, CHN$\underline{H}_{Minor}$), 6.06 (0.7 H, d, *J* = 10.1 Hz, CHN$\underline{H}_{Major}$), 5.94 (0.3 H, m, CHN_{Minor}), 5.77 (0.7 H, m, CHN_{Major}), 4.45 (2 H, m, CH_2Ph), 4.21 (1 H, m, C$\underline{H}CH_2$), 3.62 (2 H, m, CHC$\underline{H}_2$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 154.1 ($C{=}O_{Minor}$), 153.8 ($C{=}O_{Major}$), 137.3 ($C_{ArMinor}$), 137.2 ($C_{ArMajor}$), 137.1 ($C_{ArMinor}$), 136.9 ($C_{ArMajor}$), 129.2 (CH_{Ar}), 129.11 (CH_{Ar}), 129.07 (CH_{Ar}), 128.7 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.02 (CH_{Ar}), 127.95 (CH_{Ar}), 127.8 (CH_{Ar}), 124.53 (CH_{Ar}), 124.47 (CH_{Ar}), 121.1 (CH_{Ar}), 121.0 (CH_{Ar}), 80.5 (dd, *J* = 38.1, 19.0 Hz, CHN_{Major}), 79.7 (dd, *J* = 29.3, 19.0 Hz, CHN_{Minor}), 77.0 (dd, *J* = 27.8, 23.4 Hz, $\underline{C}HCH_{2Major}$), 76.4 (dd, *J* = 27.8, 22.0 Hz, $\underline{C}HCH_{2Minor}$), 73.8 ($CH_2Ph$), 66.4 (d, *J* = 5.9 Hz, $CH\underline{C}H_{2Minor}$), 66.1 (dd, *J* = 5.9, 2.9 Hz, $CH\underline{C}H_{2Major}$) ppm (some CH_{Ar} overlap, 2×CF_2 not visible).

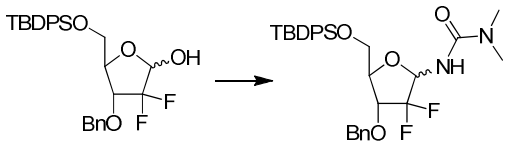
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.5 (1 F, dd, *J* = 245.0, 12.9 Hz, C$\underline{F}$F), –125.5 (1 F, d, *J* = 245.0 Hz, C$\underline{F}$F), –131.2 (1 F, dd, *J* = 245.0, 8.6 Hz, CF$\underline{F}$), –132.5 (1 F, m, *J* = 245.0, 12.9 Hz, CF$\underline{F}$) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –125.6 (1 F, d, *J* = 245.0 Hz, C<u>F</u>F), –130.0—132.7 (3 F, m, 3×CF<u>F</u>) ppm.

3-((4*R*,5*R*)-4-(Benzyloxy)-5-((*tert*-butyldiphenylsilyloxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-1,1-dimethylurea, 4.21



To lactol **2.01**, (102 mg, 0.20 mmol) in toluene (0.8 mL) was added *N*,*N*-dimethylurea (1 equiv, 0.16 mmol, 18 mg), a catalytic amount of PTSA and molecular sieves (90 mg). The reaction mixture was stirred at reflux for 5.5 h, cooled to RT and the solvents removed *in vacuo* to yield a crude residue. This residue was first purified by column chromatography on silica gel (10:90 acetone/hexane) followed by HPLC (10:90 acetone/hexane) to yield **4.21** as a colourless oil as a 1:2.9 anomeric mixture (44 mg, 38%).

IR (film) 3070 (w), 2930 (m), 2857 (m), 1472 (m), 1456 (m) cm^{-1}.

Major anomer:

^{1}H NMR (400 MHz, acetone-d_6) δ 7.76–7.67 (4 H, m, 4×ArH), 7.49–7.31 (11 H, m, 11×ArH), 4.87 (1 H, d, *J* = 11.8 Hz, OC<u>H</u>HPh), 4.66 (1 H, d, *J* = 11.6 Hz, OCH<u>H</u>Ph), 4.63 (1 H, m, CHN), 4.23 (1 H, ddd, *J* = 12.3, 11.2, 8.3 Hz, CHOBn), 3.97 (1 H, m, C<u>H</u>CH_2OSi), 3.84 (1 H, dd, *J* = 11.6, 3.5 Hz, C<u>H</u>HOSi), 3.75 (1 H, m, CH<u>H</u>OSi), 2.47 (6 H, s, N$(CH_3)_2$), 1.01 (9 H, s, C$(CH_3)_3$) ppm (NH not visible).

^{13}C NMR + DEPT (100 MHz, acetone-d_6) δ 182.2 (C=O), 138.6 (C_{Ar}), 136.5 (2×CH_{Ar}), 134.1 (2×C_{Ar}), 130.84 (2×CH_{Ar}), 130.76 (2×CH_{Ar}), 129.3 (2×CH_{Ar}), 128.8 (5×CH_{Ar}), 128.7 (2×CH_{Ar}), 125.1 (dd, *J* = 259.5, 255.1 Hz, CF_2), 96.6 (dd, *J* = 31.8, 24.3 Hz, CHN), 81.7 (<u>C</u>HCH_2), 77.7 (m, <u>C</u>HOBn), 73.3 (CH_2), 63.3 (CH_2), 41.0 (N$(CH_3)_2$), 27.3 (C(<u>C</u>$H_3)_3$), 19.9 (<u>C</u>$(CH_3)_3$) ppm.

^{19}F NMR (376 MHz, acetone-d_6) δ –112.3 (1 F, ddd, *J* = 240.3, 14.3, 11.0 Hz, C<u>F</u>F), –113.0 (1 F, dt, *J* = 240.3, 11.8 Hz, CF<u>F</u>) ppm.

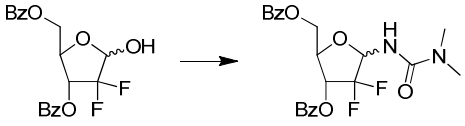
Minor anomer:

^{1}H NMR (400 MHz, acetone-d_6) δ 7.76–7.67 (4 H, m , 4×ArH), 7.49–7.31 (11 H, m, 11×ArH), 4.86 (1 H, d, *J* = 11.9 Hz, OCHHPh), 4.74 (1 H, t, *J* = 11.1 Hz, CHN), 4.65 (1 H, d, *J* = 11.7 Hz, OCHHPh), 4.39 (1 H, ddd, *J* = 12.2, 9.2, 7.1 Hz, CHOBn), 4.09 (1 H, dtd, *J* = 6.9, 3.4, 1.3 Hz, CHCH$_2$OSi), 3.86 (1 H, m, CHHOSi), 3.76 (1 H, m, CHHOSi) 2.44 (6 H, s, N(CH$_3$)$_2$), 1.02 (9 H, s, C(CH$_3$)$_3$) ppm (NH not observed).

^{13}C NMR + DEPT (100 MHz, acetone-d_6) δ 182.2 (C=O), 138.6 (C_{Ar}), 136.5 (2×CH_{Ar}), 134.0 (2×C_{Ar}), 130.9 (2×CH_{Ar}), 130.8 (2×CH_{Ar}), 129.4 (2×CH_{Ar}), 128.8 (5×CH_{Ar}), 128.7 (2×CH_{Ar}), 96.1 (dd, *J* = 36.4, 18.0 Hz, CHN), 81.6 (CHCH$_2$), 77.9 (m, CHOBn), 73.4 (CH_2), 64.4 (CH_2), 41.4 (N(CH$_3$)$_2$), 27.3 (C(CH$_3$)$_3$), 19.9 (C(CH$_3$)$_3$) ppm (CF_2 not observed).

^{19}F NMR (376 MHz, acetone-d_6) δ –105.4 (1 F, dt, *J* = 240.8, 11.8 Hz, CFF), –126.4 (1 F, dt, *J* = 240.3, 11.0 Hz, CFF) ppm.

((2*R*,3*R*)-3-(Benzoyloxy)-5-(3,3-dimethylureido)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate, 4.22



To protected lactol **1.51** (35 mg, 0.09 mmol) in toluene (1 mL) was added 3 Å molecular sieves (53 mg), *N*,*N*-dimethylurea (3 equiv, 0.30 mmol, 27 mg) and PTSA (1 equiv, 0.09 mmol, 19 mg). The reaction mixture was stirred at reflux for 20 h then cooled to RT and diluted with DCM before filtration through a plug of silica (pre-treated with Et_3N), $NaHCO_3$ and $NaSO_4$. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (15:85–25:75 acetone/hexane + 0.5% Et_3N) to yield the desired glycosylurea **4.22** as an oil, as a 1:2.7 anomeric mixture (27 mg, 65%).

IR (film) 3307 (br), 2923 (w), 2853 (w), 1724 (s), 1659 (m), 1522 (m), 1266 (s), 1095 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 919.5 (2M+Na)$^+$ (100), 471.1 (M+Na)$^+$ (71).

HRMS (ESI$^+$) for $C_{22}H_{22}F_2N_2O_6$ (M+Na)$^+$ calcd 471.1338, found 471.1342.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.03 (4 H, m, 4×CH_{Ar}), 7.65–7.39 (6 H, m, 6×CH_{Ar}), 6.12 (0.25 H, q, *J* = 8.2 Hz, CHN_{Minor}), 5.89 (0.75 H, ddd, *J* = 14.9, 9.9, 5.2 Hz, CHN_{Major}), 5.72 (0.25 H, ddd, *J* = 10.1, 8.3, 5.8 Hz, $CHOBz_{Minor}$), 5.51 (0.75 H, dd, *J* = 15.6, 5.0 Hz, $CHOBz_{Major}$), 5.41 (0.25 H, d, *J* = 9.5 Hz, NH_{Minor}), 5.28 (0.75 H, d, *J* = 9.8 Hz, NH_{Major}), 4.67–4.56 (2.25 H, m, CH_2OBz, $CHCH_{2Minor}$), 4.40 (0.75 H, q, *J* = 4.4 Hz, $CHCH_{2Major}$), 2.98 (6 H, br. s, $N(CH_3)_2$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 166.0 (PhC=O), 164.9 (PhC=O), 156.0 (NHC=O), 134.02 (CH_{Ar}), 133.98 (CH_{Ar}), 133.3 (CH_{Ar}), 130.0 (CH_{Ar}), 129.9 (CH_{Ar}), 129.8 (CH_{Ar}), 129.4 (CH_{Ar}), 129.3 (CH_{Ar}), 128.6 (CH_{Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (2×C_{Ar}), 82.1 (dd, *J* = 36.9, 18.5 Hz, CHN_{Minor}), 81.6 (dd, *J* = 34.0, 19.4 Hz, CHN_{Major}), 77.1 ($CHCH_{2Minor}$), 76.2 (t, *J* = 2.9 Hz, $CHCH_{2Major}$), 72.6 (dd, *J* = 31.1, 17.5 Hz, $CHOBz_{Minor}$), 72.0 (dd, *J* = 36.0, 17.5 Hz, $CHOBz_{Major}$), 63.8 (CH_{2Minor}), 63.3 (CH_{2Major}), 36.3 ($N(CH_3)_{2Major}$), 36.2 ($N(CH_3)_{2Minor}$) ppm (some CH_{Ar} overlap, CF_2 not visible).

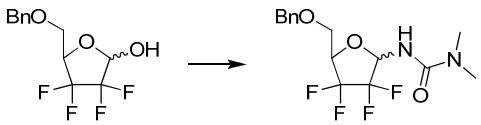
Major anomer:

^{19}F NMR (282 MHz, $CDCl_3$) δ –118.4 (1 F, dt, *J* = 247.1, 15.0 Hz, CFF), –123.3 (1 F, dd, *J* = 247.1, 5.4 Hz, CFF) ppm.

Minor anomer:

^{19}F NMR (282 MHz, $CDCl_3$) δ –114.9 (1 F, dt, *J* = 243.9, 9.7 Hz, CFF), –126.4 (1 F, dt, *J* = 242.8, 8.6 Hz, CFF) ppm.

3-((5*R*)-5-(Benzyloxymethyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-1,1-dimethylurea, 4.23



To protected lactol **2.02** (104 mg, 0.37 mmol) in toluene (0.5 mL) was added 3 Å molecular sieves (60 mg), *N*,*N*-dimethylurea (3 equiv, 1.11 mmol, 98 mg) and PTSA (1 equiv, 0.37 mmol, 71 mg). The reaction mixture was stirred at reflux for 24 h, then cooled to RT and diluted with DCM before filtration through a plug of silica (pre-treated with Et_3N), $NaHCO_3$ and $NaSO_4$. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column

chromatography on silica gel (10:90–20:80 acetone/hexane + 0.5% Et_3N) to yield the desired glycosylurea **4.23** as a colourless oil, as a 1:1.6 anomeric mixture (77 mg, 60%).

IR (film) 3307 (br), 2925 (m), 2359 (w), 1662 (s), 1522 (s), 1238 (m), 1139 (s), 1002 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 723.3 $(2M+Na)^+$ (25), 373.1 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{15}H_{18}F_4N_2O_3$ $(M+Na)^+$ calcd 373.1146, found 373.1149.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (5 H, m, 5×CH_{Ar}), 6.05 (0.4 H, m, CHN_{Minor}), 5.87 (0.6 H, m, CHN_{Major}), 5.32 (0.6 H, d, *J* = 9.9 Hz, NH_{Major}), 5.20 (0.4 H, d, *J* = 9.8 Hz, NH_{Minor}), 4.63–4.54 (2 H, m, CH_2Ph), 4.49 (0.4 H, m, C<u>H</u>CH_2), 4.25 (0.6 H, m, C<u>H</u>CH_2), 3.82–3.76 (1 H, m, C<u>H</u>HOBn), 3.72–3.67 (1 H, m, CH<u>H</u>OBn), 2.97 (1.8 H, s, CH_{3Major}), 2.96 (1.2 H, s, CH_{3Minor}), 2.85 (1.8 H, s, CH_{3Major}), 2.84 (1.2 H, s, CH_{3Minor}) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 155.7 (C=O), 137.2 (0.5×C_{Ar}), 137.0 (0.5×C_{Ar}), 128.52 (CH_{Ar}), 128.46 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 81.2 (dd, *J* = 35.0, 19.4 Hz, 0.5×CHN), 80.2 (ddd, *J* = 33.0, 18.5, 3.9 Hz, 0.5×CHN), 77.2–76.0 (m, <u>C</u>HCH_2), 73.9 (0.5×CH_2Ph), 73.8 (0.5×CH_2Ph), 66.5 (d, *J* = 6.8 Hz, 0.5×CH_2OBn), 66.3 (dd, *J* = 4.9, 2.9 Hz, 0.5×CH_2OBn), 36.2 (CH_3), 36.0 (CH_3) ppm (2×CF_2 not visible).

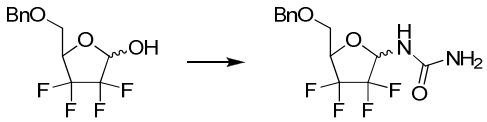
Major anomer:

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.4 (1 F, ddddd, *J* = 245.2, 13.2, 4.9, 3.1, 1.8 Hz, C<u>F</u>F), –125.3 (1 F, ddtd, *J* = 243.8, 8.8, 4.5, 1.8 Hz, CF<u>F</u>), –130.3 (1 F, dd, *J* = 244.5, 10.8 Hz, C<u>F</u>F), –132.0 (1 F, ddt, *J* = 245.3, 11.6, 3.6 Hz, CF<u>F</u>) ppm.

Minor anomer:

^{19}F NMR (376 MHz, $CDCl_3$) δ –126.2 (1 F, dtd, *J* = 246.0, 9.4, 4.3 Hz, C<u>F</u>F), –130.0 (1 F, ddd, *J* = 246.0, 15.9, 8.7 Hz, CF<u>F</u>), –131.3 (1 F, dt, *J* = 243.8, 10.8 Hz, C<u>F</u>F), –133.1 (1 F, m, CF<u>F</u>) ppm.

1-((5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)urea, 4.24



Lactol **2.02** (87 mg, 0.31 mmol), urea (3 equiv, 0.93 mmol, 56 mg), PTSA (1 equiv, 0.31 mmol, 59 mg) and 3 Å molecular sieves (98 mg) were stirred in 1,4-dioxane (0.5 mL) at reflux for 18 h. The reaction mixture was cooled to RT diluted with water and extracted with DCM (3×5 mL), the combined organic extracts were washed with $NaHCO_3$ (aq), then brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (30:70 acetone/hexane + 0.5% Et_3N) to yield the desired glycosylurea **4.24** as a colourless oil, as a 1:1.7 mixture of anomers (95 mg, 90%).

IR (film) 3341 (br), 2924 (w), 2872 (w), 1674 (s), 1604 (m), 1541 (s), 1140 (s), 1011 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 667.2 $(2M+Na)^+$ (56), 345.1 $(M+Na)^+$ (100).

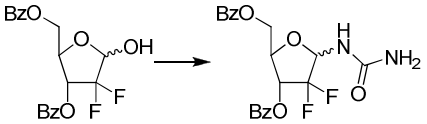
HRMS (ESI^+) for $C_{13}H_{14}F_4N_2O_3$ $(M+Na)^+$ calcd 345.0833, found 345.0832.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (5 H, m, 5×CH_{Ar}), 6.17 ($^1/_3$ H, d, *J* = 9.9 Hz, NH_{Minor}), 6.10 ($^2/_3$ H, d, *J* = 10.0 Hz, NH_{Major}), 5.91 ($^1/_3$ H, m, CHN_{Minor}), 5.73 ($^2/_3$ H, m, CHN_{Major}), 5.07 ($^2/_3$ H, br. s., NH_{2Minor}), 4.80 ($^4/_3$ H, br. s, NH_{2Major}), 4.63–4.51 (2 H, m, CH_2Ph), 4.38 ($^1/_3$ H, m, C<u>H</u>CH_{2Minor}), 4.24 ($^2/_3$ H, m, C<u>H</u>CH_{2Major}), 3.81–3.66 (2 H, m, CHC<u>H</u>$_2$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 157.0 ($C{=}O_{Minor}$), 156.7 ($C{=}O_{Major}$), 137.0 ($C_{ArMinor}$), 136.9 ($C_{ArMajor}$), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.2 (CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 80.5 (m, CHN_{Major}), 79.9 (m, CHN_{Minor}), 76.8 (m, <u>C</u>HCH_2), 73.8 (CH_2Ph), 66.4 (d, *J* = 6.8 Hz, CH<u>C</u>H_{2Minor}), 66.1 (dd, *J* = 5.8, 2.9 Hz, CH<u>C</u>H_{2Major}) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –116.9 (1 F, dd, *J* = 245.0, 12.9 Hz, C<u>F</u>F), –125.6 (2 F, d, *J* = 240.7 Hz, 2×C<u>F</u>F), –130.0—132.8 (5 F, m, 5×C<u>F</u>F) ppm.

((2*R*,3*R*)-3-(Benzoyloxy)-4,4-difluoro-5-ureidotetrahydrofuran-2-yl)methyl benzoate, 4.25



Lactol **1.51** (870 mg, 2.30 mmol), urea (3 equiv, 6.90 mmol, 414 mg), PTSA (1 equiv, 2.30 mmol, 437 mg) and Na_2SO_4 (2 equiv, 4.60 mmol, 653 mg) were stirred in 1,4-dioxane (6.5 mL) at reflux for 36 h. The reaction mixture was cooled to RT, diluted with DCM and filtered through celite. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (10:90–40:60 acetone/petrol) to yield the desired glycosylurea **4.25** as a white foam, as a 1:1.8 anomeric mixture (853 mg, 88%).

IR (film) 3366 (br), 2925 (w), 1723 (m), 1678 (m), 1266 (s) cm^{-1}.
LRMS (ESI^+) *m/z* 443.2 $(M+Na)^+$ (100).
HRMS (ESI^+) for $C_{20}H_{18}F_2N_2O_6$ $(M+Na)^+$ calcd 443.1025, found 443.1018.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (4 H, m, 4×CH_{Ar}), 7.61–7.33 (6 H, m, 6×CH_{Ar}), 6.69 ($^2/_3$ H, d, *J* = 10.0 Hz, NH_{Major}), 6.54 ($^1/_3$ H, d, *J* = 8.8 Hz, NH_{Minor}), 5.94 ($^1/_3$ H, q, *J* = 8.2 Hz, C<u>H</u>NH_{Minor}), 5.78 ($^2/_3$ H, ddd, *J* = 14.4, 10.1, 5.4 Hz, C<u>H</u>NH_{Major}), 5.67 ($^1/_3$ H, ddd, *J* = 11.5, 8.1, 6.6 Hz, $CHOBz_{Minor}$), 5.46 ($^2/_3$ H, m, $CHOBz_{Major}$), 5.34 ($^2/_3$ H, br.s, NH_{2Minor}), 5.32 ($^4/_3$ H, br.s, NH_{2Major}), 4.65–4.51 ($^7/_3$ H, m, C<u>H</u>CH_{2Minor}, CH_2), 4.36 ($^2/_3$ H, q, *J* = 4.3 Hz, C<u>H</u>CH_{2Major}) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 166.3 (C=O), 165.0 ($C{=}O_{Major}$), 165.9 ($C{=}O_{Minor}$), 157.8 ($C{=}O_{Minor}$), 157.7 ($C{=}O_{Major}$), 134.0 (CH_{Ar}), 133.9 (CH_{Ar}), 133.3 (CH_{Ar}), 130.0 (CH_{Ar}), 129.7 (CH_{Ar}), 129.2 (C_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.43 (CH_{Ar}), 128.38 (CH_{Ar}), 128.1 (C_{Ar}), 121.4 (dd, *J* = 262.4, 257.6 Hz, CF_{2Minor}), 120.4 (dd, *J* = 266.3, 253.7 Hz, CF_{2Major}), 81.9 (dd, *J* = 37.9, 19.4 Hz, CHN_{Minor}), 81.2 (dd, *J* = 34.0, 20.4 Hz, CHN_{Major}), 77.2 (d, *J* = 5.8 Hz, <u>C</u>HCH_{2Minor}), 76.0 (<u>C</u>HCH_{2Major}), 72.3 (dd, *J* = 31.1, 17.5 Hz, $CHOBz_{Minor}$), 72.0 (dd, *J* = 36.0, 16.5 Hz, $CHOBz_{Major}$), 63.4 (CH_{2Minor}), 63.3 (CH_{2Major}) ppm (some CH_{Ar} overlap).

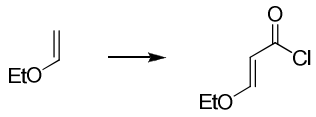
Major Anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –117.9 (1 F, dt, *J* = 246.6, 14.7 Hz, C<u>F</u>F), –122.9 (1 F, dd, *J* = 247.4, 5.2 Hz, CF<u>F</u>) ppm.

Minor Anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –113.2 (1 F, d, *J* = 243.1 Hz, C<u>F</u>F), –125.1 (1 F, dt, *J* = 244.0, 7.8 Hz, CF<u>F</u>) ppm.

(2*E*)-3-Ethoxyprop-2-enoyl chloride, 4.32



Ethyl vinyl ether **4.31** (9.57 mL, 0.10 mmol) was slowly added to oxalyl chloride (1.5 equiv, 0.15 mmol, 12.9 mL) at 0 ℃, stirred at 0 ℃ for 2 h then slowly warmed to RT overnight. The excess oxalyl chloride was removed by distillation. The reaction mixture was then heated to 120 ℃ for 30 min. The desired product **4.32** was purified by vacuum distillation (b.p 94–96 ℃, 18 mmHg) to give a colourless oil (7.405 g, 55%).

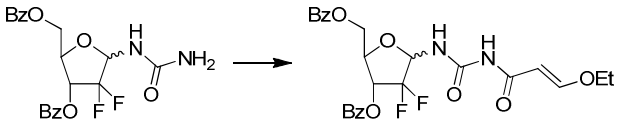
IR (film) 2988 (w), 2895 (w), 2563 (w), 1670 (s), 1601 (s), 1428 (m), 1339 (m), 1214 (s), 1171 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (1 H, d, *J* = 12.1 Hz, CH(CO)), 5.51 (1 H, d, *J* = 12.2 Hz, CHOEt), 4.06 (2 H, t, *J* = 7.0 Hz, CH_2), 1.40 (3 H, t, *J* = 7.1 Hz, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 168.1 (<u>C</u>H(CO)), 164.6 (C=O), 102.8 (CHOEt), 68.8 (CH_2), 14.3 (CH_3) ppm.

Data consistent with the literature.[107]

((2*R*,3*R*)-3-(Benzoyloxy)-5-(3-((*E*)-3-ethoxyacryloyl)ureido)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate, 4.33



To glycosylurea **4.25** (93 mg, 0.22 mmol) stirring at reflux in MeCN (0.6 mL) was added dropwise a solution of acyl chloride **4.32** (4 equiv, 0.88 mmol, 119 mg) in MeCN (0.4 mL). The reaction mixture was stirred at reflux for 18 h, then quenched with water (0.1 mL). The solvents were reduced *in vacuo* to yield a crude residue which was taken up in DCM (15 mL), washed with water (5 mL), then brine and dried over anyhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a crude residue which was purified by flash chromatography on silica gel (10:90–40:60 acetone/petrol) to yield the desired product **4.33** as a colourless oil as a 1:1.5 mixture of anomers (82 mg, 71 %).

IR (film) 3246 (br), 2981 (w), 1717 (s), 1680 (s), 1603 (m), 1537 (s), 1492 (w), 1452 (m), 1378 (w), 1316 (m), 1247 (s), 1176 (m), 1093 (s) cm^{-1}.
LRMS (ESI^+) *m/z* 1059.8 $(2M+Na)^+$ (50), 541.3 $(M+Na)^+$ (100).
HRMS (ESI^+) for $C_{25}H_{24}F_2N_2O_8$ $(M+Na)^+$ Calcd: 541.1393; Found: 541.1411.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (0.5 H, d, *J* = 9.2 Hz, 0.5×CHNH), 9.79 (0.5 H, d, *J* = 9.5 Hz, 0.5×CHNH), 9.65 (0.5 H, s, 0.5×O=CNHC=O), 9.28 (0.5 H, s, 0.5×O=CNHC=O), 8.22–8.20 (1 H, m, CH_{Ar}), 8.08–8.02 (3 H, m, 3×CH_{Ar}), 7.69 (1 H, d, *J* = 11.9 Hz, HC=CHOEt), 7.65–7.40 (6 H, m, 6×CH_{Ar}), 6.08 (0.5 H, t, *J* = 9.3 Hz, 0.5×CHN), 5.90 (0.5 H, ddd, *J* = 12.9, 9.5, 6.0 Hz, 0.5×CHN), 5.70–5.67 (0.5 H, m, 0.5×CHOBn), 5.57 (0.5 H, ddd, *J* = 14.7, 5.1, 1.0 Hz, 0.5×CHOBn), 5.37 (0.5 H, d, *J* = 12.1 Hz, 0.5×CHOEt), 5.34 (0.5 H, d, *J* = 12.0 Hz, 0.5×CHOEt), 4.69–4.58 (2.5 H, m, $CHCH_2$, 0.5×$CHCH_2$), 4.43 (0.5 H, q, *J* = 4.5 Hz, 0.5×$CHCH_2$), 3.98 (2 H, q, *J* = 7.1 Hz, CH_2CH_3), 1.34 (1.5 H, t, *J* = 7.0 Hz, 0.5×CH_3), 1.33 (1.5 H, t, *J* = 7.1 Hz, 0.5×CH_3) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 168.3 (0.5×C=OCH=CH), 168.1 (0.5×C=OCH=CH), 166.07 (0.5×PhCOCH$_2$), 166.05 (0.5×PhCOCH$_2$), 164.9 (0.5×PhCOCH), 164.7 (0.5×PhCOCH), 164.0 (0.5×CH=CHOEt), 163.6 (0.5×CH=CHOEt), 155.1 (0.5×NC=ON), 154.9 (0.5×NC=ON), 134.0 (CH_{Ar}),

133.3 (CH_{Ar}), 133.2 (CH_{Ar}), 130.4 (CH_{Ar}), 130.0 (CH_{Ar}), 129.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.4 (CH_{Ar}), 129.33 (0.5×C_{Ar}), 129.30 (0.5×C_{Ar}), 128.2 (0.5×C_{Ar}), 128.0 (0.5×C_{Ar}), 97.5 (H<u>C</u>=CHOEt), 81.2 (dd, *J* = 39.5, 22.0 Hz, 0.5×CHN), 80.5 (dd, *J* = 36.6, 22.0 Hz, 0.5×CHN), 79.3 (0.5×<u>C</u>HCH$_2$), 76.7 (0.5×<u>C</u>HCH$_2$), 72.2 (dd, *J* = 33.7, 17.6 Hz, 0.5×CHOBz), 72.0 (dd, *J* = 35.1, 17.6 Hz, 0.5×CHOBz), 68.0 (0.5×<u>C</u>H$_2$CH$_3$), 67.7 (0.5×<u>C</u>H$_2$CH$_3$), 63.3 (0.5×CH<u>C</u>H$_2$), 63.2 (0.5×CH<u>C</u>H$_2$), 14.43 (0.5×CH$_3$), 14.36 (0.5×CH$_3$) ppm (some CH_{Ar} overlap, CF_2 not visible).

Anomer X

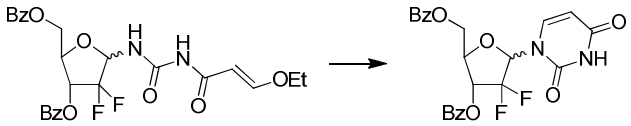
^{19}F NMR (282 MHz, $CDCl_3$) δ –109.5 (1 F, ddd, *J* = 251.4, 16.1, 6.4 Hz, C<u>F</u>F), –125.4 (1 F, d, *J* = 252.5 Hz, CF<u>F</u>) ppm.

Anomer Y

^{19}F NMR (282 MHz, $CDCl_3$) δ –123.6 (1 F, dd, *J* = 241.8, 9.7 Hz, C<u>F</u>F), –125.5 (1 F, ddd, *J* = 241.8, 10.7, 6.4 Hz, CF<u>F</u>) ppm.

(Data assigned from an earlier experiment which gave a 1:1 mixture of anomers).

((2*R*,3*R*)-3-(Benzoyloxy)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4,4-difluorotetrahydrofuran-2-yl)methyl benzoate, 4.34

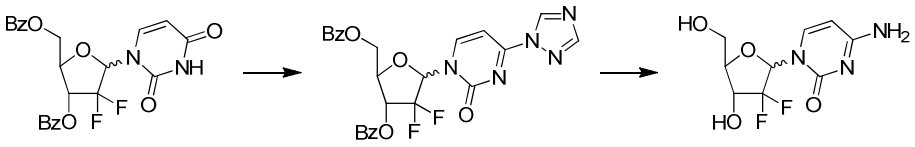


Acyl carbamate **4.33** (136 mg, 0.26 mmol) was stirred in 1:10 HCl/AcOH (2.75 mL) at RT in a stoppered flask for 24 h. The solvents were reduced *in vacuo* to yield the desired protected difluorouracil **4.34** as a yellow oil as a 1:1.2 mixture of anomers (125 mg, quantitative yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (0.5 H, br. s, 0.5×NH), 8.61 (0.5 H, br. s, 0.5×NH), 8.11–8.02 (4 H, m, 4×CH_{Ar}), 7.69–7.39 (8 H, m, 6×CH_{Ar}, NC<u>H</u>=CH), 6.55 (0.5 H, t, *J* = 7.5 Hz, 0.5×CHN), 6.40 (0.5 H, dd, *J* = 11.8, 6.4 Hz, 0.5×CHN), 5.82 (0.5 H, d, *J* = 8.1 Hz, 0.5×NCH=C<u>H</u>), 5.79 (0.5 H, m, 0.5×CHOBn), 5.68 (0.5 H, d, *J* = 8.3 Hz, 0.5×NCH=C<u>H</u>), 5.65 (0.5 H, m, 0.5×CHOBn), 4.89–4.81 (1 H, m, CHC<u>H</u>H), 4.73–4.59 (1 H, m, CHCH<u>H</u>) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –109.2 (0.5 F, dt, *J* = 250.9, 8.6 Hz, 0.5×CFF), –115.5 (0.5 F, dt, *J* = 247.4, 12.9 Hz, 0.5×CFF), –120.3 (0.5 F, d, *J* = 246.6 Hz, 0.5×CFF), –122.0 (0.5 F, d, *J* = 250.9 Hz, 0.5×CFF) ppm.
Data corresponds to the literature.[38]

4-Amino-1-((4*R*,5*R*)-3,3-difluoro-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidin-2(1H)-one 1.08



To crude protected difluorouridine **4.34** (378 mg, 0.75 mmol) in pyridine (9 mL) was added 1,2,4-triazole (3 equiv, 2.26 mmol, 156 mg) and 2-chlorophenyl phosphorodichloridate (6 equiv, 4.51 mmol, 0.74 mL). The reaction mixture was stirred at RT for 5 d. The solvents were reduced *in vacuo* to yield a crude residue which was taken up in DCM and washed with sat. $NaHCO_3$ (aq), then brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude oil which was passed through a short silica column (10:90 acetone/petrol) to yield the impure triazole **4.35** (94 mg, ~24%).

Triazole **4.35** (76.5 mg, 0.17 mmol) was stirred in 7 N NH_3 in MeOH (5 mL) at RT for 36 h. The solvents were reduced *in vacuo* and the resultant residue evaporated onto silica gel for purification by column chromatography (10:90–20:80 MeOH/DCM) to yield the desired difluorocytidine **1.08** as a 1:1.3 mixture of anomers (18.7 mg, 49%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (0.6 H, d, *J* = 7.6 Hz, NCH=CH_{Major}), 7.52 (0.4 H, dd, *J* = 7.5, 1.6 Hz, NCH=CH_{Minor}), 7.37–7.30 (2 H, m, NH_2), 6.30–6.26 (0.8 H, m, CHN_{Minor}, $CHOH_{Minor}$), 6.22 (0.6 H, d, *J* = 6.6 Hz, $CHOH_{Major}$), 6.13 (0.6 H, t, *J* = 8.3 Hz, CHN_{Major}), 5.79 (0.4 H, d, *J* = 7.5 Hz, NCH=CH_{Minor}), 5.78 (0.6 H, d, *J* = 7.6 Hz, NCH=CH_{Major}), 5.19 (0.6 H, t, *J* = 5.4 Hz, CH_2OH_{Major}), 5.07 (0.4 H, t, *J* = 5.7 Hz, CH_2OH_{Minor}), 4.34 (0.4 H, m, CHOH_{Minor}), 4.18–4.07

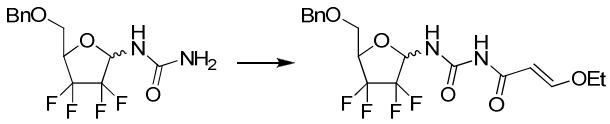
(1.2 H, m, C<u>H</u>OH$_{Major}$, C<u>H</u>CH$_{2Major}$), 3.81–3.74 (1 H, m, C<u>H</u>CH$_{2Minor}$, CHC<u>H</u>H$_{Major}$), 3.64–3.59 (1 H, m, CHC<u>H</u>H), 3.53 (0.4 H, m, CHCH<u>H</u>$_{Minor}$) ppm.

^{13}C NMR + DEPT (100 MHz, DMSO-d$_6$) δ 165.7 (0.5×NCON), 165.6 (0.5×NCON), 154.8 (0.5×N=C), 154.7 (0.5×N=C), 141.3 (0.5×NC=<u>C</u>), 140.8 (0.5×NC=<u>C</u>), 123.1 (t, *J* = 252.6 Hz, CF_2), 94.6 (0.5×N<u>C</u>=C), 94.4 (0.5×N<u>C</u>=C), 83.9–83.2 (m, CHN), 80.4 (<u>C</u>HCH$_2$), 69.6 (dd, *J* = 26.3, 17.6 Hz, 0.5×CHOH), 68.7 (t, *J* = 22.0 Hz, CHOH), 60.0 (0.5×CH_2), 59.0 (0.5×CH_2) ppm.

^{19}F NMR (282 MHz, DMSO-d$_6$) δ –114.3 (0.4 F, d, *J* = 232.8 Hz, C<u>F</u>F$_{Minor}$), –115.5—117.3 (1.2 F, m, CF_{2Major}), –124.3 (0.4 F, d, *J* = 234.5 Hz, CF<u>F</u>$_{Minor}$) ppm.

Data consistent with the literature.[30]

(2*E*)-N-({(5*R*)-5-(Benzyloxymethyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl}carbamoyl)-3-ethoxyprop-2-enamide, 4.36



Glycosylurea **4.24** (36 mg, 0.11 mmol), acyl chloride **4.32** (1.5 equiv, 0.17 mmol, 23 mg) and DMAP (0.25 equiv, 0.03 mmol, 3 mg) were stirred in pyridine (0.5 mL) at reflux for 18 h. The reaction mixture was cooled to RT, diluted with DCM (2 mL) and poured into water. The aqueous phase was extracted with DCM (3×5 mL) and the combined organic phases washed with brine then dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude brown residue which was purified by column chromatography on silica gel (10:90–25:75 acetone/hexane + 0.5% Et_3N) to yield the desired product **4.36** as a colourless oil as a 1:1.2 anomeric mixture (24 mg, 51%).

IR (film) 3242 (br), 2925 (w), 1715 (m), 1682 (s), 1615 (m), 1541 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 863.4 $(2M+Na)^+$ (24), 443.1 $(M+Na)^+$ (100).

HRMS (ESI$^+$) for $C_{18}H_{20}O_4F_4N_2$ $(M+Na)^+$ calcd 443.1201, found 443.1207.

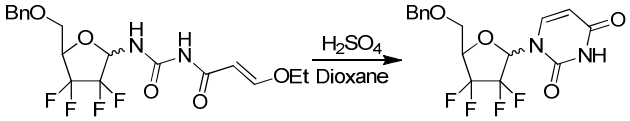
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (0.5 H, d, *J* = 9.7 Hz, 0.5×CHN<u>H</u>), 9.73 (0.5 H, d, *J* = 9.8 Hz, 0.5×CHN<u>H</u>), 9.14 (0.5 H, s, 0.5×NH), 9.13 (0.5 H, s, 0.5×NH), 7.70 (0.5 H, d, *J* = 12.2 Hz, 0.5×(CO)CH), 7.69 (0.5 H, d, *J* = 12.2 Hz,

0.5×(CO)CH), 7.38–7.29 (5 H, m, 5×CH_{Ar}), 6.05 (0.5 H, tdd, *J* = 9.9, 7.6, 2.5 Hz, 0.5×CHN), 5.86 (0.5 H, qd, *J* = 9.3, 1.8 Hz, 0.5×CHN), 5.30 (1 H, d, *J* = 12.0 Hz, CHOEt), 4.63 (0.5 H, d, *J* = 12.1 Hz, C<u>H</u>HPh), 4.62 (0.5 H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.60 (0.5 H, d, *J* = 11.9 Hz, C<u>H</u>HPh), 4.58 (0.5 H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.45 (0.5 H, m, 0.5×C<u>H</u>CH_2), 4.27 (0.5 H, m, 0.5×C<u>H</u>CH_2), 3.99 (1 H, q, *J* = 7.0 Hz, 0.5×C<u>H</u>$_2$$CH_3$), 3.99 (1 H, q, *J* = 7.0 Hz, 0.5×C<u>H</u>$_2$$CH_3$), 3.81 (0.5 H, dd, *J* = 5.1, 4.0 Hz, 0.5×CHC<u>H</u>H), 3.78 (0.5 H, dd, *J* = 5.1, 4.0 Hz, 0.5×CHC<u>H</u>H), 3.72–3.67 (1 H, m, CHCH<u>H</u>), 1.36 (3 H, t, *J* = 7.1 Hz, CH_3) ppm

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 168.2 (0.5×C=O), 168.0 (0.5×C=O), 164.2 (0.5×(CO)<u>C</u>H), 164.1 (0.5×(CO)<u>C</u>H), 154.6 (0.5×C=O), 154.5 (0.5×C=O), 137.1 (C_{Ar}), 128.5 (2×CH_{Ar}), 128.0 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 97.4 (CHOEt), 79.8–79.0 (m, CHN), 77.2–76.5 (m, <u>C</u>HCH_2), 73.8 (CH_2Ph), 68.2 (0.5×<u>C</u>$H_2$$CH_3$), 68.1 (0.5×<u>C</u>$H_2$$CH_3$), 66.3–66.1 (m, CH<u>C</u>H_2), 14.5 (CH_3) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –119.3 (dt, *J* = 246.1, 5.4 Hz, C<u>F</u>F), –124.8 (dtd, *J* = 246.0, 8.6, 3.2 Hz, C<u>F</u>F), –125.1 (dt, *J* = 243.9, 7.5 Hz, C<u>F</u>F), –128.8 (dt, *J* = 246.0, 9.7 Hz, C<u>F</u>F), –130.9—132.5 (m, 3×CF<u>F</u>), –133.3 (dd, *J* = 246.9, 14.0 Hz, CF<u>F</u>) ppm.

1-((5*R*)-5-(Benzyloxymethyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 3.36



Acyl carbamate **4.36** (56 mg, 0.13 mmol) was stirred in 2 M H_2SO_4 (1.3 mL) and dioxane (1.3 mL) at reflux for 4 h. The reaction mixture was cooled to RT and neutralized with 2 M NaOH (1.3 mL) then sat. $NaHCO_3$ (aq) until pH 7 was obtained. The solvents were reduced *in vacuo*, the resultant residue was taken up in EtOH and sonicated for 5 min, filtered and reduced *in vacuo* to yield a crude residue. Purification by column chromatography on silica gel (20:80–25:75 acetone/petrol) yielded the desired protected nucleoside **3.36** as a 1:1.1 anomeric mixture (26 mg, 52%).

IR (film) 3065 (w), 2872 (w), 1689 (s), 1497 (w), 1454 (m), 1384 (m), 1277 (m), 1213 (w), 1138 (m), 1105 (m), 1073 (m), 1028 (m) cm^{-1}.

LRMS (ESI^+) *m/z* 397.1 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{16}H_{14}F_4N_2O_4$ $(M+Na)^+$ calcd 397.0782; found 397.0777.

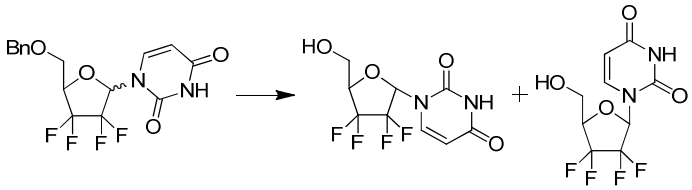
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (5.5 H, m, 5×CH_{Ar}, NC<u>H</u>=CH_{Minor}), 7.15 (0.5 H, dd, *J* = 8.3, 2.0 Hz, NC<u>H</u>=CH_{Major}), 6.47 (0.5 H, ddd, *J* = 10.9, 7.1, 2.2 Hz, CHN_{Minor}), 6.32 (0.5 H, ddd, *J* = 10.1, 8.1, 1.9 Hz, CHN_{Major}), 5.75 (0.5 H, d, *J* = 8.3 Hz, NCH=CH_{Minor}), 5.62 (0.5 H, d, *J* = 8.3 Hz, NCH=CH_{Major}), 4.58–4.50 (2.5 H, m, CH_2Ph, C<u>H</u>CH_{2Minor}), 4.31 (0.5 H, m, C<u>H</u>CH_{2Major}), 3.86 (0.5 H, dd, *J* = 11.2, 4.4 Hz, C<u>H</u>HOBn_{Major}), 3.78–3.57 (2.5 H, m, CH<u>H</u>OBn_{Major}, CH_2OBn_{Minor}, NH) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 162.7 (C=O), 150.0 (C=O), 139.2 (0.5×N<u>C</u>H=CH), 138.9 (0.5×N<u>C</u>H=CH), 136.7 (C_{Ar}), 128.6 (CH_{Ar}), 128.6 (CH_{Ar}), 128.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.2 (CH_{Ar}), 127.84 (CH_{Ar}), 127.80 (CH_{Ar}), 103.5 (NCH=<u>C</u>H), 82.9–81.9 (m, CHN), 78.8 (dd, *J* = 28.2, 23.3 Hz, 0.5×<u>C</u>HCH_2), 77.2 (dd, *J* = 27.2, 23.3 Hz, 0.5×<u>C</u>HCH_2), 74.0 (0.5×CH_2Ph), 73.9 (0.5×CH_2Ph), 66.3 (dd, *J* = 5.3, 3.4 Hz, 0.5×CH<u>C</u>H_2), 65.2 (d, *J* = 5.3 Hz, 0.5×CH<u>C</u>H_2) ppm (2×CF_2 not visible, some C_{Ar}/CH_{Ar} overlap).

^{19}F NMR (282 MHz, $CDCl_3$) δ –120.5 (0.5 F, dt, *J* = 247.1, 8.6 Hz, 0.5×C<u>F</u>F), –122.7—123.7 (1 F, m, C<u>F</u>F), –126.2 (0.5 F, ddd, *J* = 246.1, 11.8, 6.4 Hz, 0.5×C<u>F</u>F), –127.4 (0.5 F, m, 0.5×CF<u>F</u>), –129.1 (0.5 F, dt, *J* = 248.2, 9.7 Hz, 0.5×CF<u>F</u>), –130.2 (0.5 F, m, 0.5×CF<u>F</u>), –133.2 (0.5 F, ddd, *J* = 247.1, 16.1, 6.4 Hz, 0.5×CF<u>F</u>) ppm.

1-((2S,5R)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 4.37α

1-((2R,5R)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 4.37β



To protected uracil **3.36** (92 mg, 0.25 mmol) stirring in DCM (2.5 mL) was added boron trichloride (1 M in DCM, 4 equiv, 0.98 mmol, 0.98 mL). The reaction mixture was stirred at room temperature for 5 h. The solvents were reduced *in vacuo* to yield a crude yellow oil which was purified by column chromatography on silica gel (5:95–10:90 MeOH/DCM) to yield the desired product **4.37** as a white solid as a 1:1.2 mixture of anomers (61 mg, 87%). A small sample was separated by RP-HPLC (90:10–70:30 H_2O/MeOH over 30 min then 70:30–65:35 over 10 min) retention time **4.37α**: 43.3 min, retention time **4.37β**: 45.4 min.

4.37α

$[\alpha]_D$: +19.0 (c 0.3, MeOH, 26 ℃).

LRMS (ESI^+) (m/z) 307.0 $(M+Na)^+$.

HRMS (ESI^+) for $C_9H_8F_4N_2O_4$ $(M+Na)^+$ calcd 307.0312; found 307.0309.

IR (film) 3400 (br), 2504 (br), 2362 (w), 1682 (s), 1456 (m), 1392 (m), 1278 (m), 1140 (m), 1055 (s) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.61 (1 H, dt, *J* = 8.2, 0.8 Hz, NHC=C), 6.53 (1 H, td, *J* = 8.8, 2.3 Hz, CHN), 5.79 (1 H, d, *J* = 8.2 Hz, NHC=C<u>H</u>), 4.73 (1 H, m, C<u>H</u>CH_2), 3.93 (1 H, dd, *J* = 12.5, 4.9 Hz, C<u>H</u>H), 3.89 (1 H, ddd, *J* = 12.5, 4.9, 1.1 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 165.7 (NC=ON), 152.0 (N<u>C</u>=OC), 141.3 (N<u>C</u>H=C), 103.8 (NHC=<u>C</u>), 84.7 (td, *J* = 27.8, 2.9 Hz, CHN), 81.5 (dd, *J* = 27.8, 24.9 Hz, <u>C</u>HCH_2), 59.8 (d, *J* = 2.9 Hz, CH_2) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, MeOH-d_4) δ –124.2 (1 F, ddt, *J* = 248.0, 10.7, 5.4 Hz, CHC<u>F</u>F), –127.2 (2 F, s, CF_2CHN), –131.0 (1 F, dd, *J* = 248.2, 12.2 Hz, CHCF<u>F</u>) ppm.

4.37β

[α]$_D$: +5.5 (c 0.4, MeOH, 26 ℃).

LRMS (ESI^-) (m/z) 283.1 $(M–H)^-$.

HRMS (ESI^+) for $C_9H_8F_4N_2O_4$ $(M+Na)^+$ calcd 307.0312; found 307.0309.

IR (film) 3064 (br), 1695 (s), 1458 (m), 1390 (m), 1283 (m), 1215 (w), 1177 (m), 1129 (m), 1066 (m) cm^{-1}.

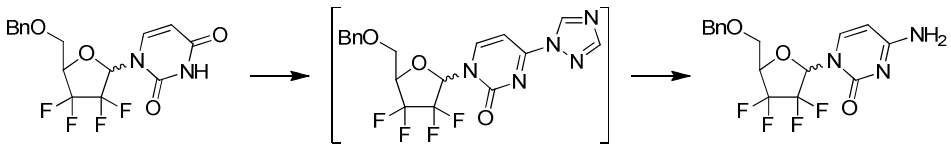
^{1}H NMR (400 MHz, MeOH-d_4) δ 7.63 (1 H, dd, *J* = 8.2, 2.1 Hz, NCH=C), 6.43 (1 H, ddd, *J* = 9.8, 8.2, 2.1 Hz, CHN), 5.78 (1 H, d, *J* = 8.2 Hz, NC=CH), 4.42 (1 H, m, C<u>H</u>CH_2), 4.00 (1 H, dd, *J* = 12.5, 4.9 Hz, C<u>H</u>H), 3.95 (1 H, ddt, *J* = 12.5, 5.2, 0.8 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 165.5 (C=O), 151.9 (C=O), 141.3 (N<u>C</u>=C), 103.9 (NC=<u>C</u>), 83.7 (dd, *J* = 39.5, 19.0 Hz, CHN), 79.7 (dd, *J* = 26.3, 22.0 Hz, <u>C</u>HCH_2), 58.8 (d, *J* = 5.9 Hz, CH_2) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, MeOH-d_4) δ –121.6 (1 F, dddt, *J* = 245.4, 9.9, 6.1, 2.4, Hz, C<u>F</u>FCHN), –123.8 (1 F, m, C<u>F</u>FCF_2CHN), –131.4 (1 F, m, CF<u>F</u>CHN), –134.6 (1 F, m, CF<u>F</u>CF_2CHN) ppm.

4-Amino-1-((5*R*)-5-(benzyloxymethyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)pyrimidin-2(1H)-one, 4.39

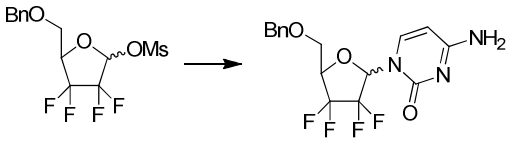
From tetrafluorouridine **4.39**:



To protected tetrafluorouridine **3.36** (54.6 mg, 0.15 mmol) in pyridine (2 mL), was added 1,2,4-triazole (3 equiv, 0.44 mmol, 30 mg) and 2-chlorophenyl phosphorodichloridate (6 equiv, 0.88 mmol, 0.14 mL). The reaction mixture was stirred at RT for 2 d, then 7 N NH_3 in MeOH (2 mL) was added at 0 ℃ and the reaction mixture stirred at RT for a further 5 d. The solvents were reduced *in*

vacuo to yield a crude residue which was purified by flash chromatography on silica gel (0.5:5:94.5 NH_4OH/MeOH/DCM) to yield the desired protected nucleoside **4.39** as a 1:1.8 anomeric mixture (23.7 mg, 43%).

From mesylate **5.01**:



Cytosine (517 mg, 4.7 mmol) and ammonium sulfate (0.018 equiv, 0.08 mmol, 11 mg) were refluxed in HMDS (3.6 equiv, 13.9 mmol, 3.5 mL) for 4 h. The HMDS was removed *in vacuo* to yield crude silylated cytosine. Mesylate **5.01** (0.07 equiv, 0.33 mmol, 120 mg) was added and the reaction mixture was heated in a sealed tube at 130 ℃ for 20 h. The rea ction mixture was diluted with sat. $NaHCO_3$ (aq) and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was purified by flash chromatography on silica gel (0.5:5:94.5 NH_4OH/MeOH/DCM) to yield the desired protected nucleoside **4.39** as a 1:1.4 anomeric mixture (88 mg, 70%).

IR (film) 3336 (br), 2927 (w), 2368 (w), 1640 (s), 1496 (m), 1455 (w), 1400 (w), 1367 (w), 1286 (m), 1211 (w), 1138 (s), 1070 (s) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.57 (0.4 H, dd, *J* = 7.7, 1.4 Hz, NC<u>H</u>=C<u>H</u>$_{Minor}$), 7.55 (0.6 H, dd, *J* = 8.0, 1.6 Hz, NC<u>H</u>=C<u>H</u>$_{Major}$), 7.37–7.30 (5 H, m, 5×CH_{Ar}), 6.58 (0.4 H, ddd, *J* = 9.8, 7.7, 2.3 Hz, CHN$_{Minor}$), 6.47 (0.6 H, ddd, *J* = 9.9, 7.9, 2.0 Hz, CHN$_{Major}$), 5.96 (0.4 H, d, *J* = 7.6 Hz, NCH=C<u>H</u>$_{Minor}$), 5.85 (0.6 H, d, *J* = 7.6 Hz, NCH=C<u>H</u>$_{Major}$), 4.65–4.56 (3 H, m, CH_2Ph, C<u>H</u>CH_2), 3.98 (0.6 H, dd, *J* = 11.2, 4.8 Hz, CHC<u>H</u>H$_{Major}$), 3.91–3.86 (1 H, m, CHCH<u>H</u>), 3.82 (0.4 H, dd, *J* = 11.1, 4.8 Hz, CHC<u>H</u>H$_{Minor}$) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 168.0 (0.5×C=O), 167.9 (0.5×C=O), 157.8 (0.5×CNH_2), 157.7 (0.5×CNH_2), 141.9 (N<u>C</u>H=CH), 139.1 (0.5×C_{Ar}), 139.0 (0.5×C_{Ar}), 129.6 (CH_{Ar}), 129.2 (CH_{Ar}), 129.09 (CH_{Ar}), 129.05 (CH_{Ar}), 97.1 (NCH=<u>C</u>H), 85.8–84.3 (m, CHN), 79.8 (m, 0.5×<u>C</u>HCH_2), 78.1 (dd, *J* = 27.8, 22.0 Hz, 0.5×<u>C</u>HCH_2), 74.9 (0.5×CH_2Ph), 74.8 (0.5×CH_2Ph), 67.7

(0.5×CH<u>C</u>H_2), 66.6 (d, *J* = 4.4 Hz, 0.5×CH<u>C</u>H_2) ppm (some CHAr overlap, 2×CF_2 not visible).

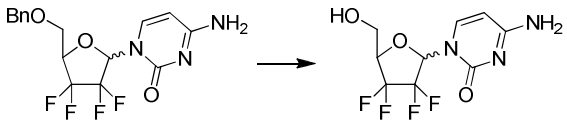
Major anomer:

^{19}F NMR (282 MHz, MeOH-d_4) δ –121.0 (1 F, dddt, *J* = 245.3, 9.9, 6.5, 2.2 Hz, C<u>F</u>F), –124.6 (1 F, ddddd, *J* = 245.7, 9.1, 6.7, 4.5, 2.4 Hz, C<u>F</u>F), –131.6 (1 F, m, CF<u>F</u>), –133.8 (1 F, m, C<u>F</u>F) ppm.

Minor anomer:

^{19}F NMR (282 MHz, MeOH-d_4) δ –124.0 (1 F, ddt, *J* = 247.0, 11.0, 5.6 Hz, C<u>F</u>F), –125.9—127.8 (2 F, m, CF_2), –130.5 (1 F, m, CF<u>F</u>) ppm

4-Amino-1-(3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)-3,4-dihydropyrimidin-2(1H)-one 4.40



To protected nucleoside **4.39** (79 mg, 0.21 mmol) in DCM (4 mL) was added BCl_3 (4 equiv, 0.84 mmol, 0.84 mL). The reaction mixture was stirred at RT for 5 h, then reduced *in vacuo* to yield a crude residue. This was taken up in MeOH and evaporated onto silica gel for purification by flash chromatography (10:90–25:75 MeOH/DCM) to yield the tetrafluorocytidine derivative **4.40** as a 1:1.2 anomeric mixture (67 mg, quant).

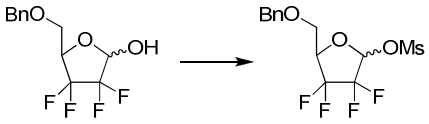
^{1}H NMR (400 MHz, MeOH-d_4) δ 7.86–7.83 (1 H, m, NC<u>H</u>=CH), 6.56 (0.45 H, t, J = 7.7 Hz, CHN_{Minor}), 6.47 (0.55 H, t, *J* = 8.1 Hz, CHN_{Major}), 6.19–6.15 (1 H, m, NC<u>H</u>=CH), 4.77 (0.45 H, m, $CHCH_{2Minor}$), 4.46 (0.55 H, m, $CHCH_{2Major}$), 4.02 (0.55 H, dd, *J* = 12.6, 4.7 Hz, $CHCHH_{Major}$), 3.97 (0.55 H, dd, *J* = 12.9, 4.8 Hz, $CHCHH_{Major}$), 3.93–3.88 (0.9 H, m, CH_{2Minor}) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 164.8 (0.5×CNH_2), 164.6 (0.5×CNH_2), 143.6 (0.5×NCH=<u>C</u>H), 143.5 (0.5×NCH=<u>C</u>H), 97.1 (0.5×N<u>C</u>H=CH), 97.0 (0.5×N<u>C</u>H=CH), 85.6 (dd, *J* = 30.7, 27.8 Hz, 0.5×CHN), 84.5 (dd, *J* = 39.5, 20.5 Hz, 0.5×CHN), 81.6 (t, *J* = 23.4 Hz, 0.5×<u>C</u>HCH_2), 79.9 (dd, *J* = 26.3, 23.4

Hz, 0.5×<u>C</u>HCH$_2$), 59.7 (d, *J* = 5.9 Hz, 0.5×CH$_2$), 58.7 (d, *J* = 5.9 Hz, 0.5×CH$_2$) ppm (quaternary peaks not visible).

^{19}F NMR (282 MHz, MeOH-d$_4$) δ –121.6 (0.5 F, dt, *J* = 246.1, 7.5 Hz, 0.5×CFF), –123.9 (0.5 F, d, *J* = 246.1 Hz, 0.5×CFF), –124.2 (0.5 F, ddt, *J* = 248.2, 10.5, 5.0 Hz, 0.5×CFF), –126.9 (1 F, br. s, CFF), –131.3 (0.5 F, dd, *J* = 248.2, 12.4 Hz, 0.5×CFF), –131.4 (0.5 F, d, *J* = 245.0 Hz, 0.5×CFF), –134.3 (0.5 F, ddd, *J* = 246.6, 17.2, 2.7 Hz, 0.5×CFF) ppm.

(5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl methanesulfonate, 5.01



To lactol **2.02** (600 mg, 2.14 mmol) in DCM (8 mL) was added triethylamine (1.4 equiv, 3.00 mmol, 0.42 mL). The reaction mixture was cooled to 0 ℃ and methane sulfonylchloride (1.2 equiv, 2.57 mmol, 0.20 mL) was added dropwise. The reaction mixture was stirred at RT for 4.5 h. The solvents were reduced *in vacuo* and the resultant residue was taken up in EtOAc and washed successively with sat. NaHCO$_3$ (aq), 1 M HCl (aq), water and brine. The organic extracts were dried over anhydrous Na$_2$SO$_4$ and the solvents reduced *in vacuo* to yield a crude yellow oil. This oil was purified by column chromatography (15:85 acetone/petrol) to yield **5.01** as a colourless oil as a 1:1.9 anomeric mixture (718 mg, 94%).

IR (film) 3032 (w), 2939 (w), 1497 (w), 1455 (w), 1371 (s), 1335 (m), 1273 (m), 1243 (m), 1206 (w), 1184 (s), 1152 (s), 1088 (s) cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42–7.33 (5 H, m, 5×CH$_{Ar}$), 6.10 (0.65 H, dd, *J* = 6.8, 2.4 Hz, CHOMs$_{Major}$), 6.04 (0.35 H, dq, *J* = 7.4, 1.1 Hz, CHOMs$_{Minor}$), 4.69–4.58 (3 H, m, CH$_2$Ph, C<u>H</u>HCH), 3.89–3.72 (2 H, m, CH<u>H</u>CH, CH$_2$C<u>H</u>), 3.15 (1.95 H, s, CH$_{3Major}$), 3.05 (1.05 H, s, CH$_{3Minor}$) ppm.

^{13}C NMR + DEPT (100 MHz, CDCl$_3$) δ 136.92 (C$_{ArMajor}$), 136.88 (C$_{ArMinor}$), 128.5 (CH$_{Ar}$), 128.4 (CH$_{Ar}$), 128.02 (CH$_{Ar}$), 127.97 (CH$_{Ar}$), 127.7 (CH$_{Ar}$), 127.6 (CH$_{Ar}$), 116.1 (ddt, *J* = 269.2, 262.4, 23.3 Hz, CF$_{2Major}$), 114.9 (ddt, *J* = 278.0, 262.4,

24.3 Hz, CF_{2Major}), 119.0–110.5 (m, 2×CF_{2Minor}), 97.3 (ddt, *J* = 43.7, 23.3, 1.9 Hz, $CHOMs_{Major}$), 97.0 (ddd, *J* = 41.8, 22.4, 2.9 Hz, $CHOMs_{Minor}$), 79.5 (ddd, *J* = 29.2, 23.3, 1.9 Hz, $\underline{C}HCH_{2Major}$), 79.4 (ddd, *J* = 28.2, 23.2, 2.9 Hz, $\underline{C}HCH_{2Minor}$), 73.7 ($CH_2Ph_{Major}$), 73.6 ($CH_2Ph_{Minor}$), 66.4 (dd, *J* = 7.8, 1.9 Hz, $CH\underline{C}H_{2Minor}$), 65.6 (dd, *J* = 6.8, 1.9 Hz, $CH\underline{C}H_{2Major}$), 40.1 ($CH_{3Minor}$), 40.0 ($CH_{3Major}$) ppm.

Major anomer

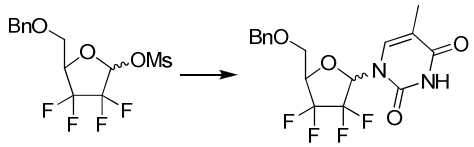
^{19}F NMR (282 MHz, $CDCl_3$) δ –114.9 (1 F, dd, *J* = 247.4, 10.3 Hz, C$\underline{F}$F), –124.7 (1 F, dd, *J* = 249.1, 6.0 Hz, CF$\underline{F}$), –127.7 (1 F, dt, *J* = 249.1, 4.3 Hz, C$\underline{F}$F), –134.6 (1 F, dd, *J* = 247.4, 9.5 Hz, CF$\underline{F}$) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –125.7 (1 F, dt, *J* = 250.9, 6.9 Hz, C$\underline{F}$F), –127.2 (1 F, ddd, *J* = 250.9, 13.8, 9.5 Hz, CF$\underline{F}$), –129.0 (1 F, m, C$\underline{F}$F), –133.0 (1 F, dt, *J* = 250.0, 7.8 Hz, CF$\underline{F}$) ppm.

Data corresponds to the literature[109].

1-((5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione, 5.02



Thymine (494 mg, 3.92 mmol) was stirred in HMDS (3.6 equiv, 14.1 mmol, 2.94 mL) with $(NH_4)_2SO_4$ (0.0018 equiv, 0.007 mmol, 1 mg) at reflux for 3 h. The HMDS was removed under high vacuum. Mesylate **5.01** (0.07 equiv, 0.28 mmol, 102 mg) was added and the reaction mixture was stirred at 130 ℃ for 18 h in a sealed tube. The reaction mixture was cooled and taken up in EtOAc (5 mL) and sat. $NaHCO_3$ (aq) (5 mL), filtered, extracted with EtOAc (3×5 mL) and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to yield a crude residue which was purified by flash chromatography on silica gel (25:75–60:40 Et_2O/petrol) to yield recovered starting material (77 mg, 75%) and the desired product **5.02** as a 1:1.1 anomeric mixture (16 mg, 14%).

IR (film) 3196 (br), 3066 (br), 1690 (s), 1281 (m), 1132 (m) cm^{-1}.

LRMS (ESI^+) *m/z* 411.2 $(M+Na)^+$ (100).

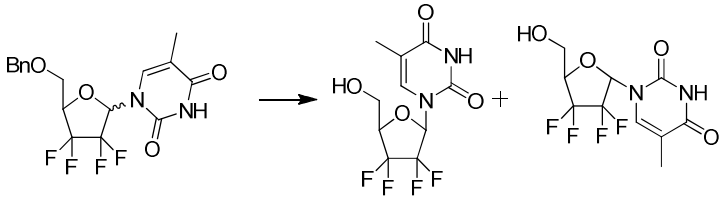
HRMS (ESI^+) for $C_{17}H_{16}F_4N_2O_4$ $(M+Na)^+$ calcd 411.0938, found 411.0946.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.31 (5 H, m, 5×CH_{Ar}), 7.11 (0.5 H, dq, *J* = 2.6, 1.3 Hz, 0.5×CH=C), 7.05 (0.5 H, dq, *J* = 2.3, 1.2 Hz, 0.5×CH=C), 6.55 (0.5 H, ddd, *J* = 11.2, 7.4, 2.3 Hz, 0.5×CHN), 6.39 (0.5 H, ddd, *J* = 10.1, 8.5, 2.0 Hz, 0.5×CHN), 4.68–4.60 (2.5 H, m, 0.5×C<u>H</u>CH_2 + CH_2Ph), 4.38 (0.5 H, m, 0.5×C<u>H</u>CH_2), 3.95 (0.5 H, dd, *J* = 11.1, 4.3 Hz, 0.5×CHC<u>H</u>H), 3.86–3.82 (1 H, m, 0.5×CHC<u>H</u>H + 0.5×CHCH<u>H</u>), 3.76 (0.5 H, ddd, *J* = 10.9, 5.4, 0.9 Hz, 0.5×CHCH<u>H</u>), 1.96 (1.5 H, d, *J* = 1.3 Hz, 0.5×CH_3), 1.83 (1.5 H, d, *J* = 1.3 Hz, 0.5×CH_3) ppm (NH not visible).

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 163.02 (0.5×C=O), 162.96 (0.5×C=O), 150.0 (C=O), 136.8 (0.5×C_{Ar}), 136.7 (0.5×C_{Ar}), 134.7 (0.5×<u>C</u>H=C), 134.5 (d, *J* = 1.9 Hz, 0.5×<u>C</u>H=C), 128.0 (CH_{Ar}), 128.22 (CH_{Ar}), 128.18 (CH_{Ar}), 127.82 (CH_{Ar}), 127.78 (CH_{Ar}), 112.1 (0.5×CH=<u>C</u>), 112.0 (0.5×CH=<u>C</u>), 82.7–81.8 (m, CHN), 78.7 (dd, *J* = 27.2, 22.4 Hz, 0.5×<u>C</u>HCH_2), 77.2 (dd, *J* = 26.2, 22.4 Hz, 0.5×<u>C</u>HCH_2), 74.0 (0.5×CH_2Ph), 73.9 (0.5×CH_2Ph), 66.3 (d, *J* = 4.9 Hz, 0.5×CH<u>C</u>H_2), 65.3 (d, *J* = 4.9 Hz, 0.5×CH<u>C</u>H_2), 12.8 (0.5×CH_3), 12.4 (0.5×CH_3) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –120.3 (0.5 F, dddt, *J* = 247.4, 9.5, 6.9, 2.6 Hz, 0.5×C<u>F</u>F), –122.7 (0.5 F, m, 0.5×C<u>F</u>F), –123.7 (0.5 F, ddt, *J* = 249.1, 12.1, 6.0 Hz, 0.5×C<u>F</u>F), –128.3—126.2 (1 F, m, CF<u>F</u>), –129.1 (0.5 F, m, 0.5×C<u>F</u>F), –130.2 (0.5 F, m, 0.5×CF<u>F</u>), –133.3 (0.5 F, dddd, *J* = 246.6, 16.4, 5.2, 2.6 Hz, 0.5×CF<u>F</u>) ppm.

5-Methyl-1-((2*R*,5*R*)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 5.04α



To protected nucleoside **5.02** (17 mg, 0.044 mmol) in DCM (0.5 mL) was added BCl_3 (4 equiv, 0.18 mmol, 0.18 mL). The reaction mixture was stirred at RT for

5 h, then reduced *in vacuo* to yield a crude residue. This was taken up in MeOH and evaporated onto silica gel for purification by flash chromatography (5:95–10:90 MeOH/DCM) to yield nucleoside **5.04** as a mixture of anomers (12 mg, 94%). A small sample was separated by RP- HPLC (70:30–55:45 H_2O/MeOH over 30 min then 55:45–50:50 over 5 min) retention time **5.04α**: 30.5 min, retention time **5.04β**: 32.8 min.

5.04α

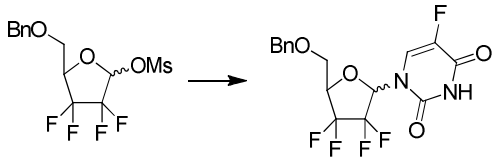
IR (film) 3401 (br), 2362 (w), 1694 (s), 1682 (s), 1470 (m), 1380 (w), 1279 (m), 1170 (w), 1141 (m), 1057 (s) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.42 (1 H, quin, *J* = 1.4 Hz, HC=C), 6.51 (1 H, ddd, *J* = 10.1, 8.2, 2.2 Hz, CHN), 4.77 (1 H, m, C<u>H</u>CH_2), 3.93 (1 H, dd, *J* = 12.5, 4.9 Hz, CHC<u>H</u>H), 3.89 (1 H, ddd, *J* = 12.6, 5.1, 1.0 Hz, CHCH<u>H</u>), 1.91 (3 H, d, *J* = 1.3 Hz, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 166.0 (C=O), 152.2 (C=O), 136.7 (<u>C</u>CH_3), 112.6 (<u>C</u>H=C), 84.5 (dd, *J* = 27.8, 22.0 Hz, CHN), 81.3 (dd, *J* = 26.3, 23.4 Hz, <u>C</u>HCH_2), 59.8 (CH_2), 12.5 (CH_3) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, MeOH-d_4) δ –124.62 (1 F, ddt, *J* = 247.8, 10.7, 4.5 Hz, CHC<u>F</u>F), –128.21—126.68 (2 F, m, CF_2CHN), –131.02 (1 F, dd, *J* = 247.8, 13.1 Hz, CHCF<u>F</u>) ppm.

1-((5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-5-fluoropyrimidine-2,4(1H,3H)-dione, 5.03



5-Fluorouracil (509 mg, 3.91 mmol) and ammonium sulfate (0.0018 equiv, 0.007 mmol, 1 mg) were refluxed in HMDS (3.6 equiv, 14.1 mmol, 2.99 mL) for 4 h. The HMDS was removed *in vacuo* to yield crude silylated 5-fluorouracil. Mesylate **5.01** (0.07 equiv, 0.28 mmol, 102 mg) was added and the reaction mixture was heated in a sealed tube at 130 ℃ for 3 0 h. The reaction mixture was diluted with sat. $NaHCO_3$ (aq) and extracted with EtOAc (3×15 mL). The

combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was purified by flash chromatography on silica gel (10:90–40:60 EtOAc/petrol) to yield the desired protected nucleoside **5.03** as a 1:1.5 anomeric mixture (19 mg, 17%).

IR (film) 3195 (br), 3072 (br), 1709 (s), 1667 (m), 1276 (m), 1133 (m), 1076 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (0.6 H, dd, *J* = 5.9, 2.1 Hz, $HC{=}C_{Major}$), 7.32–7.42 (5 H, m, 5×CH_{Ar}), 7.31 (0.4 H, dd, *J* = 5.7, 2.1 Hz, $HC{=}C_{Minor}$), 6.53 (0.4 H, ddt, *J* = 10.5, 6.6, 1.8 Hz, CHN_{Minor}), 6.36 (0.6 H, ddt, *J* = 9.6, 7.6, 1.8 Hz, CHN_{Major}), 4.58–4.69 (2.4 H, m, CH_2Ph, $C\underline{H}CH_{2Minor}$), 4.41 (0.6 H, m, $C\underline{H}CH_{2Major}$), 3.95 (0.6 H, dd, *J* = 11.4, 4.3 Hz, $CHC\underline{H}H_{Major}$), 3.73–3.88 (1.4 H, m, $CHC\underline{H}H_{Major}$, $CHC\underline{H}_{2Minor}$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 156.2 (d, *J* = 29.3 Hz, $N\underline{C}{=}OC$), 148.6 ($NC{=}ON_{Major}$), 148.5 ($NC{=}ON_{Minor}$), 136.6 ($C_{ArMinor}$), 136.5 ($C_{ArMajor}$), 140.7 (d, *J* = 241.5 Hz, $C{=}\underline{C}F_{Minor}$), 140.6 (d, *J* = 241.5 Hz, $C{=}\underline{C}F_{Major}$) 128.7 ($CH_{Ar}$), 128.6 ($CH_{Ar}$), 128.3 ($CH_{Ar}$), 127.9 ($CH_{Ar}$), 127.8 ($CH_{Ar}$), 123.6 (d, *J* = 36.6, $H\underline{C}{=}C_{Major}$), 123.3 (d, *J* = 36.6 Hz, $H\underline{C}{=}C_{Minor}$), 82.9 (dd, *J* = 36.6, 20.5 Hz, CHN_{Minor}), 82.3 (dd, *J* = 39.5, 20.5 Hz, CHN_{Major}), 79.0 (dd, *J* = 26.3, 22.0 Hz, $\underline{C}HCH_{2Minor}$), 77.1 (dd, *J* = 27.8, 23.4 Hz, $\underline{C}HCH_{2Major}$), 74.0 ($CH_2Ph$), 66.2 (t, *J* = 4.4 Hz, $CH\underline{C}H_{2Minor}$), 65.2 (d, *J* = 4.4 Hz, $CH\underline{C}H_{2Major}$) ppm (2×$CF_2$ not visible).

Major anomer

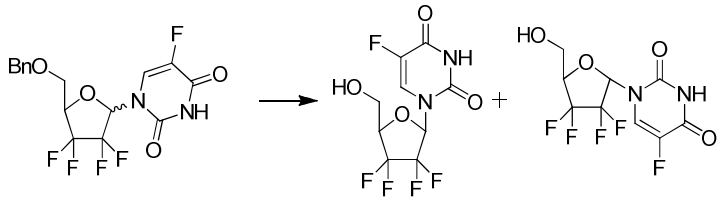
^{19}F NMR (282 MHz, $CDCl_3$) δ –121.3 (1 F, dddt, *J* = 247.6, 9.9, 7.8, 2.4 Hz, $C\underline{F}F$), –122.5 (1 F, ddddd, *J* = 247.8, 9.9, 7.5, 4.1, 2.4 Hz, $CF\underline{F}$), –130.2 (1 F, m, $C\underline{F}F$), –133.0 (1 F, dddd, *J* = 247.6, 15.1, 6.0, 1.9 Hz, $CF\underline{F}$), –162.6 (1 F, d, *J* = 4.3 Hz, C=CF) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –123.0 (1 F, dddd, *J* = 249.1, 11.4, 6.6, 4.4 Hz, $C\underline{F}F$), –126.1 (1 F, dtd, *J* = 245.9, 6.9, 4.5 Hz, $C\underline{F}F$), –127.6 (1 F, m, $CF\underline{F}$), –129.0 (1 F, ddd, *J* = 249.1, 9.9, 7.8 Hz, $CF\underline{F}$), –162.8 (1 F, d, *J* = 6.5 Hz, C=CF) ppm.

5-Fluoro-1-((2*S*,5*R*)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 5.05α

5-fluoro-1-((2*R*,5*R*)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione, 5.05β



To protected nucleoside **5.03** (31.7 mg, 0.081 mmol) in DCM (1.5 mL) was added BCl_3 (3 equiv, 0.24 mmol, 0.24 mL). The reaction mixture was stirred at RT for 5 h, then reduced *in vacuo* to yield a crude residue. This was taken up in MeOH and evaporated onto silica gel for purification by flash chromatography (5:95–15:85 MeOH/DCM) to yield nucleoside **5.05** as a mixture of anomers (24.1 mg, 99%). A small sample was separated by RP-HPLC (75:25–60:40 H_2O/MeOH over 30 min then 60:40–50:50 over 10 min) retention time **5.05α**: 31.6 min, retention time **5.05β**: 33.8 min.

5.05α

[α]$_D$: +11.3 (c 0.2, MeOH, 26 ℃).

LRMS (ESI^+) (m/z) 325.0 $(M+Na)^+$.

HRMS (ESI^+) for $C_9H_7F_5N_2O_4$ $(M+Na)^+$ calcd 325.0218; found 325.0223.

IR (film) 3435 (br), 3087 (br), 2829 (w), 1716 (s), 1670 (m), 1472 (w), 1378 (w), 1276 (m), 1206 (w), 1143 (m), 1057 (m) cm^{-1}

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.83 (1 H, dd, *J* = 6.4, 1.4 Hz, HC=C), 6.50 (1 H, ddt, *J* = 9.7, 7.9, 1.9 Hz, CHN), 4.77 (1 H, ddtd, *J* = 13.4, 11.0, 4.8, 2.4 Hz, C<u>H</u>CH_2), 3.92 (1 H, dd, *J* = 12.4, 4.8 Hz, C<u>H</u>H), 3.89 (1 H, ddd, *J* = 12.5, 4.8, 1.1 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 159.2 (d, *J* = 26.3 Hz, NC=OC), 150.8 (NC=ON), 142.2 (d, *J* = 234.2 Hz, C=<u>C</u>F), 125.1 (d, *J* = 36.6 Hz, H<u>C</u>=C), 83.8 (dd, *J* = 38.1, 19.0 Hz, CHN), 80.0 (dd, *J* = 27.8, 23.4 Hz, $CHCH_2$), 58.8 (d, *J* = 5.9 Hz, CH_2) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, MeOH-d_4) δ –124.7 (1 F, ddt, *J* = 248.0, 10.4, 5.0 Hz, C<u>F</u>FCF_2CHN), –127.0—128.4 (2 F, m, CF_2CHN), –131.0 (1 F, dd, *J* = 248.6, 12.7 Hz, CF<u>F</u>CF_2CHN), –166.9 (1 F, d, *J* = 5.7 Hz, C=CF) ppm.

5.05β

[α]$_D$: +11.7 (c 0.3, MeOH, 26 ℃).

IR (film) 3378 (br), 2498 (br), 1725 (s), 1666 (s), 1474 (w), 1372 (m), 1329 (w), 1281 (m), 1218 (w), 1183 (w), 1126 (s), 1036 (m) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.86 (1 H, dd, *J* = 6.4, 1.9 Hz, HC=C), 6.41 (1 H, tt, *J* = 8.8, 1.9 Hz, CHN), 4.43 (1 H, m, C<u>H</u>CH_2), 4.02 (1 H, dd, *J* = 12.8, 4.7 Hz, C<u>H</u>H), 3.97 (1 H, dd, *J* = 12.8, 4.8 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 159.5 (d, *J* = 27.8 Hz, NC=OC), 151.0 (s, NC=ON), 142.3 (d, *J* = 235.7 Hz, C=<u>C</u>F), 125.2 (d, *J* = 36.6 Hz, H<u>C</u>=C), 84.8 (ddd, *J* = 32.2, 23.4, 2.9 Hz, CHN), 81.4 (dd, *J* = 27.8, 23.4 Hz, <u>C</u>HCH_2), 59.7 (t, *J* = 4.4 Hz, CH_2) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –122.6 (1 F, dt, *J* = 246.1, 7.5 Hz, C<u>F</u>F), –122.8 (1 F, ddt, *J* = 246.1, 10.7, 5.4 Hz, CF<u>F</u>), –131.7 (1 F, m, C<u>F</u>F), –134.3 (1 F, dd, *J* = 247.1, 16.1 Hz, CF<u>F</u>), –166.8 (1 F, d, *J* = 6.5 Hz, C=CF) ppm.

***tert*-Butyl-2-amino-6-chloro-9H-purine-9-carboxylate, 5.17**

To 2-amino-6-chloropurine **5.16** (1.00 g, 5.90 mmol) in DMSO (20 mL) was added Boc_2O (1 equiv, 5.90 mmol, 1.29 g). The reaction mixture was stirred vigorously at 0 ℃ for 5 min. The reaction mixture was removed from the ice bath and DMAP (0.05 equiv, 0.29 mmol, 36 mg) was added. A venting needle was added and the reaction mixture was stirred at RT for 40 min, then diluted with water (130 mL) and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with water (5×40 mL), dried over anhydrous Na_2SO_4 and the solvents removed *in vacuo* to yield the Boc-protected purine **5.17** as a white solid (1.56 g, 98%).

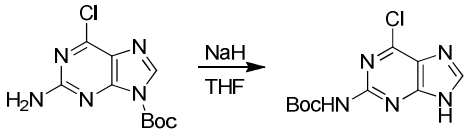
IR (film) 3317 (m), 3203 (m), 2982 (w), 1771 (s), 1623 (s), 1556 (s), 1368 (s), 1300 (s), 1146 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (1 H, s, CH_{Ar}), 5.63 (2 H, br. s., NH_2), 1.68 (9 H, s, $C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 160.4 (C), 153.3 (C), 152.4 (C), 145.6 (C), 140.2 (CH_{Ar}), 125.5 (C), 87.1 ($\underline{C}(CH_3)_3$), 27.9 ($C(\underline{C}H_3)_3$) ppm.

Data corresponds to literature[114].

tert-Butyl (6-chloro-9H-purin-2-yl)carbamate, 5.18



To purine **5.17** (1.547 g, 5.74 mmol) in THF (60 mL) was added sodium hydride (60% dispersion in mineral oil, 2.25 equiv, 12.9 mmol, 516 mg). The reaction mixture was stirred at RT for 2.5 h, then cooled to 0 ℃ and quenched with brine (2.5 mL). The reaction mixture was reduced in volume *in vacuo* to 20 mL, then poured into sat. $NaHCO_3$ (aq) extracted with $CHCl_3$ (5×40 mL), dried over anhydrous Na_2SO_4 and reduced *in vacuo* to yield a crude white solid. This residue was evaporated onto silica gel and purified by column chromatography on silica gel (4:96–6:94 MeOH/DCM + 0.5% NH_4OH) to yield the desired product **5.18** as a white solid (1.255 g, 81%).

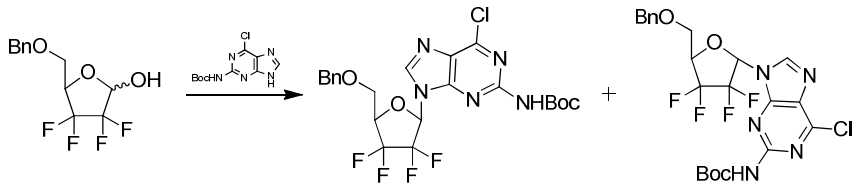
IR (film) 3157 (m), 2980 (w), 1742 (s), 1617 (m), 1577 (s), 1514 (m), 1150 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.42 (1 H, br. s., NH), 8.44 (1 H, s, CH_{Ar}), 7.70 (1 H, s, NH), 1.60 (9 H, s, $C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 153.3 (C), 151.6 (C), 151.4 (C), 151.0 (C), 145.5 (NCH), 128.3 (C), 82.4 ($\underline{C}(CH_3)_3$), 28.3 ($C(\underline{C}H_3)_3$) ppm.

Data corresponds to literature[114].

***tert*-Butyl-(9-((2S,5R)-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-6-chloro-9H-purin-2-yl)carbamate, 5.19α**
***tert*-butyl-(9-((2*R*,5*R*)-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-6-chloro-9H-purin-2-yl)carbamate, 5.19β**



To purine derivative **5.18** (1.8 equiv, 0.71 mmol, 192 mg) in THF (5 mL) was added lactol **2.02** (111 mg, 0.40 mmol) and triphenylphosphine (1.8 equiv, 0.71 mmol, 187 mg). The reaction mixture was stirred at RT for 5 min then DIAD (1.8 equiv, 0.71 mmol, 0.14 mL) was added dropwise. The reaction mixture was stirred at RT for 22 h then the solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (10:90–30:70 EtOAc/petrol) then HPLC (35:65 EtOAc/hexane) to yield β guanosine derivative **5.19β** (46 mg, 22%) and a 5:1 α/β anomeric mixture (81 mg, 38%).

5.19β:

[α]$_D$: +30.1 (c 0.82, $CHCl_3$, 25 ℃).

IR (film) 3255 (br), 2981 (w), 1744 (m), 1608 (w), 1575 (m), 1509 (m), 1345 (w), 1218 (m), 1145 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 556.2 $(M^{37}Cl+Na)^+$ (36), 554.2 $(M^{35}Cl+Na)^+$ (100).

HRMS (ESI^+) for $C_{22}H_{22}{}^{35}ClF_4N_5O_4$ $(M+Na)^+$ calcd 554.1189, found 554.1185.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (1 H, d, *J* = 2.9 Hz, CH=N), 7.55 (1 H, s, NH), 7.40–7.31 (5 H, m, 5×CH_{Ar}), 6.51 (1 H, td, *J* = 9.0, 1.6 Hz, CHN), 4.63 (2 H, s, CH_2Ph), 4.49 (1 H, m, C<u>H</u>CH_2), 3.94 (1 H, dd, *J* = 11.2, 4.6 Hz, CHC<u>H</u>H), 3.83 (1 H, dd, *J* = 11.3, 5.8 Hz, CHCH<u>H</u>), 1.56 (9 H, s, C(CH_3)) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 153.1 (C), 152.8 (C), 152.0 (C), 149.9 (C), 141.8 (CH=N), 136.7 (C_{Ar}), 128.6 (2×CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (2×CH_{Ar}), 127.1 (C), 82.0 (<u>C</u>(CH_3)), 81.2 (dd, *J* = 37.9, 20.4 Hz, CHN), 77.6 (dd, *J* = 49.6, 25.3 Hz, C<u>H</u>CH_2), 73.9 (CH_2Ph), 65.4 (d, *J* = 5.8 Hz, CH<u>C</u>H_2), 28.2 (C(<u>C</u>H_3)$_3$) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –121.4 (1 F, dt, *J* = 246.6, 8.6 Hz, C<u>F</u>F), –121.7 (1 F, m, CF<u>F</u>), –128.3 (1 F, m, C<u>F</u>F), –133.0 (1 F, ddd, *J* = 248.3, 15.5, 5.2 Hz, CF<u>F</u>) ppm.

5.19α:

IR (film) 3252 (br), 2980 (w), 2926 (w), 2873 (w), 1748 (m), 1508 (m), 1133 (s), 1068 (s) cm^{-1}.

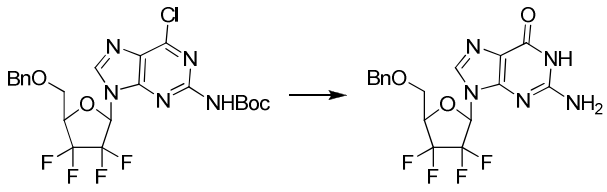
LRMS (ESI^+) *m/z* 556.2 $(M^{37}Cl+Na)^+$ (37), 554.2 $(M^{35}Cl+Na)^+$ (100).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (1 H, d, *J* = 2.6 Hz, CH=N), 7.53 (1 H, br. s, NH), 7.39–7.31 (5 H, m, 5×CH_{Ar}), 6.60 (1 H, ddd, *J* = 11.1, 7.1, 1.7 Hz, CHN), 5.09 (1 H, m, C<u>H</u>CH_2), 4.67 (1 H, d, *J* = 12.0 Hz, C<u>H</u>HPh), 4.63 (1 H, d, *J* = 12.0 Hz, CH<u>H</u>Ph), 3.92 (1 H, dd, *J* = 11.0, 4.6 Hz, CHC<u>H</u>H), 3.83 (1 H, dd, *J* = 10.9, 5.4 Hz, CHCH<u>H</u>), 1.54 (9 H, s, $C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 153.0 (C), 152.7 (C), 152.0 (C), 149.8 (C), 141.8 (d, *J* = 3.9 Hz, CH=N), 136.9 (C), 128.5 (2×CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (2×CH_{Ar}), 127.4 (C), 82.6 (dd, *J* = 38.9, 17.5 Hz, CHN), 81.9 (<u>C</u>$(CH_3)_3$), 78.8 (dd, *J* = 28.2, 22.4 Hz, <u>C</u>HCH_2), 73.9 (CH_2Ph), 66.2 (d, *J* = 5.8 Hz, CH<u>C</u>H_2), 28.1 (C(<u>C</u>$H_3)_3$) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, $CDCl_3$) δ –123.1 (1 F, m, C<u>F</u>F), –124.4 (1 F, dddd, *J* = 247.4, 9.9, 7.8, 4.3 Hz, CF<u>F</u>), –127.2 (1 F, dtd, *J* = 244.0, 6.9, 4.3 Hz, CF<u>F</u>), –129.5 (1 F, ddd, *J* = 247.4, 14.2, 6.9 Hz, C<u>F</u>F) ppm.

2-Amino-9-((2*R*,5*R*)-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-1H-purin-6(9H)-one, 5.20β



Protected nucleoside **5.19β** (26.5 mg, 0.05 mmol) was stirred in formic acid (0.6 mL) and water (0.15 mL) at 75 ℃ for 3 h. The solvents were reduced *in vacuo* and the residue purified by column chromatography on silica gel (MeOH/DCM 2:98–10:90) to yield the protected nucleoside **5.20β** as a colourless oil (16.0 mg, 79%).

IR (film) 3130 (w), 2934 (w), 2332 (w), 1685 (s), 1607 (m) cm^{-1}.

LRMS (ESI^+) *m/z* 849.5 $(2M+Na)^+$ (100), 477.3 $(M+Na+MeCN)^+$ (64), 436.2 $(M+Na)^+$ (46).

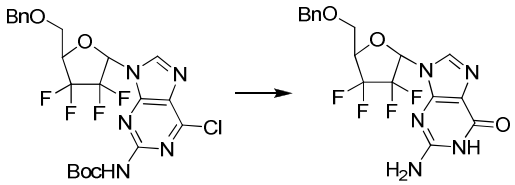
HRMS (ESI^+) for $C_{17}H_{15}F_4N_5O_3$ $(M+Na)^+$ Calcd 436.1003; Found 436.1010.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.75 (1 H, d, *J* = 2.3 Hz, NCH=N), 7.36–7.29 (5 H, m, 5×CH_{Ar}), 6.42 (1 H, td, *J* = 9.2, 1.5 Hz, CHN), 4.69–4.60 (3 H, m, CH_2Ph, C<u>H</u>CH_2), 3.98 (1 H, dd, *J* = 11.2, 4.9 Hz, C<u>H</u>HCH), 3.89 (1 H, dd, *J* = 11.0, 5.4 Hz, CH<u>H</u>CH) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 159.35 (C), 156.2 (C), 153.5 (C), 139.0 (C), 136.9 (NCH=N), 129.6 (2×CH_{Ar}), 129.13 (CH_{Ar}), 129.08 (2×CH_{Ar}), 117.2 (CNH_2), 82.8 (dd, *J* = 37.9, 19.4 Hz, CHN), 78.7 (dd, *J* = 27.2, 22.4 Hz, <u>C</u>HCH_2), 74.8 (CH_2Ph), 66.8 (CH<u>C</u>H_2) ppm (2×CF_2 not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –121—123.5 (2 F, m, C<u>F</u>F, CF<u>F</u>), –129.9 (1 F, m, C<u>F</u>F), –133.7 (1 F, m, CF<u>F</u>) ppm.

2-Amino-9-((2*S*,5*R*)-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-1H-purin-6(9H)-one, 5.20α



Protected nucleoside **5.19α** (predominantly α anomer) contaminated with spent DIAD (158 mg) was stirred in formic acid (2 mL) and water (0.5 mL) at 75 ℃ for 4 h then the solvents were reduced *in vacuo* and the resultant residue purified by column chromatography on silica gel (MeOH/DCM 5:95–10:90) to yield the protected nucleoside **5.20α** as a colourless oil (45 mg, 29% over 1 steps).

IR (film) 3120 (w), 2933 (w), 2329 (w), 1682 (s), 1580 (m), 1537 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 414.3 $(M+H)^+$ (100).

HRMS (ESI^+) for $C_{17}H_{15}F_4N_5O_3$ $(M+Na)^+$ Calcd 436.1003; Found 436.0999.

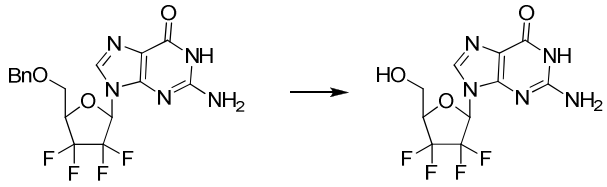
^{1}H NMR (400 MHz, MeOH-d_4) δ 7.86 (1 H, d, *J* = 2.0 Hz, NCH=N), 7.37–7.28 (5 H, m, 5×CH_{Ar}), 6.55 (1 H, ddd, *J* = 10.9, 7.8, 1.9 Hz, CHN), 5.13 (1 H, ddtd,

J = 14.8, 9.8, 4.9, 3.1 Hz, C<u>H</u>CH$_2$), 4.62 (2 H, br. s, CH$_2$Ph), 3.91 (1 H, dd, *J* = 11.0, 5.0 Hz, C<u>H</u>H), 3.83 (1 H, dd, *J* = 11.0 Hz, 4.9 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d$_4$) δ 159.4 (C), 156.0 (C), 153.4 (C), 139.0 (C), 137.5 (NCH=N), 129.6 (CH$_{Ar}$), 129.1 (CH$_{Ar}$), 117.5 (C), 83.9 (ddd, *J* = 37.9, 19.4, 2.9 Hz, CHN), 79.9 (dd, *J* = 27.2, 23.3 Hz, <u>C</u>HCH$_2$), 74.9 (CH$_2$Ph), 67.6 (d, *J* = 4.9 Hz, CH<u>C</u>H$_2$) ppm (2×CF$_2$ not visible, some CH$_{Ar}$ overlap).

^{19}F NMR (282 MHz, MeOH-d$_4$) δ –123.9 (1 F, m, C<u>F</u>F), –124.9 (1 F, dddd, *J* = 246.6, 10.3, 6.9, 4.3 Hz, CF<u>F</u>), –128.3 (1 F, m, C<u>F</u>F), –130.6 (1 F, ddd, *J* = 246.6, 15.5, 6.0 Hz, CF<u>F</u>) ppm.

2-Amino-9-((2*R*,5*R*)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-purin-6(9H)-one, 5.21β



To protected nucleoside **5.20β** (12.2 mg, 0.030 mmol) in DCM (0.75 mL) was added boron trichloride (1 M in DCM, 4 equiv, 0.12 mmol, 0.12 mL). The reaction mixture was stirred at RT for 5 h then reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (MeOH/DCM 5:95–15:85) to yield nucleoside **5.21β** a white solid (9.6 mg, 99%).

IR (film) 3119 (br), 2305 (br), 1682 (s), 1591 (m), 1533 (m), 1044 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 387.2 (M+Na+MeCN)$^+$, 324.1 (M+H)$^+$.

HRMS (ESI$^+$) for $C_{10}H_9F_4N_5O_3$ (M+Na)$^+$ Calcd 346.0534; Found 346.0535.

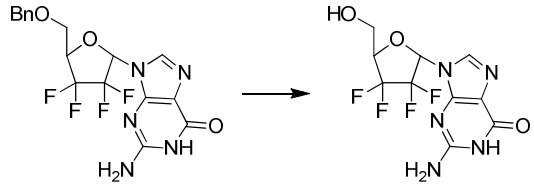
^{1}H NMR (400 MHz, MeOH-d$_4$) δ 7.82 (1 H, d, *J* = 1.6 Hz, NCH=N), 6.41 (1 H, td, *J* = 9.2, 1.9 Hz, CHN), 4.47 (1 H, ddtd, *J* = 15.7, 10.6, 5.1, 1.9 Hz, C<u>H</u>CH$_2$), 4.02 (1 H, dd, *J* = 12.6, 5.2 Hz, C<u>H</u>H), 3.95 (1 H, dd, *J* = 12.5, 5.2 Hz, CH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d$_4$) δ 136.7 (NCH=N), 82.5 (dd, *J* = 38.9, 21.4 Hz, CHN), 79.9 (dd, *J* = 27.2, 23.3 Hz, <u>C</u>HCH$_2$), 58.8 (d, *J* = 5.8 Hz, CH$_2$) ppm (quaternary peaks not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –117.8 (1 F, d, *J* = 246.6 Hz, C<u>F</u>F), –120.2 (1 F, dt, *J* = 244.0, 7.8 Hz, C<u>F</u>F), –126.7 (1 F, d, *J* = 244.0 Hz, CF<u>F</u>), –130.9 (1 F, ddd, *J* = 247.4, 14.7, 3.4 Hz, CF<u>F</u>) ppm.

GOESY shows an NOE response at CHN when C<u>H</u>CH_2 is irradiated, proving the β anomer to be present.

2-Amino-9-((2*S*,5*R*)-3,3,4,4-tetrafluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)-1H-purin-6(9H)-one, 5.21



To protected nucleoside **5.20** (44 mg, 0.11 mmol) in DCM (2 mL) was added boron trichloride (1 M in DCM, 3 equiv, 0.33 mmol, 0.33 mL). The reaction mixture was stirred at RT for 6 h. The solvents were reduced *in vacuo* to yield a crude residue which was evaported onto silica gel and purified by flash chromatography on silica gel (5:95–25:75 MeOH/DCM) to yield the desired nucleoside **5.21** as a 6:1 α/β mixture of anomers (31 mg, 91%).

IR (film) 3386 (br), 2506 (br), 2324 (br), 1671 (s), 1591 (m), 1533 (m), 1353 (w), 1249 (w), 1155 (s), 1062 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 669.2 $(2M+Na)^+$ (31), 387.1 $(M+Na+MeCN)^+$ (100).

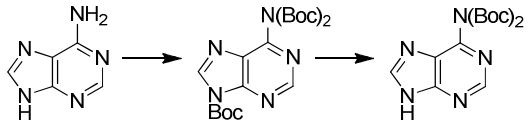
HRMS (ESI^+) for $C_{10}H_9F_4N_5O_3$ $(M+Na)^+$ calcd 346.0534, found 346.0529.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.88 (1 H, s, NC=N), 6.57 (1 H, t, *J* = 8.4 Hz, CHN), 4.94 (1 H, m, C<u>H</u>CH_2), 4.00–3.89 (2 H, m, CHC<u>H</u>$_2$) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 156.0 (NCH=N), 84.0 (ddd, *J* = 38.1, 22.0, 4.4 Hz, CHN), 81.4 (t, *J* = 24.9 Hz, <u>C</u>HCH_2), 59.7 (d, *J* = 5.9 Hz, CH_2) ppm (quaternary peaks not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –124.5 (1 F, m, C<u>F</u>F), –124.6 (1 F, dddd, *J* = 247.6, 10.3, 7.1, 3.4 Hz, CF<u>F</u>), –128.5 (1 F, m, C<u>F</u>F), –131.0 (1 F, dddd, *J* = 246.8, 14.7, 6.5, 1.3 Hz, CF<u>F</u>) ppm.

tert-Butyl N-tert-butoxycarbonyl-N-(9H-purin-6-yl)carbamate, 5.24[115]



To adenine **5.22** (500 mg, 3.70 mmol) and DMAP (0.1 equiv, 0.37 mmol, 452 mg) was added THF (25 mL), di-*tert*-butyl dicarbonate (4 equiv, 14.8 mmol, 3.23 g) was added to the stirring suspension. The reaction mixture was stirred at RT for 14 h. Additional DMAP (0.1 equiv, 0.37 mmol, 452 mg) and di-*tert*-butyl dicarbonate (1 equiv, 3.70 mmol, 808 mg) were added and the reaction mixture stirred for a further 5 h at RT, before the solvents were reduced *in vacuo* to yield a crude yellow oil. This oil was dissolved in EtOAc (125 mL) and washed with 1 M HCl (aq) (10 mL), then brine (3×30 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvents reduced *in vacuo* to yield a pale yellow oil. This oil was dissolved in MeOH (35 mL) and sat. $NaHCO_3$ (aq) (15 mL) was added. The turbid solution was stirred at 50 ℃ for 1 h, the MeOH was then reduced *in vacuo*, water (35 mL) was added and the solution extracted with $CHCl_3$ (2×30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvents reduced *in vacuo* to yield the desired bis-Boc-adenine **5.24** as a white solid (987 mg, 80%).

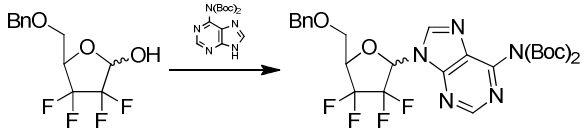
IR (film) 3233 (br), 2981 (w), 2360 (w), 1781 (s), 1734 (m), 1611 (m), 1585 (m), 1456 (w), 1395 (w), 1370 (m), 1328 (m), 1277 (s), 1252 (s), 1136 (s), 1109 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (1 H, s, CH), 8.53 (1 H, s, CH), 1.39 (18 H, s, 2×$C(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 151.7 (CH), 150.1 (C=O), 144.7 (CH), 84.3 ($\underline{C}(CH_3)_3$), 27.6 ($C(\underline{C}H_3)_3$) ppm.

Data corresponds to the literature

9-(5*R*)-{5-[(Benzyloxy)methyl]-3,3,4,4-tetrafluorotetrahydrofuran-2-yl}-6-chloro-N-Boc-9H-purin-2-amine, 5.25α/β



To bis-Boc-adenine **5.24** (1.8 equiv, 0.88 mmol, 295 mg) in THF (5 mL) was added lactol **2.02** (137 mg, 0.49 mmol) and triphenylphosphine (1.8 equiv, 0.88 mmol, 231 mg). The reaction mixture was stirred at RT for 5 min then DIAD (1.8 equiv, 0.88 mmol, 0.17 mL) was added dropwise. The reaction mixture was stirred at RT for 22 h then the solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (0:100–5:95 MeOH/DCM) then HPLC (30:70 acetone/petrol) to yield protected adenosine derivative **5.25** as a colourless oil as a 1:1.7 anomeric mixture (147 mg, 50%).

IR (film) 2981 (w), 1789 (m), 1731 (m), 1599 (m), 1582 (m), 1454 (w), 1274 (m), 1248 (m), 1136 (s), 1101 (s) cm^{-1}.

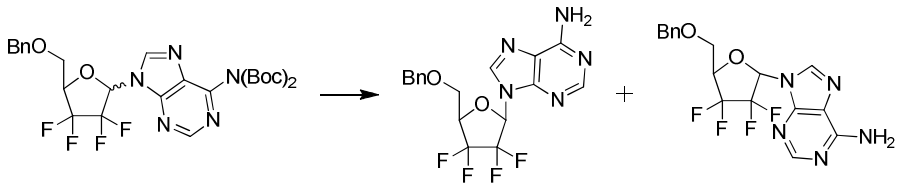
LRMS (ESI^+) *m/z* 661.3 (M+Na+MeCN) (100), 620.2 $(M+Na)^+$ (5).

HRMS (ESI^+) for $C_{27}H_{31}F_4N_5O_6$ $(M+Na)^+$ calcd 620.2103, found 620.2087.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (0.6 H, s, C<u>H</u>NCNH_{2Major}), 8.87 (0.4 H, s, C<u>H</u>NCNH_{2Minor}), 8.21 (1 H, d, *J* = 2.4 Hz, CHN=C<u>H</u>N), 7.39–7.29 (5 H, m, 5×CH_{Ar}), 6.76 (0.6 H, ddd, *J* = 11.2, 6.8, 2.1 Hz, CHN_{Major}), 6.59 (0.4 H, td, *J* = 8.9, 1.6 Hz, CHN_{Minor}), 5.12–4.83 (1 H, m, C<u>H</u>CH_2), 4.69–4.49 (2 H, m, CH_2Ph), 3.97–3.75 (2 H, m, CHC<u>H</u>$_2$), 1.46–1.43 (18 H, m, 2×C$(CH_3)_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –121.4—124.6 (2 F, m, CF_2), –126—129.3 (1.6 F, m, CF_{2Major}, CFF_{Minor}), –133.0 (0.4 F, ddd, *J* = 246.1, 16.1, 6.4 Hz, CFF_{Minor}) ppm.

9-((2*R*,5*R*)-5-((Benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-9H-purin-6-amine 5.26α,
9-((2*S*,5*R*)-5-((benzyloxy)methyl)-3,3,4,4-tetrafluorotetrahydrofuran-2-yl)-9H-purin-6-amine, 5.26β



Protected adenosine derivative **5.25** (146 mg, 0.24 mmol) was stirred in formic acid (3 mL) and water (0.75 mL) at 75 ℃ for 5 h. T he solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (30:70–40:60 acetone/petrol) then HPLC (45:55 acetone/petrol) to yield **5.26β** (6 mg, 6%) and 9.5:1 α/β anomers (9 mg, 9%).

5.26α

IR (film) 3324 (m), 3165 (m), 3033 (w), 2872 (w), 1738 (w), 1650 (s), 1600 (s), 1581 (m), 1475 (m), 1427 (w), 1368 (m), 1252 (m), 1141 (s), 1070 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 817.3 $(2M+Na)^+$ (100), 461.1 $(M+Na+MeCN)^+$ (94), 420.1 $(M+Na)^+$ (96).

HRMS (ESI^+) for $C_{17}H_{15}F_4N_5O_2$ $(M+Na)^+$ calcd 420.1054, found 420.1068.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1 H, s, C<u>H</u>NCNH_2), 7.95 (1 H, d, *J* = 2.8 Hz, CHN=C<u>H</u>N), 7.40–7.31 (5 H, m, 5×CH_{Ar}), 6.66 (1 H, ddd, *J* = 11.9, 6.7, 2.1 Hz, CHN), 5.84 (2 H, br. s, NH_2), 4.86 (1 H, m, C<u>H</u>CH_2), 4.64 (2 H, s, CH_2Ph), 3.90 (1 H, dd, *J* = 11.0, 4.5 Hz, CHC<u>H</u>H), 3.81 (1 H, dd, *J* = 11.0, 5.6 Hz, CHCH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 155.6 (C_{Ar}), 153.8 (N<u>C</u>HNCN_2), 150.2 (C_{Ar}), 138.4 (d, *J* = 4.4 Hz, NCHN), 136.8 (OCH_2C_{Ar}), 128.6 (2×CH_{Ar}), 128.1 (CH_{Ar}), 127.8 (2×CH_{Ar}), 119.1 (CNH_2), 81.9 (ddd, *J* = 36.6, 19.0, 2.9 Hz, CHN), 78.7 (dd, *J* = 26.3, 23.4 Hz, C<u>H</u>CH_2), 73.9 (CH_2Ph), 66.2 (d, *J* = 4.4 Hz, CHC<u>H</u>$_2$) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, $CDCl_3$) δ –123.8 (1 F, dddd, *J* = 247.5, 10.4, 7.8, 3.9 Hz, C<u>F</u>FCHCH_2), –124.7 (1 F, dddt, *J* = 243.9, 11.3, 8.1, 3.2 Hz, CF<u>F</u>CHN), –128.1 (1 F, dtd, *J* = 243.9, 7.1, 3.9 Hz, C<u>F</u>FCHN), –129.0 (1 F, m, CF<u>F</u>CHCH_2) ppm.

5.26β

[α_D] +12.6 (c 0.3, $CHCl_3$, 23 ℃).

IR (film) 3323 (m), 3165 (m), 2872 (w), 1652 (s), 1600 (s), 1582 (m), 1475 (m), 1370 (m), 1287 (m), 1253 (m), 1138 (s), 1098 (m), 1041 (m) cm^{-1}.

LRMS (ESI^+) *m/z* 420.1 $(M+Na)^+$ (33), 398.1 $(M+H)^+$ (49).

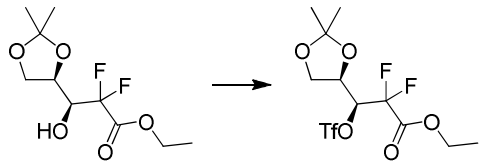
HRMS (ESI^+) for $C_{17}H_{15}F_4N_5O_2$ $(M+H)^+$ Calcd 398.1235, Found 398.1245.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (1 H, s, C<u>H</u>NCNH_2), 7.94 (1 H, d, *J* = 3.0 Hz, CHN=C<u>H</u>N), 7.40–7.32 (5×CH_{Ar}), 6.50 (1 H, *J* = 9.2, 1.8 Hz, CHN), 5.76 (2 H, br. s. NH_2), 4.66 (1 H, d, *J* = 12.1 Hz, C<u>H</u>HPh), 4.63 (1 H, d, *J* = 12.1 Hz, CH<u>H</u>Ph), 4.53 (1 H, m, C<u>H</u>CH_2), 3.95 (1 H, *J* = 11.1, 5.1 Hz, CHC<u>H</u>H), 3.85 (1 H, d, *J* = 11.1, 6.1 Hz, CHCH<u>H</u>) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 155.5 (C_{Ar}), 153.9 (N<u>C</u>HNCN_2), 150.2 (C_{Ar}), 138.4 (NCHN), 136.8 (OCH_2C_{Ar}), 128.6 (2×CH_{Ar}), 128.2 (CH_{Ar}), 127.8 (2×CH_{Ar}), 118.9 (CNH_2), 81.2 (dd, *J* = 38.1, 20.5 Hz, CHN), 77.6 (dd, *J* = 27.8, 24.9 Hz, C<u>H</u>CH_2), 73.9 (CH_2Ph), 65.6 (d, *J* = 5.9 Hz, CHC<u>H_2</u>) ppm (2×CF_2 not visible).

^{19}F NMR (376 MHz, $CDCl_3$) δ –121.5 (1 F, ddddd, *J* = 247.1, 9.8, 7.6, 4.1, 1.9 Hz, C<u>F</u>FCHCH_2), –121.8 (1 F, dddt, *J* = 245.5, 9.5, 7.5, 2.3 Hz, C<u>F</u>FCHN), –128.8 (1 F, m, CF<u>F</u>CHN), –133.1 (1 F, m, CF<u>F</u>CHCH_2) ppm.

Ethyl-(3*S*)-3-[(4*R*-2,2–dimethyl-1,3-dioxolan-4-yl]-2,2-difluoro-3-trifluoromethylsulfonyloxypropanoate, 5.29

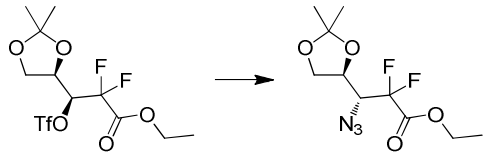


To alcohol **2.05a** (2.161 g, 8.50 mmol) in DCM (20 mL) was added pyridine (2 equiv, 17.0 mmol, 1.37 mL), the reaction mixture was cooled to –35 ℃ and triflic anhydride (1.2 equiv, 10.2 mmol, 1.72 mL) was added. The reaction mixture was stirred at –25 ℃ for 3 h, warmed to RT and water (10 mL) and sat. $NaHCO_3$ (aq) (10 mL) were added successively. The aqueous phase was extracted with DCM (3×25 mL) and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to yield a crude residue which was purified by column

chromatography on silica gel (10:90 Et_2O/hexane) to yield the desired product **5.29** as a yellow oil (2.942 g, 90%).

[α_D] +4.3 (c 0.7, $CHCl_3$, 28 ℃).
IR (film) 2992 (w), 1767 (m), 1419 (m), 1208 (s), 1136 (s) cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (1 H, td, *J* = 8.9, 7.5 Hz, CHOTf), 4.50 (1 H, dddd, *J* = 7.8, 6.7, 5.6, 1.1 Hz, C<u>H</u>CH_2), 4.39 (2 H, qd, *J* = 7.2, 1.0 Hz, C<u>H</u>$_2CH_3$), 4.20 (1 H, ddt, *J* = 9.5, 6.5, 0.9 Hz, C<u>H</u>HO), 4.01 (1 H, ddt, *J* = 9.5, 5.6, 1.2 Hz, CH<u>H</u>O), 1.46–1.37 (9 H, m, 3×CH_3) ppm.
^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 160.7 (t, *J* = 30.1 Hz, C=O), 118.3 (t, *J* = 318.8 Hz, CF_3), 111.0 (<u>C</u>$(CH_3)_2$), 110.9 (dd, *J* = 259.5, 256.6 Hz, CF_2), 82.9 (t, *J* = 28.2 Hz, CHOTf), 71.6 (<u>C</u>HCH_2), 65.5 (t, *J* = 4.4 Hz, <u>C</u>H_2CH), 64.2 (<u>C</u>H_2CH_3), 25.7 (CH_3), 25.0 (CH_3), 13.7 (CH_2<u>C</u>H_3) ppm.
^{19}F NMR (282 MHz, $CDCl_3$) δ –74.0 (3 F, s, CF_3), –111.2 (1 F, d, *J* = 275.1 Hz, C<u>F</u>F), –114.3 (1 F, dd, *J* = 275.1, 8.6 Hz, CF<u>F</u>) ppm.

Ethyl-(3*R*)-3-azido-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-difluoropropanoate, 5.30



To triflate **5.29** (542 mg, 1.40 mmol) in DMF (12 mL) at 0 ℃ was carefully added NaN_3 (1.2 equiv, 1.68 mmol, 109 mg). The reaction mixture was stirred at RT for 20 h, diluted with water (15 mL), and extracted with DCM (4×15 mL). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed *in vacuo* to yield a crude oil which was purified by column chromatography on silica gel (10:90 Et_2O/hexane) to yield the desired product **5.30** as a colourless oil (361 mg, 92%).

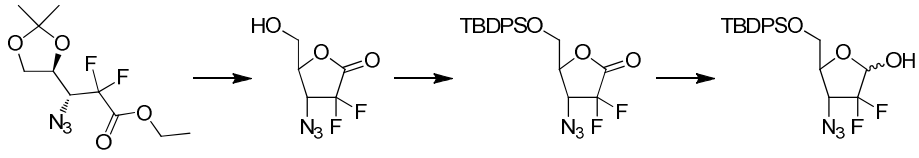
[α_D] –25.1 (c 0.8, $CHCl_3$, 27 ℃).
IR (film) 2989 (w), 2115 (s), 1778 (m), 1759 (m) cm^{-1}.
LRMS (CIMS) *m/z* 280 $(M+H)^+$ (100).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42–4.18 (4 H, m, CHO, CHN_3, $C\underline{H}_2CH_3$), 4.11–4.07 (1 H, m, OC<u>H</u>H), 4.01 (1 H, m, OCH<u>H</u>), 1.43 (3 H, s, CCH_3), 1.37 (3 H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.33 (3 H, s, CCH_3) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 162.2 (t, *J* = 31.1 Hz, C=O), 113.6 (dd, *J* = 256.6, 254.6 Hz, CF_2), 110.1 ($\underline{C}(CH_3)_2$), 72.7 (CHO), 65.9 (d, *J* = 2.9 Hz, OCH_2), 64.0 (dd, *J* = 24.3, 21.4 Hz, CHN_3), 63.4 ($\underline{C}H_2CH_3$), 25.9 ($C\underline{C}H_3$), 24.9 ($C\underline{C}H_3$), 13.8 ($CH_2\underline{C}H_3$) ppm.

^{19}F NMR (282 MHz, $CDCl_3$) δ –112.9 (1 F, dd, *J* = 263.8, 10.4 Hz, C<u>F</u>F), –116.1 (1 F, dd, *J* = 264.7, 12.9 Hz, CF<u>F</u>) ppm.

(5*S*)-4-Azido-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-ol, 5.33a



To azide **5.30** (1.90 g, 6.80 mmol) in MeOH (30 mL) and water (15 mL) was added Dowex 50 (12.5 g). The reaction mixture was stirred at RT for 5 d, filtered and the solvents removed *in vacuo*, azeotroping twice with toluene, to yield the crude lactone **5.31**.

To a portion of the crude lactone **5.31** (475 mg) in DMF (10 mL) was added imidazole (2.2 equiv, 5.90 mmol, 402 mg) and *tert*-butyldiphenylsilyl chloride (1.5 equiv, 4.02 mmol, 1.05 mL). The reaction mixture was stirred at 80 ℃ for 18 h. The reaction mixture was cooled to RT, diluted with water and extracted with Et_2O (3×25 mL), the combined organic extracts were washed successively with water and brine, then dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield the crude lactone **5.32a**.

To crude lactone **5.32a** (1.443 g) in toluene (15 mL) at –78 ℃ was added DIBAL (1 M in hexanes, approx 3 equiv, 6.70 mmol, 6.70 mL) dropwise. The reaction mixture was stirred at –78 ℃ for 5.5 h, quenched with MeOH (1 mL) and warmed to RT. The reaction mixture was poured into 1.5 M HCl (aq) and

extracted with Et_2O (3×25 mL), the combined organic extracts were washed with brine and dried over anhydrous $MgSO_4$. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (10:90–40:60 acetone/petrol, then 20:80 petrol/DCM) to yield lactol **5.33a** as a 1:1.5 mixture of anomers contaminated with TBDPSOH (680 mg, 60%)

IR (film) 3417 (br), 2932 (w), 2859 (w), 2110 (s), 1112 (m), 1087 (m) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.66 (4 H, m, 4×CH_{Ar}), 7.51–7.39 (6 H, m, 6×CH_{Ar}), 5.35 (0.4 H, d, *J* = 6.1 Hz, C<u>H</u>OH_{Minor}), 5.16 (0.6 H, d, *J* = 5.0 Hz, C<u>H</u>OH_{Major}), 4.27 (0.6 H, d, *J* = 15.2, 9.3, 7.4 Hz, CHN_{3Major}), 4.20–4.12 (0.8 H, m, CHN_{3Minor}, C<u>H</u>CH_{2Minor}), 4.04 (0.6 H, dt, *J* = 7.3, 2.8 Hz, C<u>H</u>CH_{2Major}), 3.92–3.83 (1.4 H, m, CH_{2Minor}, C<u>H</u>H_{Major}), 3.69 (0.6 H, dd, *J* = 11.7, 2.5 Hz, CH<u>H</u>$_{Major}$), 3.61 (0.6 H, br. s, OH_{Major}), 3.11 (0.4 H, br.s, OH_{Minor}), 1.12 (5.4 H, s, $C(CH_3)_{3Major}$), 1.09 (3.6 H, s, $C(CH_3)_{3Minor}$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 135.6 (CH_{Ar}), 136.5 (CH_{Ar}), 134.8 (CH_{Ar}), 130.4 (CH_{Ar}), 130.2 (CH_{Ar}), 130.00 (CH_{Ar}), 129.95 (CH_{Ar}), 129.7 (CH_{Ar}), 128.1 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 127.8 (CH_{Ar}), 127.7 (CH_{Ar}), 132.8 (C_{Ar}), 132.6 (C_{Ar}), 131.9 (C_{Ar}), 122.7 (dd, *J* = 264.4, 254.6 Hz, CF_{2Major}), 122.6 (dd, *J* = 267.3, 254.6 Hz, CF_{2Minor}), 95.9 (dd, *J* = 40.8, 23.3 Hz, $CHOH_{Minor}$), 95.3 (dd, *J* = 36.0, 25.3 Hz, $CHOH_{Major}$), 81.1 (<u>C</u>HCH_{2Minor}), 79.9 (d, *J* = 6.8 Hz, <u>C</u>HCH_{2Major}), 62.8 (CH_{2Major}), 62.4 (CH_{2Minor}), 61.3 (dd, *J* = 30.1, 18.5 Hz, CHN_{3Minor}), 59.3 (dd, *J* = 25.3, 18.5 Hz, CHN_{3Major}), 26.8 (C(<u>C</u>$H_3)_{3Major}$), 26.7 (C(<u>C</u>$H_3)_{3Major}$), 19.24 (<u>C</u>$(CH_3)_{3Minor}$), 19.21 (<u>C</u>$(CH_3)_{3Major}$) ppm (some C_{Ar}/CH_{Ar} overlap).

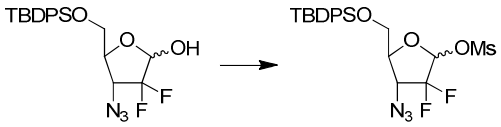
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –122.3 (1 F, dd, *J* = 235.3, 10.3 Hz, C<u>F</u>F), –123.4 (1 F, ddd, *J* = 235.3, 14.7, 4.3 Hz, CF<u>F</u>) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –107.7 (1 F, ddd, J = 244.0, 14.7, 4.3 Hz, C<u>F</u>F), –124.6 (1 F, m, CF<u>F</u>) ppm.

(5*S*)-4-Azido-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-yl methanesulfonate, 5.34



To lactol **5.33a** (150 mg, 0.35 mmol) stirring in DCM (1.5 mL) was added Et_3N (1.4 equiv, 0.52 mmol, 0.072 mmol). The reaction mixture was cooled to 0 ℃ and MsCl (1.2 equiv, 0.42 mmol, 0.032 mL) was added dropwise. The reaction mixture was stirred at RT for 20 h. The solvents were reduced *in vacuo* and the resultant residue taken up in EtOAc. The organic phase was washed successively with sat. $NaHCO_3$ (aq), 1 M HCl and brine, then dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was purified by column chromatography on silica gel (15:85–20:80 Et_2O/petrol) then HPLC (20:80 acetone/hexane) to yield the desired product **5.34** as a colourless oil as a 1:1.8 mixture of anomers (144 mg, 81%).

IR (film) 2933 (w), 2859 (w), 2112 (s), 1589 (w), 1463 (w), 1428 (w), 1372 (m), 1259 (w), 1181 (s), 1104 (s) cm^{-1}.

LRMS (ESI^+) *m/z* 534.2 $(M+Na)^+$ (100).

HRMS (ESI^+) for $C_{22}H_{27}F_2N_3O_5SSi$ $(M+Na)^+$ calcd 534.1301; found 534.1293.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.68 (4 H, m, 4×CH_{Ar}), 7.51–7.42 (6 H, m, 6×CH_{Ar}), 6.04 ($^2/_3$ H, d, *J* = 6.0 Hz, $CHOMs_{Major}$), 5.94 ($^1/_3$ H, dd, *J* = 6.8, 1.1 Hz, $CHOMs_{Minor}$), 4.40 ($^1/_3$ H, ddd, *J* = 18.7, 8.5, 7.3 Hz, CHN_{3Minor}), 4.25 ($1^1/_3$ H, m, CHN_{3Major}, C<u>H</u>CH_{2Major}), 4.10 ($^1/_3$ H, dt, *J* = 8.7, 3.4 Hz, C<u>H</u>CH_{2Minor}), 4.02–3.89 ($1^2/_3$ H, m, CH_{2Major}, C<u>H</u>H_{Minor}), 3.85 ($^1/_3$ H, dd, *J* = 12.1, 3.5 Hz, CH<u>H</u>$_{Minor}$), 3.12 (2 H, s, OMs_{Major}), 3.01 (1H, s, OMs_{Minor}), 1.15 (3 H, s, $C(CH_3)_{3Minor}$), 1.11 (6 H, s, $C(CH_3)_{3Major}$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 132.6 ($C_{ArMajor}$), 132.4 ($C_{ArMinor}$), 132.3 ($C_{ArMajor}$), 132.2 ($C_{ArMinor}$), 135.6 (CH_{Ar}), 135.5 (CH_{Ar}), 135.4 (CH_{Ar}), 130.21 (CH_{Ar}), 130.13 (CH_{Ar}), 130.08 (CH_{Ar}), 130.06 (CH_{Ar}), 128.03 (CH_{Ar}), 127.97 (CH_{Ar}), 127.92 (CH_{Ar}), 127.87 (CH_{Ar}), 122.2 (dd, *J* = 272.1, 252.7 Hz, CF_{2Major}), 121.3 (dd, *J* = 269.2, 250.8 Hz, CF_{2Minor}), 99.5 (dd, *J* = 46.7, 24.3 Hz, $CHOMs_{Major}$), 98.4 (dd, *J* = 42.8, 25.3 Hz, $CHOMs_{Minor}$), 84.0 (<u>C</u>HCH_{2Major}), 81.2

(d, *J* = 7.8 Hz, CHCH$_{2Minor}$), 62.1 (CH$_{2Minor}$), 61.8 (CH$_{2Major}$), 61.0 (dd, *J* = 31.1, 19.4 Hz, CHN$_{3Major}$), 58.7 (dd, *J* = 23.3, 17.5 Hz, CHN$_{3Minor}$), 40.2 (SO$_2$CH$_{3Minor}$), 40.1 (SO$_2$CH$_{3Major}$), 26.8 (C(CH$_3$)$_{3Minor}$), 26.6 (C(CH$_3$)$_{3Major}$), 19.3 (C(CH$_3$)$_{3Minor}$), 19.2 (C(CH$_3$)$_{3Major}$) ppm.

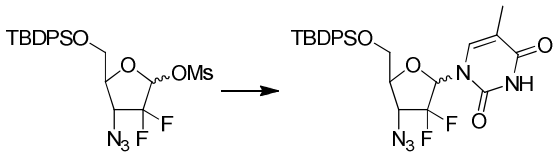
Major anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –102.6 (1 F, ddd, *J* = 247.4, 19.0, 6.0 Hz, CFF), –119.9 (1 F, d, *J* = 247.4 Hz, CFF) ppm.

Minor anomer

^{19}F NMR (282 MHz, $CDCl_3$) δ –120.6 (1 F, dd, *J* = 237.9, 6.9 Hz, CFF), 123.6 (1 F, ddd, *J* = 238.8, 19.0, 6.9 Hz, CFF) ppm.

1-((5*S*)-4-Azido-5-(((tert-butyldiphenylsilyl)oxy)methyl)-3,3-difluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione, 5.35



Thymine (314 mg, 2.49 mmol) and catalytic $(NH_4)_2SO_4$ were suspended in HMDS (3.6 equiv, 8.96 mmol, 1.87 mL) and stirred at reflux for 2.5 h. The reaction mixture was reduced *in vacuo*, then taken up in anhydrous toluene and reduced *in vacuo* twice, before drying under high vacuum. Mesylate **5.34** (91 mg, 0.18 mmol) and protected thymine (10 equiv, 1.8 mmol, 475 mg) were stirred slowly at 130 ℃ for 20 h then cooled to RT and taken up in EtOAc and sat. $NaHCO_3$ (aq). The phases were separated and the aqueous phase extracted with EtOAc (2×10 mL). The combined organic phases were dried over anhydrous Na_2SO_4. The solvents were reduced *in vacuo* to yield a crude residue which was evaporated onto silica gel and purified by column chromatography on silica gel (10:90–40:60 Et_2O/petrol) to yield the desired product **5.35** as a colourless oil as a 1:1 mixture of anomers (59 mg, 61%).

IR (film) 2931 (w), 2113 (s), 1693 (s), 1463 (m), 1274 (m), 1112 (s) cm^{-1}.

LRMS (ESI$^+$) *m/z* 564.3 (M+Na)$^+$ (100).

HRMS (ESI$^+$) for $C_{26}H_{29}F_2N_5O_4Si$ (M+Na)$^+$ Calcd 564.1849; Found 564.1853.

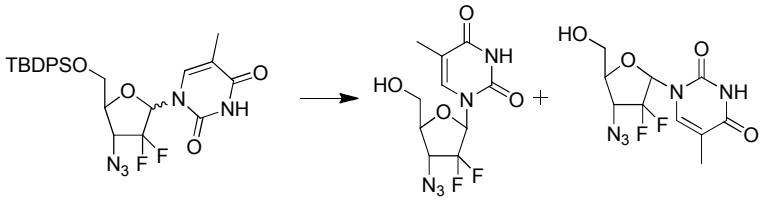
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (0.5 H, br. s., 0.5×NH), 9.18 (0.5 H, br. s., 0.5×NH), 7.69–7.66 (4 H, m, 4×CH_{Ar}), 7.51–7.40 (6 H, m, 6×CH_{Ar}), 7.22 (0.5 H, s, 0.5×HC=C), 7.09 (0.5 H, s, 0.5×HC=C), 6.41 (0.5 H, dd, *J* = 11.2, 5.5 Hz, 0.5×CHN), 6.23 (0.5 H, t, *J* = 8.7 Hz, 0.5×CHN), 4.52 (0.5 H, ddd, *J* = 11.6, 9.8, 7.2 Hz, 0.5×CHN_3), 4.35 (0.5 H, dt, *J* = 14.4, 8.6 Hz, 0.5×CHN_3), 4.23–4.21 (0.5 H, m, 0.5×C<u>H</u>CH_2), 4.11–4.09 (0.5 H, m, 0.5×CHC<u>H</u>H), 3.96–3.87 (1.5 H, m, CHC<u>H</u>$_2$, 0.5×C<u>H</u>CH_2), 3.81 (0.5 H, dd, *J* = 11.8, 2.9 Hz, 0.5×CHCH<u>H</u>), 1.96 (1.5 H, s, 0.5×C=CCH_3), 1.72 (1.5 H, s, 0.5×C=CCH_3), 1.14 (4.5 H, s, 0.5×C$(CH_3)_3$), 1.12 (4.5 H, s, 0.5×C$(CH_3)_3$) ppm.

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 163.4 (0.5×C=O), 163.3 (0.5×C=O), 150.2 (0.5×C=O), 150.1 (0.5×C=O), 132.4 (C), 132.2 (0.5×C), 132.1 (0.5×C), 135.53 (CH_{Ar}), 135.46 (CH_{Ar}), 135.3 (CH_{Ar}), 130.3 (CH_{Ar}), 130.2 (CH_{Ar}), 130.1 (CH_{Ar}), 128.1 (CH_{Ar}), 128.01 (CH_{Ar}), 127.95 (CH_{Ar}), 135.0 (0.5×C=<u>C</u>H), 134.8 (0.5×C=<u>C</u>H), 122.7 (dd, *J* = 263.4, 260.5 Hz, 0.5×CF_2), 122.6 (t, *J* = 262.4 Hz, 0.5×CF_2), 111.7 (0.5×C=C<u>C</u>H_3), 111.4 (0.5×C=C<u>C</u>H_3), 83.74 (dd, *J* = 38.4, 19.4 Hz, 0.5×CHN), 83.73 (dd, *J* = 41.3, 22.4 Hz, 0.5×CHN), 81.7 (d, *J* = 5.8 Hz, 0.5×<u>C</u>HCH_2), 79.0 (d, *J* = 5.8 Hz, 0.5×<u>C</u>HCH_2), 62.1 (0.5×CH_2), 61.3 (dd, *J* = 26.2, 18.0 Hz, 0.5×CHN_3), 61.0 (0.5×CH_2), 60.7 (dd, *J* = 28.2, 18.5 Hz, 0.5×CHN_3), 26.9 (0.5×C(<u>C</u>$H_3)_3$), 26.8 (0.5×C(<u>C</u>$H_3)_3$), 19.4 (0.5×<u>C</u>$(CH_3)_3$), 19.2 (0.5×<u>C</u>$(CH_3)_3$), 12.6 (0.5×C=C<u>C</u>H_3), 12.1 (0.5×C=C<u>C</u>H_3) ppm (some CH_{Ar} overlap).

^{19}F NMR (282 MHz, $CDCl_3$) δ –110.1 (0.5 F, ddd, *J* = 240.5, 13.8, 6.0 Hz, 0.5×C<u>F</u>F), –111.5 (0.5 F, d, *J* = 240.0 Hz, 0.5×C<u>F</u>F), –113.7 (0.5 F, d, *J* = 240.5 Hz, 0.5×CF<u>F</u>), –122.1 (0.5 F, dt, *J* = 237.9, 10.3 Hz, 0.5×CF<u>F</u>) ppm.

1-((2S,5S)-4-Azido-3,3-difluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione, 5.36α

1-((2R,5S)-4-azido-3,3-difluoro-5-(hydroxymethyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione, 5.36β



To protected nucleoside **5.35** (42 mg, 0.078 mmol) in THF (0.75 mL) was added TBAF (1 M in THF, 2 equiv, 0.016 mmol, 0.016 mL). The reaction mixture was stirred at RT for 22 h. The solvents were reduced *in vacuo* and purified by column chromatography on silica gel (MeOH/DCM 2:98–6:94) to yield the desired nucleoside **5.36** as a colourless oil as a 1:1 anomeric mixture (16 mg, 68%). A small sample was separated by RP-HPLC (85:10–70:30 H_2O/MeCN over 30 min then 70:30 for 10 min) retention time **5.36β**: 29.0 min, retention time **5.36α**: 30.4 min.

5.36α

IR (film) 3396 (br), 2359 (m), 2330 (m), 2160 (w), 2117 (s), 2007 (w), 1970 (w), 1958 (w), 1697 (s), 1471 (w), 1375 (w), 1276 (m), 1116 (m), 1066 (m) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.42 (1 H, dd, *J* = 2.3, 1.3 Hz, HC=C), 6.37 (1 H, dd, *J* = 11.5, 5.6 Hz, CHN), 4.62 (1 H, m, CHN_3), 4.38 (1 H, m, C<u>H</u>CH_2), 3.85 (1 H, ddd, *J* = 12.6, 3.3, 2.0 Hz, CHC<u>H</u>H), 3.71 (1 H, dd, *J* = 12.6, 3.7 Hz, CHCH<u>H</u>), 1.91 (3 H, d, *J* = 1.1 Hz, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 166.2 (C=O), 152.4 (C=O), 137.3 (H<u>C</u>=C), 85.4 (dd, *J* = 39.5, 19.0 Hz, CHN), 83.5 (d, *J* = 5.9 Hz, <u>C</u>HCH_2), 62.3 (dd, *J* = 26.3, 17.6 Hz, CHN_3), 61.5 (CH_2), 12.5 (CH_3) ppm (CF_2 and CCH_3 not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –113.8 (1 F, d, *J* = 237.1 Hz, C<u>F</u>F), –122.8 (1 F, dt, *J* = 236.2, 12.9 Hz, CF<u>F</u>) ppm.

5.36β

IR (film) 3395 (br), 3071 (br), 2057 (w), 2359 (w), 2117 (s), 1694 (s), 1470 (m), 1391 (w), 1317 (w), 1275 (m), 1196 (w), 1128 (w), 1096 (m) cm^{-1}.

^{1}H NMR (400 MHz, MeOH-d_4) δ 7.72 (1 H, s, HC=C), 6.17 (1 H, t, *J* = 7.9 Hz, CHN), 4.50 (1 H, td, *J* = 12.7, 9.2 Hz, CHN_3), 4.00–3.95 (2 H, m, $CHCH_2$, CHC<u>H</u>H), 3.78 (1 H, m, CH<u>H</u>), 1.88 (3 H, d, *J* = 1.3 Hz, CH_3) ppm.

^{13}C NMR + DEPT (100 MHz, MeOH-d_4) δ 166.2 (C=O), 152.3 (C=O), 137.3 (H<u>C</u>=C), 112.2 (<u>C</u>CH_3), 86.1–85.3 (m, CHN), 80.9 (t, *J* = 4.4 Hz, <u>C</u>HCH_2), 61.2 (t, *J* = 22.0 Hz, CHN_3), 60.3 (CH_2), 12.5 (CH_3) ppm (CF_2 not visible).

^{19}F NMR (282 MHz, MeOH-d_4) δ –112.9—114.8 (2 F, m, CF_2) ppm.

9 References

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APPENDIX

UNIVERSITY OF Southampton
School of Chemistry

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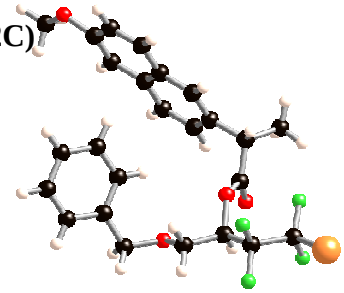
Table 1. Crystal data and structure refinement details.



Identification code	**2008sot1027 (KJB/5248/22C)**
Empirical formula	$C_{25}H_{23}BrF_4O_4$
Formula weight	543.34
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 12.2255(3) Å
	b = 5.55230(10) Å β = 105.3861(14)°
	c = 17.7773(4) Å
Volume	1163.47(4) Å^3
Z	2
Density (calculated)	1.551 Mg / m^3
Absorption coefficient	1.829 mm^{-1}
$F(000)$	552
Crystal	Rod; Colourless
Crystal size	0.18 × 0.02 × 0.02 mm^3
θ range for data collection	3.29 – 25.02°
Index ranges	$-14 \le h \le 14$, $-6 \le k \le 6$, $-21 \le l \le 21$
Reflections collected	15350
Independent reflections	3908 [R_{int} = 0.0442]
Completeness to θ = 25.02°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9643 and 0.7243
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3908 / 1 / 310
Goodness-of-fit on F^2	1.038
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0345, $wR2$ = 0.0713
R indices (all data)	$R1$ = 0.0412, $wR2$ = 0.0751
Absolute structure parameter	0.129(9) C9=R, C13=S
Largest diff. peak and hole	0.229 and –0.275 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, C13=S

Table 2. Atomic coordinates [× 10⁴], equivalent isotropic displacement parameters [Å² × 10³] 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	6583(1)	2977(1)	6209(1)	40(1)	1
F1	5089(2)	7589(5)	5808(1)	36(1)	1
F2	4045(2)	4445(4)	5881(1)	32(1)	1
F3	6508(2)	6556(4)	7211(1)	38(1)	1
F4	5536(2)	3388(5)	7337(1)	41(1)	1
O1	2732(2)	10614(4)	6751(1)	28(1)	1
O2	3661(2)	5996(4)	7241(1)	23(1)	1
O3	4645(2)	7825(7)	8351(1)	30(1)	1
O4	–2547(2)	5400(5)	8981(1)	32(1)	1
C1	573(3)	8489(6)	6682(2)	29(1)	1
C2	–456(3)	7320(6)	6578(2)	33(1)	1
C3	–1413(3)	8149(10)	6032(2)	32(1)	1
C4	–1331(3)	10149(7)	5586(2)	31(1)	1
C5	–312(3)	11330(6)	5681(2)	25(1)	1
C6	657(3)	10523(6)	6235(2)	24(1)	1
C7	1748(3)	11913(7)	6352(2)	27(1)	1
C8	3107(3)	9004(7)	6252(2)	28(1)	1
C9	4093(3)	7659(8)	6773(2)	24(1)	1
C10	4736(3)	6139(7)	6315(2)	27(1)	1
C11	5801(3)	4856(7)	6813(2)	29(1)	1
C12	4053(3)	6176(7)	8032(2)	23(1)	1
C13	3639(3)	4070(6)	8415(2)	21(1)	1
C14	4551(3)	3338(8)	9161(2)	28(1)	1
C15	2519(3)	4731(6)	8588(2)	21(1)	1
C16	1578(2)	3309(7)	8329(2)	21(1)	1
C17	532(3)	3844(6)	8497(2)	22(1)	1
C18	–453(3)	2399(6)	8226(2)	25(1)	1
C19	–1437(2)	2991(10)	8394(2)	27(1)	1
C20	–1504(3)	5052(7)	8848(2)	25(1)	1
C21	–575(3)	6502(7)	9123(2)	25(1)	1
C22	464(3)	5896(6)	8948(2)	23(1)	1
C23	1442(3)	7360(6)	9212(2)	26(1)	1
C24	2435(3)	6802(7)	9039(2)	27(1)	1
C25	–2688(3)	7553(8)	9387(2)	32(1)	1

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

Br1–C11	1.922(4)	C6–C7	1.506(5)
F1–C10	1.361(4)	C8–C9	1.508(5)
F2–C10	1.359(4)	C9–C10	1.528(5)
F3–C11	1.347(4)	C10–C11	1.542(5)
F4–C11	1.341(4)	C12–C13	1.507(5)
O1–C8	1.418(4)	C13–C15	1.525(4)
O1–C7	1.420(4)	C13–C14	1.543(4)
O2–C12	1.363(4)	C15–C16	1.371(5)
O2–C9	1.434(4)	C15–C24	1.421(5)
O3–C12	1.210(5)	C16–C17	1.419(4)
O4–C20	1.371(4)	C17–C22	1.408(5)
O4–C25	1.430(5)	C17–C18	1.421(5)
C1–C2	1.384(5)	C18–C19	1.355(5)
C1–C6	1.400(5)	C19–C20	1.415(6)
C2–C3	1.386(5)	C20–C21	1.372(5)
C3–C4	1.383(6)	C21–C22	1.426(5)
C4–C5	1.378(5)	C22–C23	1.419(5)
C5–C6	1.398(5)	C23–C24	1.364(5)

C8–O1–C7	112.3(3)	F4–C11–Br1	107.8(3)
C12–O2–C9	117.9(3)	F3–C11–Br1	109.2(2)
C20–O4–C25	116.5(3)	C10–C11–Br1	113.5(2)
C2–C1–C6	120.2(3)	O3–C12–O2	122.8(3)
C1–C2–C3	120.4(4)	O3–C12–C13	127.3(3)
C4–C3–C2	119.5(3)	O2–C12–C13	109.9(3)
C5–C4–C3	120.9(3)	C12–C13–C15	109.4(3)
C4–C5–C6	120.2(3)	C12–C13–C14	109.8(3)
C5–C6–C1	118.8(3)	C15–C13–C14	111.9(3)
C5–C6–C7	119.1(3)	C16–C15–C24	118.4(3)
C1–C6–C7	122.0(3)	C16–C15–C13	120.8(3)
O1–C7–C6	114.2(3)	C24–C15–C13	120.8(3)
O1–C8–C9	105.5(3)	C15–C16–C17	122.1(3)
O2–C9–C8	108.6(3)	C22–C17–C16	118.8(3)
O2–C9–C10	105.9(3)	C22–C17–C18	118.5(3)
C8–C9–C10	112.7(3)	C16–C17–C18	122.7(3)
F2–C10–F1	107.0(3)	C19–C18–C17	120.7(3)
F2–C10–C9	110.8(3)	C18–C19–C20	120.7(3)
F1–C10–C9	108.9(3)	O4–C20–C21	125.1(3)
F2–C10–C11	108.0(3)	O4–C20–C19	114.1(3)
F1–C10–C11	106.6(3)	C21–C20–C19	120.7(3)
C9–C10–C11	115.1(3)	C20–C21–C22	119.0(3)
F4–C11–F3	107.5(3)	C17–C22–C23	118.6(3)
F4–C11–C10	110.9(3)	C17–C22–C21	120.4(3)
F3–C11–C10	107.7(3)	C23–C22–C21	120.9(3)

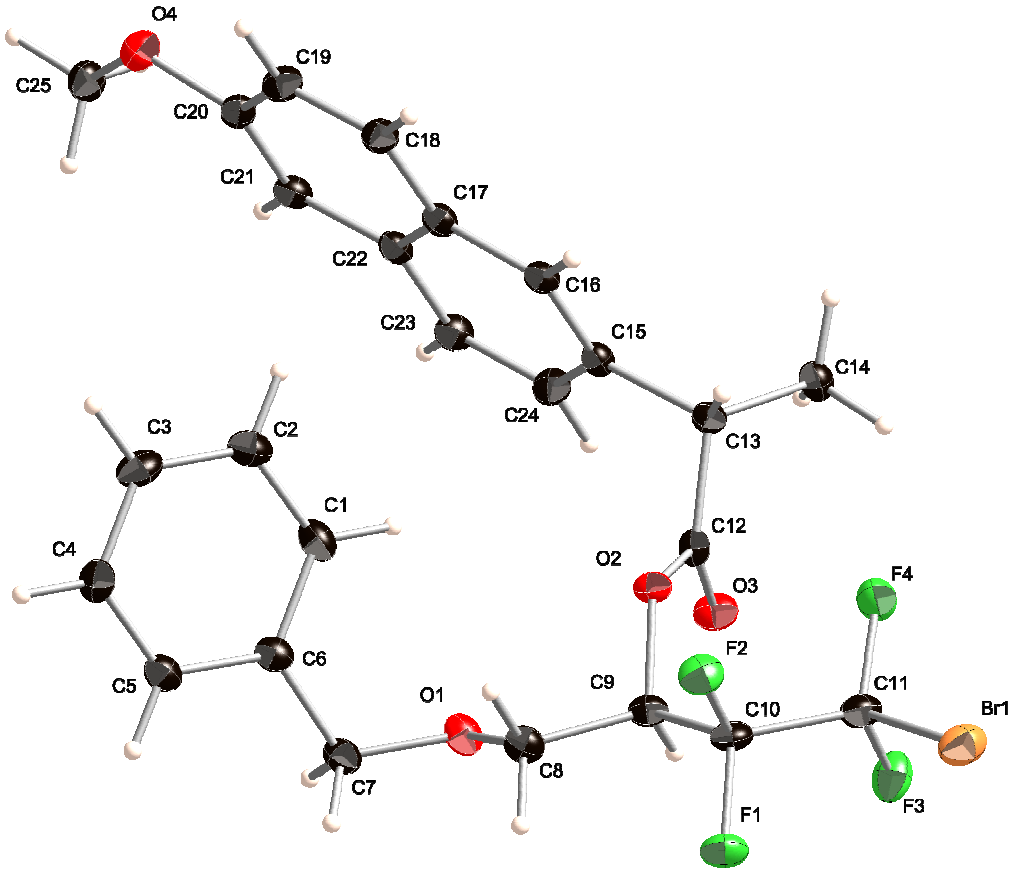
C24–C23–C22	121.2(3)	C23–C24–C15	120.9(3)

Table 4. Anisotropic displacement parameters [Å^2× 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	41(1)	35(1)	49(1)	–6(1)	23(1)	0(1)
F1	43(1)	37(2)	32(1)	7(1)	19(1)	–4(1)
F2	34(1)	30(1)	34(1)	–10(1)	9(1)	–8(1)
F3	29(1)	40(1)	42(1)	–12(1)	2(1)	–3(1)
F4	40(1)	45(2)	42(1)	16(1)	20(1)	12(1)
O1	33(1)	23(1)	26(1)	–4(1)	3(1)	4(1)
O2	24(1)	24(1)	21(1)	0(1)	6(1)	–5(1)
O3	33(1)	30(1)	25(1)	–5(2)	5(1)	–10(2)
O4	27(1)	37(2)	32(1)	–2(1)	9(1)	–1(1)
C1	36(2)	24(3)	25(2)	1(2)	2(2)	3(2)
C2	40(2)	25(3)	34(2)	2(2)	13(2)	–2(2)
C3	32(2)	29(2)	39(2)	–10(2)	14(2)	–12(2)
C4	27(2)	35(2)	30(2)	–1(2)	7(2)	5(2)
C5	32(2)	21(2)	23(2)	–1(2)	9(2)	3(2)
C6	31(2)	19(2)	21(2)	–4(1)	7(2)	–1(1)
C7	30(2)	21(2)	28(2)	2(2)	3(2)	–2(2)
C8	33(2)	28(2)	23(2)	–1(2)	8(2)	0(2)
C9	29(2)	25(2)	21(2)	0(2)	9(1)	–5(2)
C10	30(2)	22(2)	30(2)	0(2)	11(2)	–9(2)
C11	29(2)	30(2)	32(2)	1(2)	15(2)	–3(2)
C12	21(2)	24(2)	23(2)	–1(2)	4(1)	4(2)
C13	24(2)	18(2)	21(2)	–1(1)	6(1)	–1(1)
C14	27(2)	30(2)	26(2)	2(2)	5(1)	5(2)
C15	24(2)	21(2)	19(2)	1(1)	6(1)	3(2)
C16	27(2)	17(2)	18(2)	–1(2)	6(1)	0(2)
C17	27(2)	21(2)	18(2)	1(1)	5(1)	1(1)
C18	26(2)	22(2)	26(2)	–1(1)	6(1)	–3(1)
C19	26(2)	29(2)	26(2)	–3(2)	5(1)	–7(2)
C20	25(2)	29(2)	22(2)	5(2)	8(1)	2(2)
C21	31(2)	21(2)	23(2)	1(2)	8(2)	–1(2)
C22	27(2)	21(2)	21(2)	4(1)	7(1)	4(2)
C23	32(2)	21(2)	24(2)	–5(1)	10(2)	0(1)
C24	25(2)	22(2)	31(2)	–5(2)	4(2)	–5(2)
C25	29(2)	37(3)	32(2)	3(2)	13(1)	5(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	1225	7910	7057	35	1
H2	–507	5942	6884	39	1
H3	–2119	7348	5964	39	1
H4	–1986	10716	5211	37	1
H5	–268	12696	5368	30	1
H7A	1833	12408	5835	32	1
H7B	1697	13395	6650	32	1
H8A	3351	9900	5843	33	1
H8B	2493	7876	5997	33	1
H9	4624	8820	7117	29	1
H13	3503	2680	8044	25	1
H14A	5274	3063	9033	42	1
H14B	4316	1857	9373	42	1
H14C	4644	4629	9548	42	1
H16	1627	1921	8027	25	1
H18	–421	1003	7924	30	1
H19	–2089	2011	8205	33	1
H21	–623	7888	9426	30	1
H23	1406	8753	9515	31	1
H24	3078	7812	9222	32	1
H25A	–2183	7506	9917	47	1
H25B	–3477	7674	9413	47	1
H25C	–2501	8953	9109	47	1



Thermal ellipsoids drawn at the 35% probability level

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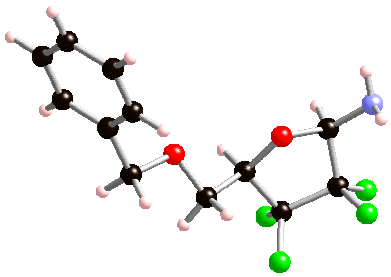
Table 1. Crystal data and structure refinement details.

Identification code	**2010sot0628** (KJB/5868/40A)
Empirical formula	$C_{12}H_{13}F_4NO_2$
Formula weight	279.23
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 6.3057(2) Å
	b = 10.4827(4) Å
	c = 18.6529(7) Å
Volume	1232.97(8) Å^3
Z	4
Density (calculated)	1.504 Mg / m^3
Absorption coefficient	0.142 mm^{-1}
$F(000)$	576
Crystal	Lath; Colourless
Crystal size	0.26 × 0.07 × 0.02 mm^3
θ range for data collection	2.92 – 27.47°
Index ranges	$-8 \le h \le 8$, $-13 \le k \le 13$, $-24 \le l \le 24$
Reflections collected	9813
Independent reflections	1646 [R_{int} = 0.0693]
Completeness to θ = 27.47°	99.8 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9972 and 0.9641
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1646 / 0 / 180
Goodness-of-fit on F^2	1.219
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0578, $wR2$ = 0.1022
R indices (all data)	$R1$ = 0.0777, $wR2$ = 0.1112
Absolute structure parameter	Unknown
Largest diff. peak and hole	0.302 and –0.278 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, those of the NH2 were freely refined.

Table 2. Atomic coordinates [× 10⁴], equivalent isotropic displacement parameters [Å² × 10³] 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.*
F1	7875(4)	1790(2)	2626(1)	36(1)	1
F2	6604(4)	3675(2)	2429(1)	38(1)	1
F3	11341(4)	2278(3)	2016(1)	45(1)	1
F4	10457(5)	4256(3)	2157(1)	52(1)	1
O1	4452(4)	717(3)	845(1)	21(1)	1
O2	8200(4)	2180(3)	906(1)	21(1)	1
N1	11512(6)	3192(4)	656(2)	24(1)	1
C1	648(6)	–396(4)	–175(2)	23(1)	1
C2	131(6)	–728(4)	–873(2)	26(1)	1
C3	1523(7)	–1453(4)	–1272(2)	27(1)	1
C4	3463(7)	–1839(4)	–982(2)	26(1)	1
C5	3957(6)	–1499(4)	–289(2)	24(1)	1
C6	2566(6)	–781(4)	125(2)	21(1)	1
C7	3173(7)	–420(4)	878(2)	25(1)	1
C8	5529(6)	941(4)	1505(2)	20(1)	1
C9	6558(6)	2226(4)	1437(2)	19(1)	1
C10	7679(6)	2706(4)	2118(2)	22(1)	1
C11	9852(6)	3173(4)	1846(2)	25(1)	1
C12	9601(6)	3254(4)	1040(2)	21(1)	1

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

F1–C10	1.354(4)
F2–C10	1.352(4)
F3–C11	1.365(5)
F4–C11	1.331(5)
O1–C8	1.426(4)
O1–C7	1.441(5)
O2–C9	1.434(4)
O2–C12	1.453(5)
N1–C12	1.403(5)
C1–C2	1.388(6)
C1–C6	1.393(5)
C2–C3	1.379(6)
C3–C4	1.398(6)
C4–C5	1.376(5)
C5–C6	1.390(5)
C6–C7	1.503(5)
C8–C9	1.500(5)
C9–C10	1.538(5)
C10–C11	1.541(5)
C11–C12	1.514(5)

C8–O1–C7	111.5(3)
C9–O2–C12	107.1(3)
C2–C1–C6	120.6(4)
C3–C2–C1	119.7(4)
C2–C3–C4	120.5(4)
C5–C4–C3	119.1(4)
C4–C5–C6	121.3(4)
C5–C6–C1	118.8(4)
C5–C6–C7	119.7(4)
C1–C6–C7	121.5(4)
O1–C7–C6	108.2(3)
O1–C8–C9	106.3(3)
O2–C9–C8	109.9(3)
O2–C9–C10	104.5(3)
C8–C9–C10	115.0(3)
F2–C10–F1	106.1(3)
F2–C10–C9	111.7(3)
F1–C10–C9	112.8(3)
F2–C10–C11	110.4(3)
F1–C10–C11	111.9(3)
C9–C10–C11	104.0(3)
F4–C11–F3	106.7(3)
F4–C11–C12	114.5(4)

F3–C11–C12	109.9(3)
F4–C11–C10	112.5(3)
F3–C11–C10	108.5(3)
C12–C11–C10	104.5(3)
N1–C12–O2	113.4(3)
N1–C12–C11	114.5(3)
O2–C12–C11	101.1(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 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}
F1	44(2)	42(2)	21(1)	13(1)	–11(1)	–14(1)
F2	35(1)	48(2)	31(1)	–19(1)	3(1)	9(1)
F3	27(1)	76(2)	33(1)	15(1)	–3(1)	17(2)
F4	63(2)	56(2)	36(2)	–23(1)	10(2)	–39(2)
O1	23(1)	21(1)	19(1)	2(1)	–4(1)	–5(1)
O2	21(1)	24(1)	18(1)	–3(1)	2(1)	–7(1)
N1	21(2)	27(2)	24(2)	1(2)	1(2)	–3(2)
C1	22(2)	15(2)	31(2)	2(2)	5(2)	–1(2)
C2	26(2)	28(2)	25(2)	6(2)	–4(2)	4(2)
C3	33(2)	26(2)	22(2)	1(2)	–3(2)	–5(2)
C4	31(2)	20(2)	27(2)	2(2)	5(2)	–3(2)
C5	21(2)	23(2)	28(2)	2(2)	–2(2)	–1(2)
C6	25(2)	17(2)	20(2)	4(2)	1(2)	–8(2)
C7	28(2)	24(2)	23(2)	3(2)	–1(2)	–8(2)
C8	21(2)	25(2)	15(2)	3(2)	–2(2)	2(2)
C9	19(2)	24(2)	15(2)	1(2)	–3(2)	1(2)
C10	23(2)	25(2)	17(2)	–1(2)	–1(2)	0(2)
C11	22(2)	28(2)	24(2)	–2(2)	–3(2)	–3(2)
C12	19(2)	20(2)	25(2)	1(2)	–2(2)	–2(2)

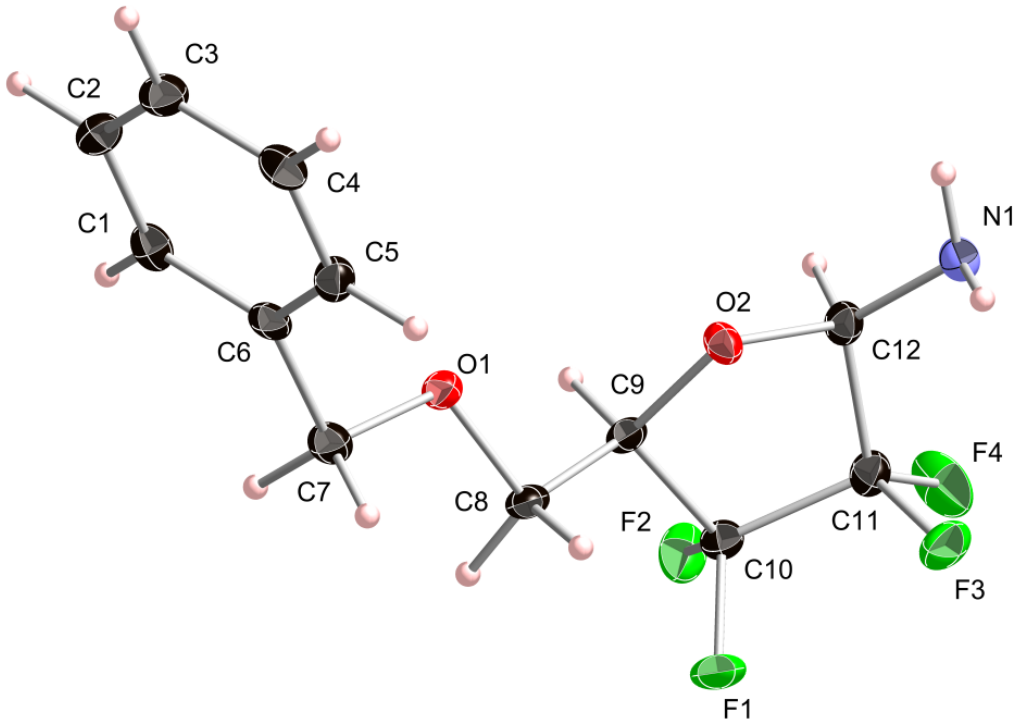
Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H901	11330(80)	3290(50)	210(30)	38(14)	1
H902	12210(80)	2350(50)	670(30)	48(15)	1
H1	–315	99	101	27	1
H2	–1176	–457	–1076	32	1
H3	1160	–1692	–1748	32	1
H4	4428	–2330	–1259	32	1
H5	5274	–1760	–90	29	1
H7A	1884	–260	1167	30	1
H7B	3983	–1121	1104	30	1
H8A	6611	274	1590	24	1
H8B	4514	936	1910	24	1
H9	5466	2865	1288	23	1
H12	8847	4063	916	26	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
N1–H901···O2^{i}	0.86(5)	2.44(5)	3.126(4)	138(4)
N1–H901···O1^{i}	0.86(5)	2.51(5)	3.292(5)	152(4)
N1–H902···O1^{ii}	0.99(5)	2.24(6)	3.208(5)	165(4)

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



Thermal ellipsoids drawn at the 35% probability level

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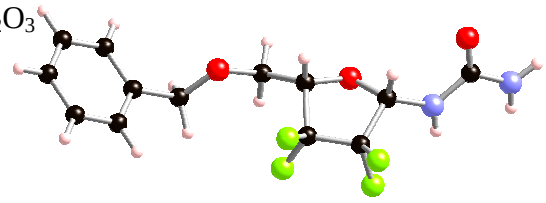
Table 1. Crystal data and structure refinement details.



Identification code	**2009sot1240** (KJB/5584/27B)
Empirical formula	$C_{13}H_{14}F_4N_2O_3$
Formula weight	322.26
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	*P*–1
Unit cell dimensions	a = 8.787(5) Å α = 72.939(5)°
	b = 12.816(5) Å β = 89.428(5)°
	c = 13.376(5) Å γ = 83.867(5)°
Volume	1431.4(11) Å^3
Z	4
Density (calculated)	1.495 Mg / m^3
Absorption coefficient	0.140 mm^{-1}
F(000)	664
Crystal	Lath; Colourless
Crystal size	0.22 × 0.06 × 0.01 mm^3
θ range for data collection	2.92 – 25.02°
Index ranges	$-10 \le h \le 10$, $-15 \le k \le 15$, $-15 \le l \le 15$
Reflections collected	20383
Independent reflections	5033 [R_{int} = 0.0860]
Completeness to θ = 25.02°	99.5 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9986 and 0.9699
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5033 / 573 / 410
Goodness-of-fit on F^2	1.035
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1917, *wR2* = 0.4219
R indices (all data)	*R1* = 0.2564, *wR2* = 0.4681
Largest diff. peak and hole	2.297 and –1.355 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. This structure has 2 chemically identical molecules in the asymmetric unit. The first is well behaved, but the second shows > 50% disorder. This has proved hard to model well, and the resulting refinement is of poor quality.

Table 2. Atomic coordinates [× 10⁴], equivalent isotropic displacement parameters [Å² × 10³] 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.*
C101	5661(11)	952(8)	–7136(8)	40(2)	1
C102	6165(12)	411(8)	–7852(8)	45(2)	1
C103	6523(12)	972(8)	–8826(8)	43(2)	1
C104	6368(12)	2101(8)	–9115(8)	43(2)	1
C105	5863(10)	2652(8)	–8418(7)	37(2)	1
C106	5493(10)	2087(7)	–7417(7)	37(2)	1
C107	4933(9)	2698(8)	–6653(7)	46(2)	1
O101	6209(6)	3002(4)	–6220(4)	32(1)	1
C108	5766(9)	3632(6)	–5536(5)	39(2)	1
C109	6757(9)	3217(5)	–4541(4)	36(2)	1
C110	6310(7)	2129(5)	–3807(5)	37(2)	1
F101	4953(5)	1892(5)	–3955(4)	52(2)	1
F102	7313(6)	1233(4)	–3905(5)	57(2)	1
C111	6687(7)	2210(5)	–2760(5)	43(2)	1
F103	5202(6)	2210(5)	–2222(5)	68(2)	1
F104	7576(8)	1422(4)	–2106(5)	82(2)	1
C112	7218(9)	3350(5)	–2929(5)	33(2)	1
O102	6533(7)	3925(4)	–3928(4)	32(1)	1
N101	6765(7)	3907(6)	–2168(5)	30(2)	1
C113	7747(9)	4519(6)	–1869(6)	26(2)	1
N102	7214(8)	5010(6)	–1178(6)	35(2)	1
O103	9067(6)	4566(5)	–2209(5)	34(2)	1
C201	10875(11)	1630(8)	–4201(7)	40(2)	1
C202	11164(11)	2140(9)	–3476(8)	47(2)	1
C203	11377(11)	3231(9)	–3788(8)	49(2)	1
C204	11349(11)	3810(9)	–4836(8)	46(2)	1
C205	11062(10)	3303(8)	–5586(8)	39(2)	1
C206	10837(10)	2196(8)	–5259(7)	38(2)	1
C7A	10438(11)	1586(8)	–6012(6)	44(2)	0.760(7)
O1A	10945(13)	2075(7)	–7022(5)	68(3)	0.760(7)
C8A	10649(17)	1511(8)	–7746(5)	54(2)	0.760(7)
C9A	10457(10)	2277(6)	–8870(5)	62(2)	0.760(7)
C10A	10477(8)	1631(6)	–9673(5)	67(1)	0.760(7)
F1A	10143(10)	648(5)	–9290(5)	64(1)	0.760(7)
F2A	9684(9)	2166(6)	–10618(5)	64(1)	0.760(7)
C11A	12019(9)	1725(5)	–10139(5)	64(1)	0.760(7)
F3A	12849(10)	715(5)	–9384(5)	64(1)	0.760(7)
F4A	12325(10)	1572(6)	–11053(4)	64(1)	0.760(7)
C12A	12312(11)	2870(5)	–10124(5)	57(2)	0.760(7)
O2A	11602(8)	2936(5)	–9182(5)	34(2)	0.760(7)

C7B	10438(11)	1586(8)	–6012(6)	44(2)	0.240(7)
O1B	10590(30)	2320(11)	–7010(6)	68(3)	0.240(7)
C8B	10156(15)	1849(15)	–7783(8)	54(2)	0.240(7)
C9B	11451(14)	1819(8)	–8550(6)	62(2)	0.240(7)
C10B	10856(10)	1411(7)	–9443(7)	67(1)	0.240(7)
F1B	10543(18)	422(6)	–9128(13)	64(1)	0.240(7)
F2B	9590(13)	2074(10)	–10021(12)	64(1)	0.240(7)
C11B	12070(11)	1735(6)	–10207(6)	64(1)	0.240(7)
F3B	13364(13)	895(11)	–9667(9)	64(1)	0.240(7)
F4B	12120(20)	1655(12)	–11155(7)	64(1)	0.240(7)
C12B	12312(11)	2870(5)	–10124(5)	57(2)	0.240(7)
O2B	11800(20)	2846(8)	–9109(7)	34(2)	0.240(7)
N201	11758(8)	3823(6)	–10946(5)	41(2)	1
C213	12690(9)	4609(7)	–11446(6)	29(2)	1
N202	12005(9)	5447(7)	–12222(6)	44(2)	1
O203	14046(6)	4529(5)	–11182(5)	35(2)	1

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

C101–C102	1.383(14)	C205–C206	1.392(14)
C101–C106	1.384(13)	C206–C7A	1.509(13)
C102–C103	1.343(14)	C7A–O1A	1.402(9)
C103–C104	1.376(14)	O1A–C8A	1.409(9)
C104–C105	1.370(14)	C8A–C9A	1.534(9)
C105–C106	1.377(13)	C9A–O2A	1.366(9)
C106–C107	1.509(13)	C9A–C10A	1.536(9)
C107–O101	1.408(8)	C10A–F1A	1.278(8)
O101–C108	1.414(8)	C10A–F2A	1.400(8)
C108–C109	1.523(8)	C10A–C11A	1.488(9)
C109–O102	1.388(7)	C11A–F4A	1.315(8)
C109–C110	1.540(8)	C11A–F3A	1.509(8)
C110–F101	1.293(7)	C11A–C12A	1.523(9)
C110–F102	1.408(7)	C12A–O2A	1.420(8)
C110–C111	1.478(8)	C12A–N201	1.426(6)
C111–F104	1.312(7)	O1B–C8B	1.413(11)
C111–F103	1.484(7)	C8B–C9B	1.530(10)
C111–C112	1.534(8)	C9B–O2B	1.375(9)
C112–O102	1.427(7)	C9B–C10B	1.553(10)
C112–N101	1.436(10)	C10B–F1B	1.273(9)
N101–C113	1.363(11)	C10B–F2B	1.409(9)
C113–O103	1.243(10)	C10B–C11B	1.476(10)
C113–N102	1.319(11)	C11B–F4B	1.303(9)
C201–C202	1.358(14)	C11B–F3B	1.507(9)
C201–C206	1.387(12)	N201–C213	1.379(11)
C202–C203	1.370(15)	C213–O203	1.232(10)
C203–C204	1.379(14)	C213–N202	1.346(11)
C204–C205	1.384(15)		

C102–C101–C106	120.3(9)	F101–C110–C111	117.3(5)
C103–C102–C101	120.9(9)	F102–C110–C111	104.1(5)
C102–C103–C104	119.3(10)	F101–C110–C109	115.9(5)
C105–C104–C103	120.6(9)	F102–C110–C109	111.0(5)
C104–C105–C106	120.6(9)	C111–C110–C109	102.7(5)
C105–C106–C101	118.1(9)	F104–C111–C110	120.2(6)
C105–C106–C107	120.5(8)	F104–C111–F103	103.9(5)
C101–C106–C107	121.4(9)	C110–C111–F103	104.9(5)
O101–C107–C106	108.6(7)	F104–C111–C112	113.3(6)
C107–O101–C108	111.8(6)	C110–C111–C112	106.6(5)
O101–C108–C109	109.6(5)	F103–C111–C112	106.9(5)
O102–C109–C108	111.2(5)	O102–C112–N101	111.0(6)
O102–C109–C110	102.7(5)	O102–C112–C111	100.9(5)
C108–C109–C110	112.7(6)	N101–C112–C111	116.8(6)
F101–C110–F102	105.3(5)	C109–O102–C112	106.5(5)

C113–N101–C112	120.1(6)	C10A–C11A–F3A	97.8(5)
O103–C113–N102	123.6(8)	F4A–C11A–C12A	111.6(6)
O103–C113–N101	121.0(8)	C10A–C11A–C12A	101.7(6)
N102–C113–N101	115.4(7)	F3A–C11A–C12A	121.0(6)
C202–C201–C206	120.6(10)	O2A–C12A–N201	108.4(6)
C201–C202–C203	119.9(9)	O2A–C12A–C11A	101.7(5)
C202–C203–C204	120.6(10)	N201–C12A–C11A	121.4(7)
C203–C204–C205	120.3(10)	C9A–O2A–C12A	114.8(6)
C204–C205–C206	118.6(9)	O1B–C8B–C9B	110.7(10)
C201–C206–C205	120.0(9)	O2B–C9B–C8B	113.2(10)
C201–C206–C7A	117.4(9)	O2B–C9B–C10B	100.6(7)
C205–C206–C7A	122.5(8)	C8B–C9B–C10B	108.5(8)
O1A–C7A–C206	111.6(8)	F1B–C10B–F2B	108.9(8)
C7A–O1A–C8A	113.7(7)	F1B–C10B–C11B	121.0(10)
O1A–C8A–C9A	112.4(7)	F2B–C10B–C11B	99.5(8)
O2A–C9A–C8A	114.6(7)	F1B–C10B–C9B	113.0(9)
O2A–C9A–C10A	103.7(6)	F2B–C10B–C9B	114.7(9)
C8A–C9A–C10A	111.8(6)	C11B–C10B–C9B	99.2(6)
F1A–C10A–F2A	111.8(6)	F4B–C11B–C10B	126.7(10)
F1A–C10A–C11A	114.8(7)	F4B–C11B–F3B	102.1(7)
F2A–C10A–C11A	94.6(6)	C10B–C11B–F3B	99.4(7)
F1A–C10A–C9A	113.6(6)	C213–N201–C12A	122.3(7)
F2A–C10A–C9A	115.9(6)	O203–C213–N202	123.8(8)
C11A–C10A–C9A	104.5(6)	O203–C213–N201	121.0(7)
F4A–C11A–C10A	122.6(7)	N202–C213–N201	115.2(7)
F4A–C11A–F3A	102.8(6)		

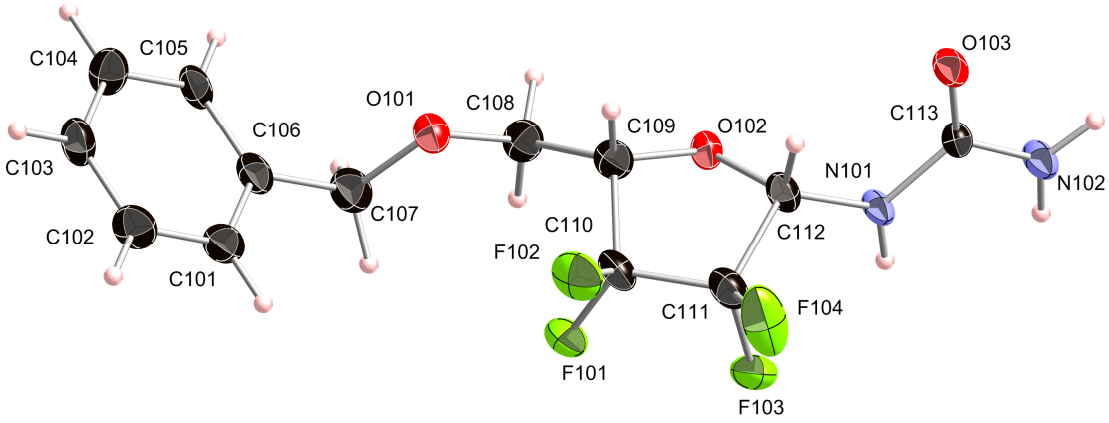
Table 4. Anisotropic displacement parameters [Å²× 10³]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C101	38(4)	41(3)	43(4)	–11(3)	–2(3)	–9(3)
C102	50(4)	31(3)	53(4)	–15(3)	–1(4)	1(3)
C103	53(4)	39(3)	43(4)	–23(3)	–6(3)	–1(4)
C104	51(4)	42(4)	37(4)	–12(3)	–5(3)	0(4)
C105	40(4)	37(3)	39(3)	–17(3)	–13(3)	–4(3)
C106	32(3)	41(3)	43(3)	–19(3)	–3(3)	–11(3)
C107	41(4)	52(4)	50(4)	–19(4)	–1(4)	–11(4)
O101	27(3)	36(3)	38(3)	–17(3)	0(2)	–1(2)
C108	44(4)	34(4)	40(4)	–13(3)	2(4)	–1(4)
C109	35(4)	35(3)	41(4)	–15(3)	3(3)	–5(3)
C110	38(3)	33(3)	47(3)	–19(3)	–3(3)	–10(3)
F101	47(3)	65(3)	49(3)	–16(3)	–2(2)	–30(3)
F102	63(3)	35(3)	76(4)	–25(3)	5(3)	2(3)
C111	54(4)	32(3)	47(3)	–16(3)	–3(3)	–12(3)
F103	90(4)	72(4)	59(3)	–32(3)	34(3)	–52(3)
F104	131(5)	34(3)	74(4)	–9(3)	–57(4)	9(3)
C112	33(4)	33(3)	39(4)	–19(3)	–3(3)	–6(3)
O102	40(3)	31(3)	29(3)	–14(2)	1(3)	–8(3)
N101	19(3)	42(4)	40(4)	–27(3)	10(3)	–12(3)
C113	28(4)	28(4)	25(4)	–10(3)	–2(3)	–5(3)
N102	26(4)	43(4)	46(4)	–27(3)	8(3)	–12(3)
O103	26(3)	43(3)	39(3)	–19(3)	1(2)	–11(3)
C201	36(4)	55(4)	30(3)	–17(3)	1(3)	2(3)
C202	38(4)	74(4)	34(3)	–30(3)	1(3)	8(4)
C203	34(4)	74(4)	50(3)	–42(3)	1(3)	5(4)
C204	29(4)	60(4)	58(4)	–33(3)	5(3)	–2(3)
C205	22(3)	53(3)	45(3)	–21(3)	8(3)	–7(3)
C206	36(3)	53(3)	31(3)	–19(3)	1(3)	–7(3)
C7A	45(4)	58(3)	32(3)	–17(3)	1(3)	–10(3)
O1A	138(8)	57(5)	26(3)	–28(3)	37(4)	–49(5)
C8A	92(4)	43(3)	34(3)	–17(3)	–1(3)	–26(3)
C9A	97(3)	54(3)	39(3)	–14(2)	–2(3)	–22(3)
C10A	99(3)	60(2)	43(2)	–15(2)	–2(2)	–22(2)
F1A	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
F2A	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
C11A	96(3)	58(2)	45(2)	–22(2)	5(2)	–19(2)
F3A	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
F4A	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
C12A	84(4)	56(3)	38(3)	–23(3)	10(3)	–19(3)
O2A	44(4)	32(3)	33(3)	–15(3)	3(3)	–15(3)
C7B	45(4)	58(3)	32(3)	–17(3)	1(3)	–10(3)

O1B	138(8)	57(5)	26(3)	–28(3)	37(4)	–49(5)
C8B	92(4)	43(3)	34(3)	–17(3)	–1(3)	–26(3)
C9B	97(3)	54(3)	39(3)	–14(2)	–2(3)	–22(3)
C10B	99(3)	60(2)	43(2)	–15(2)	–2(2)	–22(2)
F1B	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
F2B	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
C11B	96(3)	58(2)	45(2)	–22(2)	5(2)	–19(2)
F3B	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
F4B	100(2)	60(2)	37(2)	–19(1)	–11(2)	–19(2)
C12B	84(4)	56(3)	38(3)	–23(3)	10(3)	–19(3)
O2B	44(4)	32(3)	33(3)	–15(3)	3(3)	–15(3)
N201	30(4)	64(5)	27(4)	–4(4)	4(3)	–26(4)
C213	32(4)	34(4)	28(4)	–17(3)	3(3)	–11(4)
N202	28(4)	61(5)	42(4)	–7(4)	3(3)	–21(4)
O203	14(3)	48(3)	47(3)	–22(3)	2(2)	–4(2)

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H101	5429	542	–6446	48	1
H102	6259	–369	–7653	54	1
H103	6879	593	–9311	52	1
H104	6614	2502	–9804	52	1
H105	5768	3432	–8627	45	1
H10A	4242	3361	–7016	55	1
H10B	4356	2224	–6092	55	1
H10C	4676	3573	–5359	47	1
H10D	5887	4414	–5883	47	1
H109	7861	3131	–4722	43	1
H112	8358	3296	–2986	39	1
H10E	5851	3852	–1895	36	1
H10F	7803	5397	–933	42	1
H10G	6269	4951	–961	42	1
H201	10698	879	–3982	48	1
H202	11217	1741	–2754	56	1
H203	11546	3592	–3278	58	1
H204	11527	4561	–5044	55	1
H205	11020	3701	–6308	46	1
H7A1	10914	817	–5759	52	0.760(7)
H7A2	9314	1575	–6036	52	0.760(7)
H8A1	9704	1149	–7549	64	0.760(7)
H8A2	11503	932	–7715	64	0.760(7)
H9A	9458	2748	–8938	74	0.760(7)
H12A	13439	2876	–10036	68	0.760(7)
H7B1	11147	908	–5914	52	0.240(7)
H7B2	9378	1387	–5910	52	0.240(7)
H8B1	9231	2285	–8168	64	0.240(7)
H8B2	9902	1094	–7443	64	0.240(7)
H9B	12381	1343	–8191	74	0.240(7)
H12B	13447	2882	–10095	68	0.240(7)
H20A	10788	3913	–11141	49	1
H20B	12532	5979	–12573	53	1
H20C	11030	5463	–12378	53	1



Thermal ellipsoids drawn at the 35% probability level. The second molecule in the asymmetric unit is heavily disordered and is not shown.

UNIVERSITY OF Southampton
School of Chemistry

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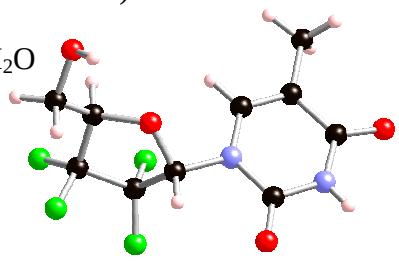
Table 1. Crystal data and structure refinement details.



Identification code	**2011sot0455** (KJB/5977/30X)
Empirical formula	$C_{20}H_{22}F_8N_4O_9$
	$2(C_{10}H_{10}F_4N_2O_4), H_2O$
Formula weight	614.42
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.7879(2) Å
	b = 10.71960(10) Å β = 104.9740(10)°
	c = 11.9674(2) Å
Volume	1213.01(3) Å^3
Z	2
Density (calculated)	1.682 Mg / m^3
Absorption coefficient	0.169 mm^{-1}
F(000)	628
Crystal	Slab; Colourless
Crystal size	0.40 × 0.12 × 0.08 mm^3
θ range for data collection	3.12 – 27.48°
Index ranges	$-12 \le h \le 12$, $-13 \le k \le 13$, $-15 \le l \le 15$
Reflections collected	16410
Independent reflections	2918 [R_{int} = 0.0445]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9866 and 0.9354
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2918 / 1 / 396
Goodness-of-fit on F^2	1.126
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0344, $wR2$ = 0.0793
R indices (all data)	$R1$ = 0.0379, $wR2$ = 0.0815
Absolute structure parameter	From synthetic procedures
Largest diff. peak and hole	0.205 and –0.289 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, except those of the NH, OH and water which were freely refined.

Table 2. Atomic coordinates [× 10⁴], equivalent isotropic displacement parameters [Å² × 10³] 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.*
F13A	9957(2)	–2862(2)	5568(2)	26(1)	1
F13E	8769(2)	–1842(2)	6589(1)	27(1)	1
F14A	9894(2)	284(1)	6240(1)	25(1)	1
F14E	9699(2)	–648(2)	4584(1)	28(1)	1
O101	12831(2)	–3303(2)	8778(2)	24(1)	1
O102	12431(2)	–1383(2)	7045(2)	21(1)	1
O106	13043(2)	365(2)	4304(2)	22(1)	1
O107	14045(2)	4039(2)	6212(2)	19(1)	1
N101	12611(2)	511(2)	6100(2)	16(1)	1
N102	13608(2)	2157(2)	5327(2)	15(1)	1
C101	11670(3)	–3307(3)	7778(3)	25(1)	1
C102	11272(3)	–1986(2)	7371(2)	17(1)	1
C103	10026(3)	–1895(3)	6312(2)	19(1)	1
C104	10350(3)	–697(2)	5722(2)	18(1)	1
C105	11974(3)	–732(2)	5980(2)	17(1)	1
C106	13076(3)	965(2)	5170(2)	16(1)	1
C107	13629(2)	2945(2)	6242(2)	14(1)	1
C108	13169(3)	2408(2)	7195(2)	15(1)	1
C109	12691(3)	1223(2)	7082(2)	16(1)	1
C110	13256(3)	3184(3)	8254(2)	20(1)	1
F23A	10626(2)	–2909(2)	10274(2)	34(1)	1
F23E	9552(2)	–1111(2)	10154(2)	38(1)	1
F24A	10499(2)	–703(2)	12366(2)	32(1)	1
F24E	10237(2)	–2729(2)	12330(2)	34(1)	1
O201	13235(2)	761(2)	10144(2)	30(1)	1
O202	13141(2)	–1333(2)	11638(2)	18(1)	1
O206	12933(2)	–3000(2)	14592(2)	21(1)	1
O207	14364(2)	–6712(2)	13441(2)	19(1)	1
N201	13061(2)	–3174(2)	12710(2)	15(1)	1
N202	13685(2)	–4838(2)	13988(2)	16(1)	1
C201	11955(3)	278(3)	10310(3)	26(1)	1
C202	12094(3)	–1115(2)	10550(2)	19(1)	1
C203	10751(3)	–1721(3)	10695(2)	24(1)	1
C204	10962(3)	–1784(3)	12011(2)	22(1)	1
C205	12576(3)	–1878(2)	12498(2)	17(1)	1
C206	13202(3)	–3623(2)	13826(2)	16(1)	1
C207	13977(2)	–5626(2)	13164(2)	15(1)	1
C208	13812(3)	–5094(2)	12025(2)	17(1)	1
C209	13370(3)	–3910(2)	11851(2)	16(1)	1
C210	14148(3)	–5881(2)	11094(2)	21(1)	1
O1W	5053(2)	1168(2)	2283(2)	24(1)	1

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

F13A–C103	1.357(3)	F23E–C203	1.354(3)
F13E–C103	1.355(3)	F24A–C204	1.352(3)
F14A–C104	1.354(3)	F24E–C204	1.348(3)
F14E–C104	1.347(3)	O201–C201	1.416(4)
O101–C101	1.421(3)	O201–H201	0.86(5)
O101–H101	0.83(4)	O202–C205	1.414(3)
O102–C105	1.420(3)	O202–C202	1.452(3)
O102–C102	1.444(3)	O206–C206	1.217(3)
O106–C106	1.213(3)	O207–C207	1.242(3)
O107–C107	1.245(3)	N201–C209	1.390(3)
N101–C109	1.387(3)	N201–C206	1.393(3)
N101–C106	1.394(3)	N201–C205	1.468(3)
N101–C105	1.462(3)	N202–C206	1.382(3)
N102–C106	1.375(3)	N202–C207	1.383(3)
N102–C107	1.379(3)	N202–H202	0.85(3)
N102–H102	0.81(4)	C201–C202	1.521(4)
C101–C102	1.516(4)	C201–H20A	0.9900
C101–H10A	0.9900	C201–H20B	0.9900
C101–H10B	0.9900	C202–C203	1.516(4)
C102–C103	1.518(3)	C202–H20C	1.0000
C102–H10C	1.0000	C203–C204	1.535(4)
C103–C104	1.538(4)	C204–C205	1.540(4)
C104–C105	1.540(4)	C205–H205	1.0000
C105–H105	1.0000	C207–C208	1.448(3)
C107–C108	1.449(3)	C208–C209	1.339(4)
C108–C109	1.347(4)	C208–C210	1.500(3)
C108–C110	1.500(3)	C209–H209	0.9500
C109–H109	0.9500	C210–H21A	0.9800
C110–H11A	0.9800	C210–H21B	0.9800
C110–H11B	0.9800	C210–H21C	0.9800
C110–H11C	0.9800	O1W–H1W	0.85(6)
F23A–C203	1.364(3)	O1W–H2W	0.91(5)

C101–O101–H101	108(3)	O101–C101–H10B	109.5
C105–O102–C102	111.99(18)	C102–C101–H10B	109.5
C109–N101–C106	121.7(2)	H10A–C101–H10B	108.1
C109–N101–C105	121.0(2)	O102–C102–C101	110.5(2)
C106–N101–C105	117.3(2)	O102–C102–C103	105.3(2)
C106–N102–C107	127.2(2)	C101–C102–C103	114.4(2)
C106–N102–H102	114(2)	O102–C102–H10C	108.8
C107–N102–H102	119(2)	C101–C102–H10C	108.8
O101–C101–C102	110.5(2)	C103–C102–H10C	108.8
O101–C101–H10A	109.5	F13E–C103–F13A	107.3(2)
C102–C101–H10A	109.5	F13E–C103–C102	112.5(2)

F13A–C103–C102	113.1(2)	C202–C201–H20B	109.6
F13E–C103–C104	112.7(2)	H20A–C201–H20B	108.1
F13A–C103–C104	108.5(2)	O202–C202–C203	105.1(2)
C102–C103–C104	102.7(2)	O202–C202–C201	109.6(2)
F14E–C104–F14A	107.9(2)	C203–C202–C201	113.8(2)
F14E–C104–C103	113.4(2)	O202–C202–H20C	109.4
F14A–C104–C103	107.9(2)	C203–C202–H20C	109.4
F14E–C104–C105	113.4(2)	C201–C202–H20C	109.4
F14A–C104–C105	111.9(2)	F23E–C203–F23A	106.9(2)
C103–C104–C105	102.2(2)	F23E–C203–C202	114.1(2)
O102–C105–N101	109.3(2)	F23A–C203–C202	110.8(2)
O102–C105–C104	105.2(2)	F23E–C203–C204	112.5(2)
N101–C105–C104	112.9(2)	F23A–C203–C204	108.2(2)
O102–C105–H105	109.8	C202–C203–C204	104.2(2)
N101–C105–H105	109.8	F24E–C204–F24A	108.1(2)
C104–C105–H105	109.8	F24E–C204–C203	112.5(2)
O106–C106–N102	122.3(2)	F24A–C204–C203	108.5(2)
O106–C106–N101	123.7(2)	F24E–C204–C205	114.0(2)
N102–C106–N101	113.9(2)	F24A–C204–C205	109.4(2)
O107–C107–N102	119.4(2)	C203–C204–C205	104.1(2)
O107–C107–C108	124.6(2)	O202–C205–N201	110.3(2)
N102–C107–C108	116.0(2)	O202–C205–C204	104.67(19)
C109–C108–C107	117.8(2)	N201–C205–C204	112.5(2)
C109–C108–C110	123.4(2)	O202–C205–H205	109.8
C107–C108–C110	118.9(2)	N201–C205–H205	109.8
C108–C109–N101	123.1(2)	C204–C205–H205	109.8
C108–C109–H109	118.4	O206–C206–N202	123.0(2)
N101–C109–H109	118.4	O206–C206–N201	123.1(2)
C108–C110–H11A	109.5	N202–C206–N201	113.9(2)
C108–C110–H11B	109.5	O207–C207–N202	119.1(2)
H11A–C110–H11B	109.5	O207–C207–C208	124.9(2)
C108–C110–H11C	109.5	N202–C207–C208	115.9(2)
H11A–C110–H11C	109.5	C209–C208–C207	118.2(2)
H11B–C110–H11C	109.5	C209–C208–C210	122.8(2)
C201–O201–H201	108(3)	C207–C208–C210	119.0(2)
C205–O202–C202	113.64(18)	C208–C209–N201	123.1(2)
C209–N201–C206	121.8(2)	C208–C209–H209	118.4
C209–N201–C205	122.1(2)	N201–C209–H209	118.4
C206–N201–C205	116.1(2)	C208–C210–H21A	109.5
C206–N202–C207	127.0(2)	C208–C210–H21B	109.5
C206–N202–H202	116(2)	H21A–C210–H21B	109.5
C207–N202–H202	117(2)	C208–C210–H21C	109.5
O201–C201–C202	110.2(2)	H21A–C210–H21C	109.5
O201–C201–H20A	109.6	H21B–C210–H21C	109.5
C202–C201–H20A	109.6	H1W–O1W–H2W	115(4)
O201–C201–H20B	109.6		

Table 4. Anisotropic displacement parameters [Å²× 10³]. 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}
F13A	28(1)	17(1)	30(1)	–8(1)	3(1)	–5(1)
F13E	16(1)	31(1)	35(1)	1(1)	8(1)	–3(1)
F14A	22(1)	15(1)	37(1)	–4(1)	8(1)	3(1)
F14E	29(1)	31(1)	19(1)	3(1)	–3(1)	–3(1)
O101	24(1)	25(1)	24(1)	6(1)	7(1)	3(1)
O102	17(1)	18(1)	26(1)	8(1)	2(1)	–4(1)
O106	31(1)	18(1)	19(1)	–5(1)	10(1)	–2(1)
O107	25(1)	14(1)	18(1)	–1(1)	6(1)	–4(1)
N101	20(1)	11(1)	16(1)	0(1)	7(1)	–4(1)
N102	18(1)	13(1)	14(1)	1(1)	5(1)	–1(1)
C101	21(1)	19(1)	32(2)	7(1)	2(1)	–3(1)
C102	19(1)	14(1)	19(1)	0(1)	7(1)	–2(1)
C103	18(1)	17(1)	22(1)	–5(1)	6(1)	–3(1)
C104	21(1)	15(1)	18(1)	–2(1)	3(1)	0(1)
C105	21(1)	10(1)	21(1)	0(1)	6(1)	–1(1)
C106	16(1)	15(1)	17(1)	1(1)	3(1)	2(1)
C107	14(1)	14(1)	14(1)	0(1)	1(1)	1(1)
C108	16(1)	14(1)	15(1)	0(1)	3(1)	1(1)
C109	18(1)	16(1)	14(1)	0(1)	5(1)	0(1)
C110	28(1)	18(1)	17(1)	–4(1)	9(1)	–4(1)
F23A	32(1)	28(1)	39(1)	–7(1)	4(1)	–13(1)
F23E	19(1)	50(1)	39(1)	14(1)	–2(1)	6(1)
F24A	34(1)	29(1)	36(1)	4(1)	16(1)	15(1)
F24E	24(1)	34(1)	48(1)	17(1)	14(1)	–2(1)
O201	37(1)	25(1)	28(1)	7(1)	10(1)	–6(1)
O202	18(1)	17(1)	19(1)	5(1)	2(1)	0(1)
O206	29(1)	18(1)	19(1)	–2(1)	9(1)	2(1)
O207	25(1)	13(1)	20(1)	2(1)	9(1)	3(1)
N201	19(1)	11(1)	16(1)	1(1)	4(1)	3(1)
N202	21(1)	14(1)	14(1)	1(1)	6(1)	0(1)
C201	29(1)	20(1)	25(1)	7(1)	4(1)	3(1)
C202	19(1)	21(1)	15(1)	1(1)	1(1)	1(1)
C203	19(1)	23(1)	27(1)	2(1)	0(1)	2(1)
C204	21(1)	17(1)	29(1)	6(1)	9(1)	3(1)
C205	21(1)	13(1)	17(1)	2(1)	6(1)	1(1)
C206	15(1)	14(1)	17(1)	–1(1)	4(1)	–1(1)
C207	14(1)	14(1)	15(1)	0(1)	4(1)	–1(1)
C208	18(1)	16(1)	16(1)	–2(1)	4(1)	–1(1)
C209	19(1)	15(1)	13(1)	–1(1)	4(1)	0(1)
C210	33(1)	17(1)	16(1)	–1(1)	9(1)	6(1)
O1W	34(1)	16(1)	23(1)	1(1)	11(1)	2(1)

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.*
H101	13560(40)	–3410(40)	8570(30)	37(10)	1
H102	13860(30)	2420(30)	4780(30)	22(8)	1
H10A	10850	–3722	7960	30	1
H10B	11926	–3785	7153	30	1
H10C	11047	–1505	8017	20	1
H105	12262	–1203	5356	21	1
H109	12395	860	7704	19	1
H11A	12999	2673	8848	31	1
H11B	12602	3890	8056	31	1
H11C	14223	3495	8550	31	1
H201	13800(50)	910(40)	10810(40)	58(13)	1
H202	13800(30)	–5130(30)	14670(30)	22(8)	1
H20A	11176	432	9609	31	1
H20B	11722	709	10969	31	1
H20C	12399	–1539	9911	23	1
H205	12877	–1386	13230	20	1
H209	13263	–3557	11105	19	1
H21A	13974	–5399	10375	32	1
H21B	13545	–6625	10968	32	1
H21C	15143	–6134	11331	32	1
H1W	5250(50)	530(60)	2710(40)	74(16)	1
H2W	4880(40)	1870(50)	2660(40)	48(11)	1

Table 6. Torsion angles [°].

C105–O102–C102–C101	134.7(2)
C105–O102–C102–C103	10.8(3)
O101–C101–C102–O102	62.1(3)
O101–C101–C102–C103	–179.3(2)
O102–C102–C103–F13E	–150.1(2)
C101–C102–C103–F13E	88.4(3)
O102–C102–C103–F13A	88.1(2)
C101–C102–C103–F13A	–33.4(3)
O102–C102–C103–C104	–28.7(2)
C101–C102–C103–C104	–150.2(2)
F13E–C103–C104–F14E	–81.2(3)
F13A–C103–C104–F14E	37.5(3)
C102–C103–C104–F14E	157.5(2)
F13E–C103–C104–F14A	38.2(3)
F13A–C103–C104–F14A	156.91(19)
C102–C103–C104–F14A	–83.1(2)
F13E–C103–C104–C105	156.3(2)
F13A–C103–C104–C105	–85.0(2)
C102–C103–C104–C105	35.0(2)
C102–O102–C105–N101	133.5(2)
C102–O102–C105–C104	12.0(3)
C109–N101–C105–O102	–42.5(3)
C106–N101–C105–O102	140.2(2)
C109–N101–C105–C104	74.2(3)
C106–N101–C105–C104	–103.1(2)
F14E–C104–C105–O102	–151.7(2)
F14A–C104–C105–O102	86.0(2)
C103–C104–C105–O102	–29.2(2)
F14E–C104–C105–N101	89.2(3)
F14A–C104–C105–N101	–33.2(3)
C103–C104–C105–N101	–148.4(2)
C107–N102–C106–O106	176.2(2)
C107–N102–C106–N101	–5.0(3)
C109–N101–C106–O106	178.9(2)
C105–N101–C106–O106	–3.8(4)
C109–N101–C106–N102	0.1(3)
C105–N101–C106–N102	177.5(2)
C106–N102–C107–O107	–174.1(2)
C106–N102–C107–C108	6.8(4)
O107–C107–C108–C109	177.3(2)
N102–C107–C108–C109	–3.7(3)
O107–C107–C108–C110	–3.1(4)
N102–C107–C108–C110	175.9(2)
C107–C108–C109–N101	–0.5(4)
C110–C108–C109–N101	179.9(2)
C106–N101–C109–C108	2.4(4)
C105–N101–C109–C108	–174.8(2)
C205–O202–C202–C203	–6.9(3)

C205–O202–C202–C201	115.8(2)
O201–C201–C202–O202	64.8(3)
O201–C201–C202–C203	–177.8(2)
O202–C202–C203–F23E	145.3(2)
C201–C202–C203–F23E	25.3(3)
O202–C202–C203–F23A	–94.0(2)
C201–C202–C203–F23A	146.0(2)
O202–C202–C203–C204	22.2(3)
C201–C202–C203–C204	–97.8(3)
F23E–C203–C204–F24E	83.1(3)
F23A–C203–C204–F24E	–34.8(3)
C202–C203–C204–F24E	–152.8(2)
F23E–C203–C204–F24A	–36.5(3)
F23A–C203–C204–F24A	–154.4(2)
C202–C203–C204–F24A	87.6(2)
F23E–C203–C204–C205	–152.9(2)
F23A–C203–C204–C205	89.2(2)
C202–C203–C204–C205	–28.8(3)
C202–O202–C205–N201	109.7(2)
C202–O202–C205–C204	–11.5(3)
C209–N201–C205–O202	–29.9(3)
C206–N201–C205–O202	149.8(2)
C209–N201–C205–C204	86.5(3)
C206–N201–C205–C204	–93.8(2)
F24E–C204–C205–O202	147.8(2)
F24A–C204–C205–O202	–91.0(2)
C203–C204–C205–O202	24.8(3)
F24E–C204–C205–N201	28.0(3)
F24A–C204–C205–N201	149.2(2)
C203–C204–C205–N201	–95.0(2)
C207–N202–C206–O206	178.0(2)
C207–N202–C206–N201	–2.5(3)
C209–N201–C206–O206	–179.7(2)
C205–N201–C206–O206	0.6(3)
C209–N201–C206–N202	0.8(3)
C205–N201–C206–N202	–178.9(2)
C206–N202–C207–O207	–177.8(2)
C206–N202–C207–C208	2.8(3)
O207–C207–C208–C209	179.3(2)
N202–C207–C208–C209	–1.3(3)
O207–C207–C208–C210	–1.1(4)
N202–C207–C208–C210	178.4(2)
C207–C208–C209–N201	–0.1(4)
C210–C208–C209–N201	–179.8(2)
C206–N201–C209–C208	0.4(4)
C205–N201–C209–C208	–179.9(2)

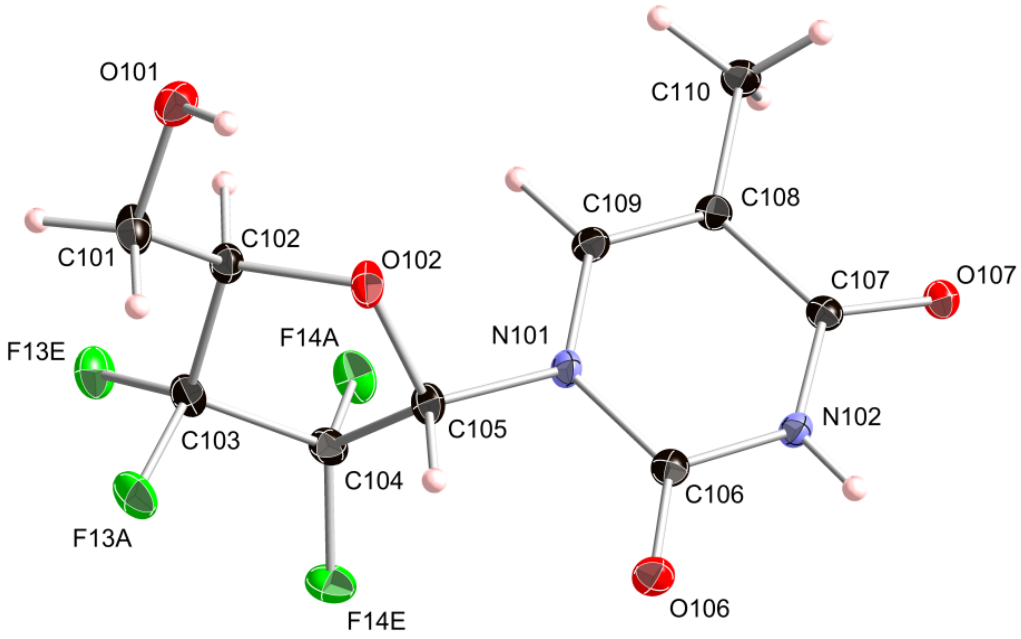
Table 7. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O101–H101···O1W^{i}	0.83(4)	1.95(4)	2.753(3)	165(4)
O1W–H1W···O107^{i}	0.85(6)	2.06(6)	2.901(3)	174(5)
N102–H102···O207^{ii}	0.81(4)	2.02(4)	2.824(3)	173(3)
O201–H201···O1W^{iii}	0.86(5)	1.89(5)	2.748(3)	178(5)
N202–H202···O107^{iv}	0.85(3)	2.01(3)	2.859(3)	175(3)
O1W–H2W···O207^{v}	0.91(5)	1.93(5)	2.833(3)	175(4)

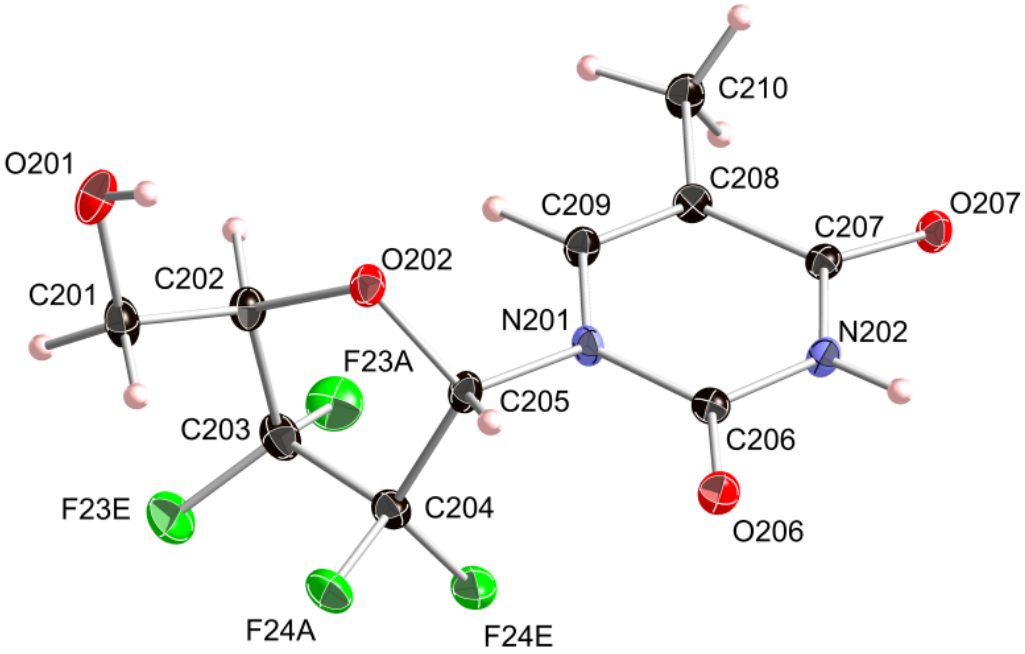
Symmetry transformations used to generate equivalent atoms:
(i) –x+2,y–1/2,–z+1 (ii) x,y+1,z–1 (iii) x+1,y,z+1
(iv) x,y–1,z+1 (v) x–1,y+1,z–1

Table 8. Cremer Pople parameters [Å and °].

	Ring 1	Ring 2
Q(2)	0.351(3)	0.285(3)
Phi(2)	269.0(4)	85.9(5)



Molecule 1, thermal ellipsoids drawn at the 35% probability level.



Molecule 2, thermal ellipsoids drawn at the 35% probability level.